CLINICAL TRIAL PROTOCOL
REGARDING A DRUG HUMAN USE

ANRS 163 ETRAL

A non-comparative phase II trial evaluating the capacity of the dual combination raltegravir/etravirine to maintain virological success in HIV-1 infected patients of at least 45 years of age with an HIV-RNA plasma viremia below 50 copies/mL under a current boosted protease inhibitor containing regimen.

Version n°*3.0 dated 19/01/2018*

EudraCT number: 2014-000828-24
Number of registration in http://clinicaltrials.gov/: NCT 02212379
Approved by the CPP Ethics Committee on 06/03/2018
Authorized by ANSM on 27/04/2015

Sponsor:

Institut National de la Santé et de la Recherche Médicale – Agence nationale de recherches sur le sida et les hépatites virales (Inserm - ANRS)
101 rue de Tolbiac
75013 Paris
France
Tél. : + 33 (0)1 53 94 60 00 - Fax : + 33 (0)1 53 94 60 01

Coordinating investigator:

Pr Christine Katlama
Service des Maladies Infectieuses et Tropicales
Groupe Hospitalier Pitié-Salpêtrière, Paris
France
☎: + 33 (0)1 42 16 01 42
💻: christine.katlama@psl.aphp.fr

Scientific director:

Pr Jacques Reynes
Département des Maladies Infectieuses et Tropicales
Hôpital Gui de Chauliac, CHU de Montpellier
France
☎: + 33 (0)4 67 33 72 20
💻: j-reynes@chu-montpellier.fr

Methodology centre:

Dominique Costagliola
Inserm UMR S 1136 Université Pierre et Marie Curie
Epidémiologie, stratégies thérapeutiques et virologie cliniques dans l'infection à VIH
56 Bd Vincent Auriol, BP 335,
75625 Paris Cedex 13
France
☎: + 33 (0)1 42 16 42 82
💻:dominique.costagliola@ccde.chups.jussieu.fr

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SIGNATURE PAGE

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Institut National de la Santé et de la Recherche Médicale – Agence nationale de recherches sur le sida et les hépatites virales (Inserm - ANRS)
Représentant du promoteur par délégation de pouvoir : Pr. François Dabis
101 rue de Tolbiac 75013 PARIS - France
Tél. : 01 53 94 60 00 - Fax : 01 53 94 60 01

à Paris, le

Pr. François Dabis
Directeur de l'ANRS
Signature :

Coordinating Investigator:

Pr Christine Katlama
Service des Maladies Infectieuses et Tropicales
Groupe Hospitalier Pitié-Salpêtrière, Paris, France
Tél: + 33 (0)1 42 16 01 42
christine.katlama@psl.aphp.fr

à Paris, le 19 avril 2018

Pr Christine Katlama
Signature :

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Version n°	Date	Amending n°	Main changes
1.0	**07/03/2014**		
2.0	**18/03/2015**	**1**	**Modification of a inclusion criteria, modification of the timeframe between the screening and the D0 and minor updates**
3.0	**19/01/2018**	**2**	**Addition of a secondary objective and a secondary endpoint**

List of abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
ANRS	Agence nationale de recherches sur le sida et les hépatites virales
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé (France)
AR	Adverse Reaction
ART	Antiretroviral Therapy
ARV	Antiretroviral
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BID	*bis in die* (twice daily)
BMD	Bone Mineral Density
BPH	Benign Prostatic Hyperplasia
Cmin	Minimal Drug Concentration
CAD	Coronary Artery Disease
CCB	Calcium-Channel Blocker
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration Calculator
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CMG	Methodology and study Management Center
CPK	Creatine Phospho-Kinase
CPP	Comité de Protection des Personnes (France)
CRA	Clinical Research Associate
CRP	C-Reactive Protein
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
DXA	Dual-energy X-Ray Absorptiometry
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDTA	Ethylene Di-Amine Tetra-Acetate
EFV	Efavirenz
EFS	Etablissement Français du Sang
EOT	End Of Treatment
ETR	Etravirine
FHDH	French Hospital Database on HIV
FTC	Emtricitabine
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GMP	Good Manufacturing Practice
HBV	Hepatitis B Virus
β HCG	β Human Chorionic Gonadotrophin
HCV	Hepatitis C Virus
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
hsCRP	high-sensitivity C-Reactive Protein
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IL-6	Interleukin-6
IL-6us	Interleukin-6 Ultra-Sensitive
IP-10	Interferon gamma induced Protein 10
IMP	Investigational Medical Product
INSERM	Institut National de la Santé et de la Recherche Médicale
IQR	Inter-Quartile Range
IRB	Institutional Review Board
ITT	Intent to Treat
LDL	Low Density Lipoprotein

LPV	Lopinavir
LSN	French translation of Upper Limit of Normal
MI	Myocardial Infarction
NNRTI	Non-Nucleosidic Reverse Transcriptase Inhibitor
NRTI	Nucleosidic Reverse Transcriptase Inhibitor
OR	Odd Ratio
PCR	Polymerase Chain Reaction
PI	Protease Inhibitor
PI/r	Protease Inhibitor Ritonavir-boosted
PO	*per os*
PY	Person-Year
RAL	Raltegravir
RNA	Ribonucleic Acid
RH	Relative Hazard
RSI	Reference Safety Information
SAE	Serious Adverse Event
SC	Scientific Committee
sCD14	Cluster of Differentiation 14soluble form
sCD163	Haemoglobin Scavenger Receptor soluble form
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
SmPC	Summary of the Product Characteristics
TDF	Tenofovir
TNF	Tumor Necrosis Factor
UDP	Uridine Diphosphate
UGT	Uridyl Glucoronosyl Transferase
ULN	Upper Limit of Normal
VL	Viral Load
WOCBP	Women of Childbearing Potential

MAIN CORRESPONDENTS

Clinical Coordination

Coordinating Investigator
Inserm UMR S 1136 and Université Pierre et Marie Curie
Pr Christine KATLAMA
Service des Maladies Infectieuses et Tropicales, Groupe Hospitalier Pitié-Salpêtrière, Paris, France
☎: + 33 (0)1 42 16 01 42
💻: christine.katlama@psl.aphp.fr

Co Investigator
Inserm UMR S 1136 and Université Pierre et Marie Curie
Dr Marc-Antoine VALANTIN
Service des Maladies Infectieuses et Tropicales, Groupe Hospitalier Pitié-Salpêtrière, Paris, France
☎: + 33 (0)1 42 16 01 71
💻: marc-antoine.valantin@psl.aphp.fr

Scientific director

Pr Jacques REYNES
Département des Maladies Infectieuses et Tropicales, Hôpital Gui de Chauliac, CHU de Montpellier, France
☎: + 33 (0)4 67 33 72 20
💻: j-reynes@chu-montpellier.fr

Principal Investigator in Spain

Dr Esteban MARTINEZ
Medicine Infectious Diseases Unit Hospital Clínic IDIBAPS University of Barcelona 08036 Barcelona, Spain
☎: +34 93 227 55 74
💻: estebanm@clinic.ub.es

Virology Coordination

Service de Virologie – Inserm UMR S 1136 and Université Pierre et Marie Curie Groupe Hospitalier Pitié-Salpêtrière

Pr Vincent CALVEZ
☎: + 33 (0)1 42 17 74 16
💻: vincent.calvez@psl.aphp.fr

Dr Anne-Geneviève MARCELIN
☎: + 33 (0)1 42 17 74 16
💻: anne-genevieve.marcelin@psl.aphp.fr

Dr Cathia SOULIE
☎: +33 (0)1 42 17 58 42
💻: cathia.soulie@psl.aphp.fr

Immunology Coordination

CDR Saint-Antoine INSERM Unité 938 Faculté de Médecine et Université Pierre et Marie Curie site Saint-Antoine

Pr Jacqueline CAPEAU
☎: + 33 (0)1 40 01 13 32
💻: jacqueline.capeau@inserm.fr

DXA Coordination

Hôpital Cochin Service de rhumatologie

Dr Sami KOLTA
☎: + 33 (0)1 58 41 25 84
💻: sami.kolta@cch.aphp.fr

Pharmacology Coordination

Laboratoire de Pharmacologie Clinique – Hôpital Bichat-Claude Bernard

Dr Gilles PEYTAVIN
☎: + 33 (0)1 40.25.80.04
💻: gilles.peytavin@bch.aphp.fr

Methodology centre:
CMG Inserm UMR S 1136 and Université Pierre et Marie Curie
Epidémiologie, stratégies thérapeutiques et virologie cliniques dans l'infection à VIH
56 Bd Vincent Auriol, BP 335,
75625 Paris Cedex 13, France
☎: + 33 (0)1 42 16 42 72 - Fax: 01 42 16 42 61

Methodology coordination:

Dominique COSTAGLIOLA
☎: + 33 (0)1 42 16 42 82
Fax: + 33 (0)1 42 16 42 61
💻: dcostagliola@ccde.chups.jussieu.fr

Lambert ASSOUMOU
☎: + 33 (0)1 42 16 42 80
Fax: + 33 (0)1 42 16 42 61
💻: klassoumou@ccde.chups.jussieu.fr

Project Manager / Clinical Trial Monitors:

Lydie BENIGUEL (Project Manager)
☎: + 33 (0)1 42 16 42 68
Fax: + 33 (0)1 42 16 42 67
💻: lbeniguel@ccde.chups.jussieu.fr

Josiane AKO
☎: + 33 (0)1 42 16 42 92
Fax: + 33 (0)1 42 16 42 61
💻: josiane.ako@iplesp.upmc.fr

Jérémy LAFABLE
☎: + 33 (0)1 42 16 42 55
Fax: + 33 (0) 1 42 16 42 67
💻: jlafable@iplesp.upmc.fr

Statistician:

Clément GUIHENEUF
☎: + 33 (0)1 42 16 42 94
Fax: + 33 (0)1 42 16 42 61
💻: clement.guiheneuf@iplesp.upmc.fr

Data Manager:

Serge RODRIGUES
☎: + 33 (0)1 42 16 42 63
Fax: + 33 (0) 1 42 16 42 61
💻: srodrigues@ccde.chups.jussieu.fr

Sponsor:
Institut national de la santé et de la recherche médicale - Agence nationale de recherches sur le sida et les hépatites virales ***(Inserm-ANRS)***
101, rue de Tolbiac. 75013 Paris - France
☎: + 33 (0)1 53 94 60 00 - Fax: + 33 (0)1 53 94 60 02

ANRS Project Manager:

Fanny CARDON
☎: + 33 (0)1 44 23 60 36
💻: fanny.cardon@anrs.fr

Clinical research safety office:

Dr Alpha DIALLO, Head of office
☎: + 33 (0)1 53 94 60 45

Séverine GIBOWSKI
Clinical research safety officer
☎: + 33 (0)1 53 94 60 08
Fax: + 33 (0)1 53 94 60 02
💻: ec.vigilance@anrs.fr

Secretariat: ☎: + 33 (0)1 53 94 80 96

1 STUDY SYNOPSIS

Version n° 3.0 dated 19/01/2018

EudraCT N°: 2014-000828-24

Title of Study	A non-comparative phase II trial evaluating the capacity of the dual combination raltegravir/etravirine to maintain virological success in HIV-1 infected patients of at least 45 years of age with an HIV-RNA plasma viremia below 50 copies/mL under a current boosted protease inhibitor containing regimen.
Short title	ANRS 163 ETRAL
Sponsor	French National Institute for Health and Medical Research - French national agency for research on AIDS and viral hepatitis (Inserm-ANRS)
Coordinating investigator	**Pr Christine Katlama** *Service des Maladies Infectieuses et Tropicales,* *Groupe Hospitalier Pitié-Salpêtrière, Paris, France*
Scientific director	**Pr Jacques Reynes** *Département des Maladies Infectieuses et Tropicales,* *Hôpital Gui de Chauliac, CHU de Montpellier, France*
Participating countries	France / Spain
Objectives	**Principal objective** To evaluate over 48 weeks of treatment the capacity to maintain virological success defined as the absence of 2 consecutive plasma viral loads (VL) > 50 copies/mL within 2 to 4 weeks of a dual raltegravir/etravirine regimen in HIV-1 infected patients, of at least 45 years of age, with suppressed plasma viremia switching from a boosted PI-containing regimen. **Secondary Objectives** To evaluate the: • *Biological efficacy* - To assess the proportion of patients in therapeutic success up to week 48 and week 96. - To assess the proportion of patients with virological success (plasma HIV-RNA ≤ 50 copies/mL) up to week 96. - To assess the proportion of patients with an interruption of therapeutic strategy. - To assess the proportion of patients with low grade virological failure (HIV-RNA plasma VL between 51 and 200 copies/mL) and the proportion of patients with high grade of virological failure defined as HIV-RNA > 200 copies/mL at time of virological failure. - Time limit to virological failure. - HIV genotypic resistance profile, in plasma, in case of virological failure - To determine the factors associated with virological rebound (plasma HIV-RNA > 50 copies/mL). - Evolution of total cell-associated HIV-DNA from D0 to W48 and W96. - Evolution of CD4+, CD8+ T cells counts and CD4/CD8 ratio at each time point from D0. • *Tolerability and Metabolic Impact* - Incidence of clinical and biological adverse effects. - Incidence of clinical and biological adverse events (grade 3 or 4). - Modification of metabolic parameters (fasting triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol and fasting glycemia). - Evolution of the calibrated Framingham risk score and of the SCORE risk equation including HDL cholesterol (from the European Cardiovascular Society) from D0 to W48 and W96. - Evolution of renal function evaluated using proteinuria and the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration Calculator) formula to estimate the Glomerular Filtration Rate (GFR) from D0 to W96.

	- Modification of peripheral and central body fat distribution at W48 and W96 compared to D0 measured by DXA scan (Dual-energy X-Ray Absorptiometry) (DXA scan sub-study, 80 patients). - Evolution of bone mineral density measured by DXA scans at W48 and W96 compared to D0 (DXA scan sub-study, 80 patients). - To assess HIV-RNA viral load and Cmin (Minimal Drug Concentration) of raltegravir and etravirine at W48 in human male genital compartment (semen sub-study, 20 patients). - Evolution of the inflammation markers (IL-6hs, sCD14, sCD163, D-Dimers, IP-10, IgG, CRPus and insulin on frozen plasma aliquots from D0 to W48, and W96. - Evaluation of health-related quality of life with a self-assessment questionnaire at D0, W48, W96 and of the compliance with a self-assessment questionnaire at W-6/W-4, W48, W96. - • *Evaluation of the evolution of the cardio-vascular disease-related markers in women according to their ovarian reserve and their menopausal status* - Evolution of the ovarian reserve from D0 to W48 measured by AMH on frozen aliquots - Evolution of the level of MCP1/CCL2 from D0 to W48 on frozen samples - Evaluation of the metabolic/inflammatory profile according to sex at inclusion and its evolution up to week 48 - Evaluation of metabolic profile, inflammatory, innate immune activation markers in women according to their status regarding ovarian reserve and menopausal status at inclusion and its evolution up to week 48
Methodology	Multicenter non-comparative phase II trial evaluating the capacity of the dual combination raltegravir/etravirine to maintain virological success defined as the absence of 2 consecutive plasma viral loads (VL) > 50 copies/mL within 2 to 4 weeks in virologically suppressed HIV-1 infected patients, of at least 45 years of age, switching from a boosted PI-containing regimen.
Estimated enrolment	By including 160 individuals and considering the strategy to be acceptable if at least 152 individuals maintain virological success, we will have a 95 % probability to discard a combination for which efficacy is smaller than 90 % and we will select with a power of 80 % a strategy for which the efficacy is above or equal to 95 %.

Study endpoints

Primary endpoint Proportion of patients remaining, at week 48 on virological success defined as the absence of 2 consecutive HIV-RNA plasma VL > 50 copies/mL within 2 to 4 weeks interval.

Secondary endpoints

- *Biological efficacy*

- Percentage of patients remaining in therapeutic success up to week 48 and week 96 defined as the absence of virological failure and the absence of treatment interruption due to adverse event judged by DSMB as related to the trial treatment or procedure.
- Percentage of patients in virological success (plasma HIV-RNA ≤ 50 copies/mL) up to week 96.
- Percentage of patients with trial treatment interruption.
- Percentage of patients with plasma HIV-RNA VL between 51 and 200 copies/mL and percentage of patients with plasma HIVRNA VL > 200 copies/mL at time of virological failure.
- Median time of virological failure (time limit between the date of the trial treatment initiation and the date of virological failure).
- Percentage of patients with RAL and/or ETR resistance mutations in case of virological failure and percentage of patients with resistant viruses to all study drug's class in case of virological failure.
- Factors associated with the occurrence of plasma HIV-RNA VL> 50 copies/mL (genotype history, pre-cART VL, plasma drug concentration (etravirine, raltegravir) at the virological rebound, viral reservoir measured by HIV-DNA at D0 and adherence assessed with a self-questionnaire).
- Evolution of total cell-associated HIV-DNA from D0 to W48 and W96.
- Evolution of CD4+, CD8+ T cells counts and CD4/CD8 ratio at each time point from D0.

- *Tolerability and Metabolic Impact*

- Percentage of patients with at least one serious adverse event as judged by DSMB as related to the trial treatment or to the trial strategy.
- Percentage of patients with grade 3 or grade 4 clinical or biological adverse events.
- Evolution of metabolic parameters (fasting triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol and fasting glycemia).
- Evolution of the calibrated Framingham risk score and of the SCORE risk equation including HDL cholesterol (from the European Cardiovascular Society) from D0 to W48 and W96.
- Evolution of renal function measured using proteinuria and the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration Calculator) formula to estimate the Glomerular Filtration Rate (GFR) from D0 to W96.
- Evolution of limb lean, limb fat, visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), measured by DXA scan (Dual-energy X-Ray Absorptiometry), from D0 to W48 and W96 (DXA scan sub-study, 80 patients).
- Evolution of bone mineral density measured by DXA scans from D0, to W48 and W96 (DXA scan sub-study, 80 patients).
- HIV-RNA viral load and Cmin (Minimal Drug Concentration) of raltegravir and etravirine in seminal fluid at W48 (seminal sub-study, 20 patients).
- Evolution of the inflammation markers (IL-6hs, sCD14, sCD163, D-Dimers, IP-10, IgG, CRPus and insulin) on frozen plasma aliquots from D0 to W48, and W96.
- Evaluation of health-related quality of life with a self-assessment questionnaire from D0 to W48, and W96 and of the compliance with a self-assessment questionnaire at W-6/W-4, W48, and W96.

- *Evaluation of metabolic impact according to the ovarian reserve and menopausal status*
-

- Evolution of the AMH and MCP1/CCL2 levels on frozen samples between D0 and W48
- Comparison of metabolic (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, non-HDL-cholesterol and triglyceride/HDL-cholesterol), inflammatory and innate immune activation (IL-6hs, sCD14, sCD163, D-Dimers, IP-10, IgG, CRPus and insulin), fat distribution and bone markers measured by DEXA scan between men and women at D0 et comparison of their evolution at W48
- Comparaison of the metabolic/inflammatory profile in women according to their ovarian reserve and menopausal status at D0 and its evolution up to week 48

Eligibility criteria

Inclusion criteria

- Documented HIV-1 infection.
- Age ≥ 45 years.
- Naïve to integrase inhibitor and etravirine.
- At least 6 months of stable antiretroviral therapy (ART) including a boosted protease inhibitor, whatever the number of combined drugs.
- HIV-RNA plasma VL ≤ 50 copies/mL during the last 24 months prior to screening visit (W-6/W-4), documented by at least 4 time-points with no more than one blip in HIV-RNA plasma viral load between 51 and 200 copies/mL.
- HIV-RNA plasma VL ≤ 50 copies/mL at screening visit (W-6/W-4).
- A genotype is available (on amplified DNA at W-6/W-4 Visit and/or on RNA in the medical history of the patient) and shows a virus sensitive to ETR OR no genotype is available (amplification failure on DNA at W-6/W-4 Visit and no genotype in the medical history of the patient), there are no virological failure on NNRTI in the medical history.
- CD4+ lymphocytes > 200 cells/mm^3.
- Creatinine < 2.5 x ULN.
- CPK (Creatine Phospho Kinase) < 6 ULN.
- AST (Aspartate Aminotransferase), ALT (Alanine Aminotransferase) < 5 ULN.
- Hemoglobin > 10 g/dL.
- Platelets > 100 000/mm^3.
- Negative urinary pregnancy test and use of efficient contraception for women of childbearing potential.
- For French participants only: subject enrolled in or a beneficiary of a Social Security programme (State Medical Aid or AME is not a Social Security programme), article L1121-11 of the Public heatlh code...
- Patients with a coverage from a social health.
- Signed informed consent.

Non-inclusion criteria

- Previous exposure to raltegravir or etravirine.
- Presence of any documented integrase inhibitor mutation on DNA genotype at W-6/W-4 and/or on RNA in the medical history of the patient.
- Positive hepatitis B HBsAg or Positive HBc Ac and negative HBs Ac.
- HIV-2 infection.
- Active viral hepatitis C requiring a specific treatment during the 24 months of the trial.
- Patient with a history of non-compliance or irregular follow-up.
- Initiation of a concomitant anti-hypercholesterolemia (e.g. statins) or anti-diabetic treatment within the last 3 months prior the screening visit (W-6/W-4).
- Patient using: Clopidogrel (Plavix®), Prasugrel (Effient®), Ticagrelor (Brilinta®), Ticlopidine (Ticlid®), Flurbiprofen (Antadys® - Cebutid®), Rifampin (Rifampicin® - Rifadin® - RofactMC - Rifater®), Rifapentine (Priftin®), St John's wort, Carbamazepine (Tegretol®), Phenobarbital, Phenytoin (Dilantin®),Avanafil (Stendra™), Triazolam (Halcion®).
- Concomitant treatment using interferon, interleukins or any other immune-therapy or chemotherapy.
- Concomitant prophylactic or curative treatment for an opportunistic infection.

	- All conditions (use of alcohol, drugs, etc.) judged by the investigator to possibly interfere with trial protocol compliance, adherence and/or trial treatment tolerance. - Subjects under "sauvegarde de justice" (judicial protection due to temporarily and slightly diminished mental or physical faculties), or under legal guardianship. - Subjects participating in another clinical trial evaluating different therapies and including an exclusion period that is still in force during the screening phase. - Pregnant women or breastfeeding women.
Intervention	In patients who had signed informed consent and fulfilled all eligibility criteria at screening (W-6/W-4) will be prescribed a switch to the dual raltegravir (400 mg BID - *bis in die*-) plus etravirine (200 mg BID) regimen: - Raltegravir 400 mg tablets will be administered as one 400 mg oral tablet PO (*per os)* twice daily (800 mg per day), after a meal - Etravirine 200 mg tablets will be administered as one 200 mg oral tablet PO twice daily (400 mg per day) after a meal
Substudies (for French centres)	- DXA sub-study: 80 patients - Seminal sub-study: 20 patients (centres located in the region of Ile-de-France (neighbourhood of Paris))
Estimated trial duration	- Inclusion duration: 18 months - Maximum trial duration per patient: 24 months (4 weeks for screening, 96 weeks of trial treatment and 2 weeks post-treatment interruption for safety reasons) - Primary endpoint and analysis: 30 months after trial initiation End of the trial: 6 months after the last visit of the last patient - Trial duration: 3.5 to 4 years - Expected trial initiation: 1st trimester 2015
Sample size	- 160 patients

2 RESUME DE L'ESSAI

Version n° 3.0 du 19/01/2018

EudraCT N°: 2014-000828-24

Titre de l'essai	Essai pilote de phase II non comparatif évaluant la capacité de la combinaison raltégravir+étravirine à maintenir le succès virologique chez des patients infectés par le VIH-1, âgés d'au moins 45 ans, avec une charge virale plasmatique inférieure à 50 copies/mL sous un traitement antirétroviral comportant un inhibiteur de protéase boosté
Titre abrégé	ANRS 163 ETRAL
Promoteur	Institut National de la Santé et de la Recherche Médicale - Agence nationale de recherches sur le sida et les hépatites virales (Inserm-ANRS)
Investigateur coordonnateur	**Pr Christine Katlama** *Service des Maladies Infectieuses et Tropicales,* *Groupe Hospitalier Pitié-Salpêtrière, Paris, France*
Responsable scientifique	**Pr Jacques Reynes** *Département des Maladies Infectieuses et Tropicales,* *Hôpital Gui de Chauliac, CHU de Montpellier, France*
Pays participants	France, Espagne
Objectifs	**Objectif principal** Evaluer la capacité d'une bithérapie associant raltégravir/étravirine à maintenir le succès virologique jusqu'à S48 défini par l'absence de 2 charges virales (CV) plasmatiques consécutives >50 copies/mL mesurées dans un intervalle de 2 à 4 semaines maximum, chez des patients infectés par le VIH-1, âgés d'au moins 45 ans et actuellement sous traitement antirétroviral efficace comportant un inhibiteur de protéase boosté. **Objectifs secondaires** • *Efficacité biologique* - Evaluer la proportion de patients en succès thérapeutique jusqu'à S48 et S96. - Evaluer la proportion de patients en succès virologique (ARN-VIH≤50 copies/mL) jusqu'à S96. - Evaluer la proportion de patients ayant arrêté la stratégie thérapeutique. - Evaluer la proportion de patients en échec virologique de bas grade (ARN-VIH entre 51 et 200 copies/mL) et la proportion de patients en échec virologique de haut grade (ARN-VIH >200 copies/mL) au moment de l'échec virologique. - Délai de survenue de l'échec virologique. - Profil de résistance génotypique dans le plasma en cas d'échec virologique. - Identifier les facteurs associés au rebond virologique (ARN-VIH>50 copies/mL). - Evolution de l'ADN-VIH total dans les cellules de J0, à S48 et à S96. - Evolution des cellules lymphocytaire T CD4+ et T CD8+ et le rapport CD4/CD8 à tous les points de mesure par rapport à J0. • *Tolérance et impact métabolique* - Incidence des effets indésirables cliniques et biologiques. - Incidence des évènements indésirables cliniques ou biologiques de grade 3 ou 4. - Modification des paramètres métaboliques mesurés à jeun (triglycérides, cholestérol total, HDL-cholestérol, LDL- cholestérol et glycémie). - Evolution du score de risque de Framingham calibré et du score de risque de la Société européenne de cardiologie issu d'une équation incluant le HDL-cholestérol (de la Société européenne de cardiologie) de J0 à S48 et S96. - Evolution de la fonction rénale mesurée par la protéinurie et la formule CKD–EPI (Chronic Kidney Disease Epidemiology Collaboration

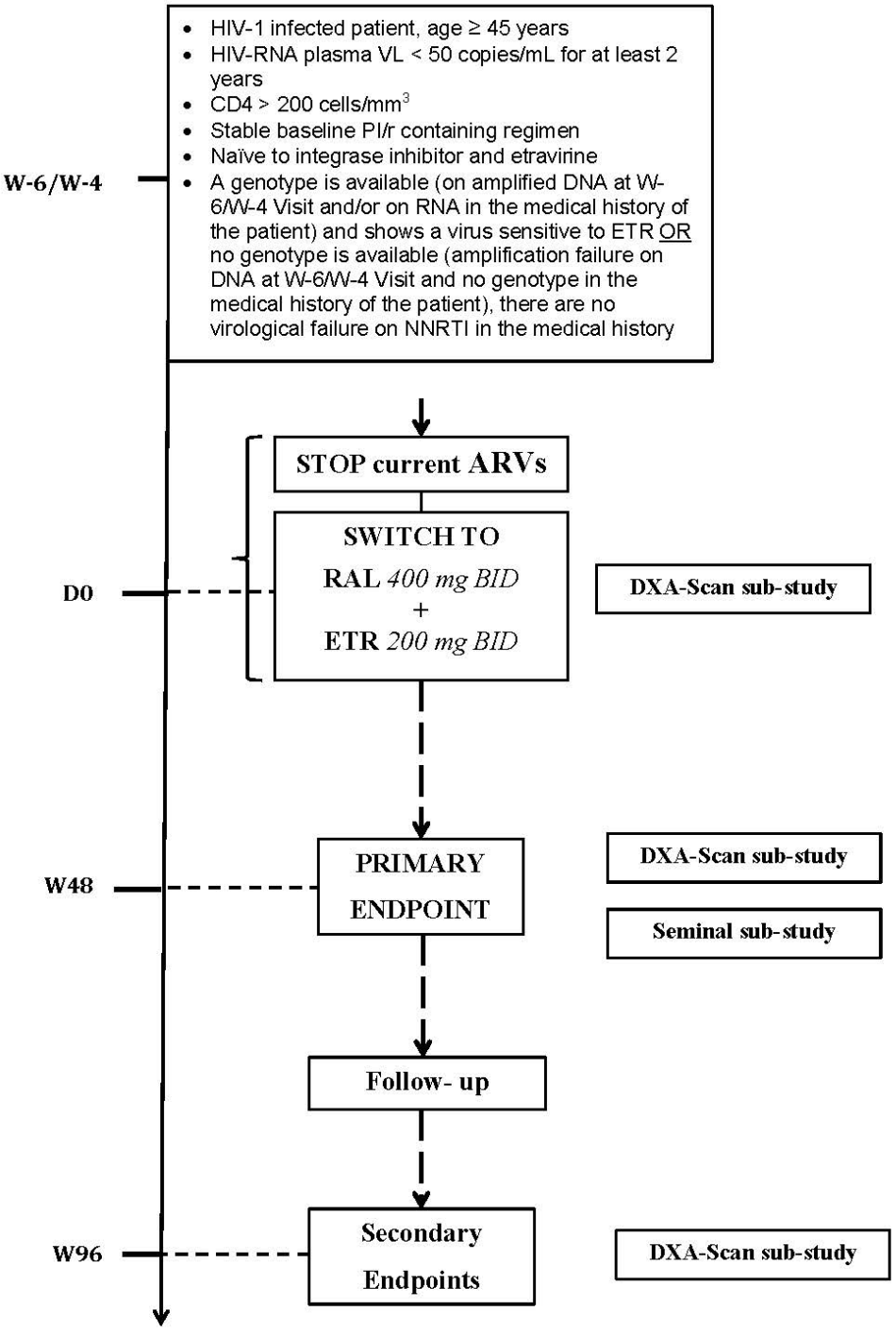
	Calculator) de J0 à S96. - Modification de la répartition du tissu adipeux des membres et du tronc, à S48 et S96 par rapport à J0 mesurée par DXA scan (sous-étude DXA scan, 80 patients). - Evolution de la densité minérale osseuse évaluée par DXA scan à S48 et S96 par rapport à J0 (sous-étude DXA scan, 80 patients). - Evaluation de la charge virale VIH et de la concentration minimale du et de l'étravirine au sein du compartiment génital masculin à S48 (sous-étude séminale, 20 patients). - Evaluation des marqueurs inflammatoires (IL-6hs, sCD14, sCD163, D-Dimère, IP-10, IgG, CRPus, insuline) mesurés sur plasma congelés de J0, à S48 et S96. - Évaluation de la qualité de vie par auto-questionnaires à J0, S48 et S96 et de l'observance par auto-questionnaires à S-6/S-4, S48 et S96. • *Evaluation de l'évolution des marqueurs de maladies cardio-vasculaires chez des femmes selon leur reserve ovarienne et leur status ménopausique* - Evolution de la réserve ovarienne de J0 à S48 par mesure de l'AMH (Hormone anti-mullërienne) sur des échantillons congelés. - Evolution du taux de MCP1/CCL2 de J0 à S48 sur échantillons congelés. - Evaluation des profils métabolique/inflammatoire selon le sexe à l'inclusion et jusqu'à S48. - Evaluation des profils métaboliques, des marqueurs inflammatoires et d'activation de l'immunité innée chez les femmes selon leur réserve ovarienne et le statis ménopausique à l'inclusion et jusqu'à S48
Méthodologie	Essai multicentrique, non comparatif, pilote de phase II, évaluant la capacité de l'association raltégravir et étravirine à maintenir le succès virologique, défini par l'absence de 2 charges virales (CV) plasmatiques consécutives > 50 copies/mL dans un intervalle de 2 à 4 semaines, chez des patients infectés par le VIH, âgés d'au moins 45 ans et recevant actuellement une thérapie antirétrovirale efficace comportant un inhibiteur de protéase boosté.
Nombre de sujets prévus	En incluant 160 sujets et en considérant la stratégie comme acceptable si on observe au moins 152 patients en succès virologique, on écartera avec une probabilité de 95% les stratégies d'efficacité inférieure à 90% et on sélectionnera avec une probabilité de 80% celles dont l'efficacité est supérieure ou égale à 95%.
Critères de jugement	**Critère principal** Proportion de patients en succès virologique jusqu'à S48 défini par l'absence de 2 CV ARN-VIH > 50 copies/mL mesurées dans un intervalle de 2 à 4 semaines maximum. **Les critères secondaires** • *Efficacité biologique* - Pourcentage de patients ayant maintenu le succès thérapeutique jusqu'à S48 et S96 défini par l'absence d'échec virologique (i.e. 2 CV consécutives >50 copies/mL mesurées dans un intervalle de 2 à 4 semaines maximum) et par l'absence d'arrêt du traitement de l'essai dû à la survenue d'un événement indésirable jugé par le comité indépendant de surveillance (CIS) comme lié au traitement ou à la stratégie de l'essai. - Pourcentage de patients en succès virologique (ARN-VIH ≤50 copies/mL) jusqu'à S96. - Pourcentage de patients ayant arrêté le traitement de l'essai. - Pourcentage de patients ayant une charge virale ARN-VIH entre 51 et 200 copies/mL et le pourcentage de patients ayant une charge virale ARN VIH >200 copies / mL au moment de l'échec virologique. - Délai médian entre la date de l'initiation du traitement de l'essai et la perte du succès virologique. - Pourcentage de patients avec des virus présentant des mutations de résistance au traitement de l'essai en cas d'échec virologique et pourcentage de patients avec des virus résistants à toutes les molécules de

	la classe thérapeutique en cas d'échec virologique. - Recherche de facteurs associés à la survenue d'une charge virale >50 copies/mL (historique des génotypes, charge virale pré-thérapeutique concentration plasmatique des médicaments de l'essai (étravirine, raltégravir) mesurée au rebond virologique, le réservoir viral mesuré par l'ADN-VIH à D0 et l'observance mesurée par auto-questionnaire). - Evolution de l'ADN-VIH total dans les cellules de J0, à S48 et à S96. - Evolution des cellules lymphocytaire T CD4+ et T CD8+ et le rapport CD4/CD8 à tous les points de mesure par rapport à J0. • *Tolérance et impact métabolique* - Pourcentage de patients présentant au moins un événement indésirable grave jugé par le CIS comme liés au traitement ou à la stratégie de l'essai. - Pourcentage de patients ayant eu des événements indésirables cliniques ou biologiques de grade 3 ou 4. - Evolution des paramètres métaboliques mesurés à jeun (triglycérides, cholestérol total, HDL-cholestérol, LDL-cholestérol et glycémie). - Evolution du score de risque de Framingham calibré et du score de risque de la Société européenne de cardiologie issue d'une équation incluant le HDL-cholestérol de J0 à S48 et S96. - Evolution de la fonction rénale mesurée par la protéinurie et la formule CKD–EPI (Chronic Kidney Disease Epidemiology Collaboration Calculator) de J0 à S96. - Evolution de la masse maigre et de la masse grasse dans les membres et du tissu adipeux sous-cutané et péri-viscéral au tronc, mesurés par DXA Scan de J0 à S48 et S96 (sous-étude DXA scan réalisée sur 80 patients). - Evolution de la densité minérale osseuse mesurée par DXA scan de J0, S48 et S96 (sous-étude DXA scan réalisée sur 80 patients). - Charge virale VIH et concentration minimale du raltégravir et l'étravirine dans le sperme à S48 (sous-étude séminale réalisée sur 20 patients). - Evolution des marqueurs inflammatoire (IL-6hs, sCD14, sCD163, D-Dimère, IP-10, IgG, CRPus, insuline) mesurés sur du plasma congelé de J0, S48 et S96. - Evolution de la qualité de vie à J0, S48, S96 et de l'observance par auto-questionnaires à S-6/S-4, S48 et S96. • *Evaluation de l'impact métabolique selon la réserve ovarienne et le status ménopausique* - Evolution des taux d'AMH (hormone anti-mullërienne) et de MCP1/CCL2 sur échantillons congelés entre J0 et S48 - Comparaison des profils métaboliques (cholesterol total, LDL-cholestérol, HDL-cholestérol, triglycérides, non-HDL cholestérol et triglycérides/HDL-cholestérol), des marqueurs d'activation inflammatoires et de l'immunité innée (IL-6hs, sCD14, sCD163, D-Dimers, IP-10, IgG, CRPus et insuline), de la distribution des graisses et des marqueurs osseux mesurés par DEXA entre les hommes et les femmes à J0 et comparaison de leur évolution jusqu'à S48. - Evaluation des profils métaboliques/inflammatoires chez les femmes et leur évolution jusqu'à S48 selon leur réserve ovarienne et leur status ménopausique
Critères d'éligibilité	**Critères d'inclusion** - Infection par le VIH-1. - Age ≥ 45 ans. - Naïf d'inhibiteur d'intégrase et d'étravirine. - Au moins 6 mois de traitement antirétroviral stable (ARV) incluant un inhibiteur de protéase boosté, quel que soit le nombre d'ARVs combinés. - ARN-VIH ≤ 50 copies/mL au cours des 24 derniers mois précédant la visite de screening (S-6/S-4), documenté par au moins 4 mesures avec autorisation d'un seul blip entre 51 et 200 copies/mL. - ARN-VIH ≤ 50 copies/mL à la visite de pré-inclusion (S-6/S-4). - Un génotype est disponible (sur ADN amplifié à S-6/S-4, et/ou sur ARN

	dans l'historique du patient), montrant un virus pleinement sensible à l'étravirine OU en l'absence de génotype disponible (échec d'amplification sur ADN à S-6/S-4 et pas de génotype sur ARN dans l'historique du patient), il n'y a pas d'antécédent d'échec aux INNTI.Lymphocytes T CD4 + > 200 cellules/mm^3. - Créatinine < 2,5 x limites supérieures normales (LSN). - CPK (créatine-phosphokinase) < 6 (LSN). - ASAT, ALAT < 5 x LSN. - Hémoglobine > 10 g/dL. - Plaquettes >100 000 /mm^3. - Test de grossesse urinaire négatif pour les femmes en âge de procréer et utilisation d'une méthode de contraception efficace. - Pour les participants français uniquement : personne affiliée ou bénéficiaire d'un régime de sécurité sociale (article L1121-11 du Code de la Santé Publique) (l'Aide Médicale d'Etat ou AME n'est pas un régime de sécurité sociale). - Patient affilié à un régime d'assurance- santé. - Signature d'un consentement libre et éclairé. **Critères de non-inclusion** - Patient ayant déjà reçu du raltégravir ou de l'étravirine. - Présence de mutations de résistance aux inhibiteurs d'intégrase documentée par la séquence génotypique extraite de l'ADN à W-6/W-4 et/ou sur l'ARN dans l'histoire médicale du patient - Antigène HBs positif ou présence de l'anticorps anti-HBc positif et anticorps HBs négatif - Infection par le VIH-2. - Hépatite virale C active nécessitant un traitement spécifique au cours des 24 mois de l'essai. - Patient ayant des antécédents d'inobservance ou de suivi irrégulier. - Initiation d'un traitement anti-hypercholestérolémie (par exemple : statines) ou d'un traitement anti- diabétique dans les 3 mois précédant la visite de pré-inclusion (S-6/S-4). - Patient traité par clopidogrel (Plavix®),prasugrel (Effient®), Ticagrelor (Brilique®), Ticlopidine (Ticlid®), Flurbiprofène (Antadys® - Cebutid®), Rifampine (Rifampicine® - Rifadin® - RofactMC - Rifater®), Rifapentine (Priftin®), Millepertuis, Carbamazepine (Tegretol®), Phénobarbital, Phénytoïne (Dilantin®), Avanafil (Stendra™), Triazolam (Halcion®). - Patient traité par interféron, interleukines ou toute autre immuno-thérapie ou chimiothérapie. - Traitement concomitant prophylactique ou curatif d'une infection opportuniste. - Toutes conditions (consommation d'alcool, de drogues, etc) jugées par l'investigateur comme pouvant interférer avec le respect du protocole de l'essai, l'observance et/ou la tolérance du traitement de l'essai. - Personnes placées sous sauvegarde de justice, sous tutelle ou curatelle. - Personnes participants à une autre recherche évaluant d'autres traitements en investigation comprenant une période d'exclusion toujours en cours à la pré-inclusion. - Femmes enceintes ou allaitantes.
Intervention	Chez les patients ayant signé un consentement éclairé et remplissant tous les critères d'éligibilité au moment de la pré-inclusion (S-6/S-4) sera prescrit une bithérapie associant le raltégravir (400 mg) et l'étravirine (200 mg): - Le raltégravir en comprimés de 400 mg sera administré par voie orale deux fois par jour (soit 800 mg par jour) après un repas - L'étravirine en comprimés de 200 mg sera administré par voie orale deux fois par jour (soit 400 mg par jour) après un repas
Sous-études (pour les centres français)	- Sous-étude DXA: 80 patients - Sous-étude séminale: 20 patients (seulement centres d'Ile de France)
Calendrier/	- Durée d'inclusion: 18 mois

Echéancier prévisionnel	- Durée de participation maximale par patient:	24 mois (4 semaines de screening, 96 semaines de traitement de l'essai et 2 semaines après la fin de traitement pour des raisons de sécurité)
	- Critère d'évaluation et analyse primaire:	30 mois après le début de l'essai
	- Fin de l'essai:	6 mois après la dernière visite du dernier patient
	- Durée de l'essai:	3.5 à 4 ans
	- Date de début de l'essai prévisionnelle:	1er trimester 2015
Nombre de sujets	- 160 participants	

3 STUDY DESIGN



4 SCHEDULE OF ASSESSMENTS

	W-6/W-4	D0	W2	W4	W12	W24	W36	W48	W64	W80	W96	EOT
Informed Consent Signature	X											
Review eligibility criteria	X	X										
Collection of adverse events		X	X	X	X	X	X	X	X	X	X	X
Quality of life, felt symptoms		X						X			X	X
Adherence evaluation	X							X			X	X
Clinical exam *(blood pressure, heart rate, body temperature, weight and targeted physical examination)*	X[1]	X[2,3,4]	X	X	X	X	X	X[2,3,4]	X	X	X[2, 3, 4]	X[2]
HBV/HCV serology	X											
Urinary pregnancy test If positive: β HCG[5]	X	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]
HIV-RNA plasma Viral Load[7]	X	X		X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]
CD4/CD8 Lymphocytes	X	X			X	X		X		X	X	X
Whole blood cells count	X					X		X		X	X	X
Creatinine, AST, ALT, CPK, bilirubin, urine analysis[9]	X			X	X	X		X		X	X	X
Lipid profile[10], fasting glycemia		X			X	X		X			X	X
Genotypic resistance on blood DNA	X											
DXA-Scan sub-study[11]		X						X			X	
Seminal sub-study[12]								X				
Study drug prescription		X		X	X	X	X	X	X	X		
Sample bank[13]												
Plasma bank: *minimal plasma ARV concentration, virological analysis*		X	X	X	X	X	X	X	X	X	X	X
Whole blood bank: Total cell-associated HIV-DNA		X						X			X	X
Plasma and serum bank: Immunologic analysis of inflammation markers[14]		X						X			X	X

[1] Electrocardiogram (ECG)
[2] Anthropometric measurements (abdominal and waist circumference)
[3] Cardiovasculor risk factors: arterial hypertension, tobacco, alcohol abuse, physical activity, diabetes
[4] Measurement of the systolic blood pressure at D0 W48 W96 according to the recommendations (Pickering et al. Circulation 2005, in Appendix A7)
[5] Only for women of childbearing potential
[6] Only in case of suspicion
[7] Plasma viral loads using a routine technique with a positivity threshold of maximum 50 copies/mL
[8] If HIV-RNA plasma viral loads > 50 copies/mL an additional blood collection have to be performed, within an interval of two to four weeks, to confirm the virological rebound. If the virological failure is confirmed, a resistance genotype and a dosage of ARV drugs concentration in plasma will be performed on the second HIV-RNA plasma VL test. A plasma bank should also be done
[9] Urine analysis: proteinuria, albuminuria, creatininuria, glycosuria
[10] Lipid profile: fasting triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol
[11] DXA-scan sub-study: evolution of the Bone Mineral Density (BMD) and of the body fat distribution in 80 patients
[12] Seminal sub-study in 20 patients. The HIV-RNA viral load and the RAL/ETR Cmin will be measured
[13] Refer to paragraph 12
[14] Immunological analysis of inflammation markers might be performed on frozen plasma aliquots. Markers of interest are: IL-6hs, sCD14, sCD163, D-Dimers, IP-10, IgG, CRPus and insulin

5 BACKGROUND / RATIONALE

5.1 Background

The objective of antiretroviral therapy (ART) is the maintenance of HIV viral suppression, the optimal condition to prevent disease progression, to optimize immune restoration, to prevent the development of viral resistance and to reduce viral transmission [1]. Antiretroviral therapy has to be maintained long life over decades in the absence of strategies for HIV cure. This is why the long-term cumulative toxicity of ARV drugs is a major issue. Indeed as a consequence of potent ART strategies, in 2011 over 88% of patients on ART in the French Hospital database (ANRS CO4 FHDH) (Prise en charge médicale des personnes vivant avec le VIH, Recommandations du groupe d'experts, Rapport 2013, sous la direction du Pr Philippe Morlat et sous l'égide du CNS et de l'ANRS. La documentation française, 2013) have achieved viral suppression with HIV-RNA plasma viral load < 50 copies/mL and nearly 60% have CD4 > 500/mm^3. As a consequence of massive reduction of mortality and morbidity related to HIV, infected patients are aging with 40% of patients over 50 years of age in the ANRS CO4 FHDH.

The current standard-of-care for antiretroviral therapy consists in a triple drug combination (ART) with 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus either a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), or an integrase inhibitor. NRTIs and PIs have been associated to cumulative long-term toxicity such as bone and renal disorders related to tenofovir and increased cardio-vascular risk with PIs [2-3]. In general population, aging is associated with well-known comorbidities such as bone demineralization, increased incidence of cardio or cerebrovascular disease, diabetes, renal dysfunction. HIV infected patients are at a greater risk for such abnormalities. Alternative strategies are needed, which must address the following questions: how to maintain the control of HIV viral replication while minimizing the occurrence of long-term clinical and metabolic complications.

5.2 Potential long-term complications of current antiretroviral treatments

5.2.1 Cardiovascular risk

The recent years have highlighted the cumulative toxicities of long-term exposure to antiretroviral drugs.

Cardiovascular disease is one of the most common comorbidities in the aging HIV-infected population [4-5]. Coronary artery disease (CAD) results from a combination of increasing age, traditional risk factor such as smoking, toxicity from long-term ART [6], and potentially related to HIV immune activation.

The French Hospital Database on HIV (ANRS CO4 FHDH) included over 80 000 patients followed over several years and measured the incidence of non-HIV related events. As early as 2003, ANRS CO4 FHDH showed that the risk of myocardial infarction (MI) was higher in HIV-infected patients exposed to PI than in the general population and dependent of cumulative exposure [7]. More recently ANRS CO4 FHDH showed that cumulative exposure to PI was associated with an increased risk of MI, and that the link to abacavir could not be considered causal [8]. We also showed a higher risk of MI in HIV infected patients than in the general population and the influence of both HIV replication and immunological status (CD4 nadir, current CD8 count) on the risk of MI, independently of traditional risk factors and exposure to antiretroviral drugs [9]. Exposure to PI was associated with a higher risk of MI [relative hazard (RH), 2.56; 95% confidence interval (CI), 1.03–6.34]. The expected incidence in the French general male population was 10.8/10 000 PY (Person-Year). The standardized morbidity ratios relative to the French general male population was 0.8 (95% CI, 0.5–1.3) for men exposed to PI for < 18 months, 1.5 (95% CI, 0.8–2.5) for men exposed for 18–29 months and 2.9 (95% CI, 1.5–5.0) for men exposed for > 30 months [8, 10].

Most of boosted PIs and the NNRTI efavirenz are associated to an increase in triglycerides and total cholesterol plasma levels [11]. In the ANRS CO8 APROCO COPILOTE cohort about 30% of patients developed hypertriglyceridemia. Prevalence of lipodystrophy and metabolic alterations and these alterations appear as early as 12 months after the initiation of PI therapy [12].

5.2.2 Bone toxicity

The prevalence of osteopenia and osteoporosis in HIV-infected individuals is higher in HIV-infected compared with HIV-negative individuals ranging, from 23 to 65% for osteopenia and from 3 to 22% for osteoporosis according to the studies [13-16] with, as consequence, a higher prevalence of patients with fracture ($p < 0.0001$) [17].

Several antiretroviral drugs have been shown to increase risk of bone demineralization [18-19]. Current exposure to tenofovir is associated with a higher risk of osteopenia and osteoporosis (OR(Odd Ratio)=1.59, p=0.0343 and

OR=2.20, p =0.0541, respectively) and a higher risk of low BMD (β= -33.35; p=0.0211). Tenofovir-containing antiretroviral regimens induce larger decrease in spine and hip bone mineral density when compared with abacavir-containing regimens [20]. Tenofovir induces renal phosphate and calcium losses leading to compensatory resorption of bone (osteoporosis) and mineralization defects in regenerating bone (osteomalacia) [21]. Long exposure to protease inhibitors has been associated with a higher risk of osteopenia, with borderline statistical significance (OR=1.05 per year of exposure, p=0.0560). HIV-infected patients have a lower bone mineral density (BMD) than the general population of the same age [13, 17, 22] and several studies have shown that there is an increased risk of fractures in HIV-infected individuals compared to the general population of same sex and age [17, 22-26]. The lowest BMD is mainly associated with a lower body mass index (BMI) [22-25] while HIV itself and its consequences may also contribute to the increased prevalence of osteopenia, osteoporosis and fracture in the HIV-infected population [13, 17, 24-28]. Data from randomized clinical trials have shown that BMD decreases when initiating antiretroviral treatment and this decrease is greater with some treatments [29-32]. Indeed, BMD decrease is more important with tenofovir than with other nucleoside reverse transcriptase analogues [33], and with protease inhibitors [18, 20, 29, 32, 34]. Moreover, when stopping antiretroviral treatment the BMD increases [35]. In addition, HIV-negative men participating in a trial examining the effects of tenofovir for pre-exposure prophylaxis experienced a small but significant decrease in BMD when taking the medication [36]. In a recent study, cumulative exposure to tenofovir and to boosted PIs was shown increasing the risk of fracture in hip, spine and wrist [37]. However, another study did not support these findings, but it first offer was belonging to a pharmaceuticals company [38].

5.2.3 Renal toxicity

Tenofovir is currently the most widely used antiretroviral drug. Globally, clinical trials have suggested that renal toxicity related to tenofovir is low (approximately 1%) in selected populations from clinical studies. However, observational cohort studies have suggested that this risk was higher with rates varying from approximately 2% [39-43].

In a systematic review and meta-analysis whereas over time with longer exposure to antiretroviral drugs [3] the overall relative risk of renal disease was 3.87 (95% CI: 2.85-6.85) in HIV-infected patients compared to HIV-uninfected in ART treated patients. 0.54 (95% CI: 0.29-0.99) compared to naïve patients and 1.56 (95% CI: 0.83-2.93) in patients treated with tenofovir compared to patients without tenofovir.

In the DAD study not only tenofovir but also abacavir, lopinavir and atazanavir were associated to high risk [44].

The use of strategies that could minimize renal toxicity has to be investigated particularly in senior HIV infected population.

5.3 An aging HIV-population at risk of cumulating drug toxicity and co-morbidities

Increased risk for drug-drug interactions: a cause of concern in the elderly.

Aging increases polypharmacy prescriptions for treatment and prevention of comorbidities such as cardio-vascular disease, hypertension or diabetes. One major issue is the risk for drug-drug interactions in elderly ART treated HIV infected patients due to the common CYP450 cytochrome pathway, shared by ARV drug and drug for comorbidities.

Calcium channel blockers (CCBs) are metabolized via CYP3A4; as a result, all boosted protease inhibitors may increase CCB serum concentrations and can potentially prolong the PR interval and augment hypotensive effect [45]. Diltiazem is massively increased with unboosted PI such as atazanavir resulting in PR prolongation and first-degree atrioventricular block and has to be reduced. On the contrary, efavirenz, etravirine and nevirapine have the potential to decrease CCB serum concentrations and dose adjustment of CCB at steady state may be needed [45]. Digoxin concentration is increased by 86% with ritonavir co-administration) [46].

Furthermore many antiarrhythmic medications are CYP450 3A4 substrates. Use of amiodarone, bepridil, flecainide, propafenone and quinidine is contraindicated with ritonavir boosted protease inhibitors (PI/r) due to the potential risk of exacerbating cardiac arrhythmias [45]. The use of disopyramide, dofetilide, lidocaine, mexiletine and procainamide with PI/r should be approached with caution due to the potential risk of significantly increasing antiarrhythmic serum concentrations [45].

Significant drug-drug interactions between warfarin, protease inhibitors and NNRTIs may further increase the risk of significant haemorrhage. Induction properties of nevirapine and lopinavir/ritonavir at steady state resulting in increased warfarin requirements have been reported [47].

Significant drug-drug interactions between antiretrovirals and anti-hyperlipidemic agents have been reported in different publications [48-49]. PI/r can significantly increase simvastatin and lovastatin concentrations. Co-

administrations of these 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors are not recommended due to the potential for rhabdomyolysis.

Monitoring concentration of these drugs is not easy in routine practice. Given these drug-drug interactions with potential severe clinical consequences, it is key to investigate alternative ART strategies with different metabolization pathways, such as raltegravir.

5.4 Raltegravir and etravirine: benefits and advantages in terms of toxicity

5.4.1 Raltegravir (RAL)

Raltegravir (RAL, Isentress® MK-0518), was the first approved integrase inhibitor in 2008 in treatment naïve and experienced HIV infected individuals.

– In the STARTMRK study, the proportion of treatment-naive patients who achieved virological suppression in the raltegravir arm was 86.1% at 48 weeks, non-inferior to a TDF (Tenofovir) /FTC (Emtricitabine)/EFV (Efavirenz). Importantly this efficacy rate was maintained over 5 years with a trend towards superiority over efavirenz mainly due to a better tolerability on long term [50]. More recently, raltegravir was compared to dolutegravir, a new integrase inhibitor currently in development, in treatment naïve patients in the SPRING 2 study which displays one of the highest efficacy rate with 85% and 88% of viral suppression (< 50 copies/mL at W48), respectively [51].

- Raltegravir is characterized by an excellent tolerability profile.

In all randomized clinical trials, the safety and the tolerability of raltegravir were excellent and the rate of side effects has been low [52]. The most common adverse events reported were: headache, other nervous system effects and gastrointestinal events and the majority were mild and transient in nature.

The most important superiority in terms of long-term tolerability is the metabolic profile of raltegravir. Raltegravir is a drug with an excellent metabolic profile [53-54]. In patients initiating ART with raltegravir in the STARTMRK trial, there were no significant changes from baseline in fasting total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglyceride levels. There was a trend toward a greater decrease from baseline in the total cholesterol:HDL-cholesterol ratio for raltegravir (−0.20) than efavirenz (+0.04) recipients (p=0.06) in a previously treatment-naive population [55].

- Switch studies

The SPIRAL and SWITCHMRK [56-57] trials also demonstrated advantages in terms of toxicity and tolerance after raltegravir initiation. Switching to raltegravir was associated with significant decreases in plasma lipids and total-to-HDL cholesterol ratio relative to continuing lopinavir/r (median decrease of triglyceride, 41% to 43% reduction from baseline at 12 weeks) [57]. The SPIRAL-LIP sub-study examined changes in body composition in 86 treatment-experienced patients switching from protease inhibitors to raltegravir [58]. After 48 weeks, total and visceral abdominal fat tissue remained stable contrasting with an increase in those maintaining protease inhibitors. Bone mineral density (BMD) increased with raltegravir, but no significant change occurred in those remaining on protease inhibitors. Furthermore, switching from IP/r to raltegravir induced a significant change in several cardiovascular markers, an improved lipid profile and a significant decrease in several biomarkers like hsCRP (high-sensitivity C-Reactive Protein), osteoprotegerin, IL-6 (Interleukin-6), TNF-α (Tumor Necrosis Factor-α), insulin and D-dimers [59].

5.4.2 Etravirine (ETR)

- Etravirine (ETR, Intelence®,TMC125) is a second-generation NNRTI with activity against both wild-type HIV-1 and NNRTI-resistant virus [60]. Efficacy of ETR has been demonstrated in treatment-naive [61] and experienced patients [62-63]. Etravirine remains fully active on virus harbouring the single K103N mutation, one of the most prevalent mutations in patients who had failed with all NNRTI generations.

- In the double blind, placebo-controlled SENSE trial, 157 treatment-naive patients were randomized 1:1 to 400 mg of etravirine once daily (n=79) or 600 mg of efavirenz once daily (n=78) plus two nucleoside analogues (either abacavir/lamivudine, zidovudine/lamivudine or tenofovir/emtricitabine) for 48 weeks. In the efavirenz arm, there was larger increase in high-density lipoprotein (HDL) (p=0.004), low-density lipoprotein (LDL) (p=0.005),

total cholesterol (p<0.0001) and triglycerides (p=0.03) compared with the etravirine arm. Also, there were fewer grade 3/4 elevations in total cholesterol, LDL and triglycerides in the etravirine versus the efavirenz arm [64].

5.5 Raltegravir and etravirine dual combination as switch alternative in virologically supressed HIV-infected patients

5.5.1 Viral efficacy

- A pilot observational study in 18 patients with suppressed HIV-RNA plasma viral load (VL<200 copies/mL), switching from a standard regimen to a raltegravir/etravirine combination has shown an intent-to-treat efficacy rate of 94.4% (n=17/18, 95% CI 74.2, 99%) at 6 months and 83.3% (n=15/18, 95% CI 60.7, 94.1%) at 12 months [65]. In per-protocol analysis, the efficacy at 12 months was 100% (n=15/15, 95% CI 80.6, 100%). No tolerability-related treatment discontinuation was recorded. In 15 patients, the lipid profile was available before and after switch which showed a median decrease in cholesterol of -0.2 mmol/L (IQR (:Inter-Quartile Range)-0.86, -0.05) and of -0.4 mmol/L (IQR -0.9, 0.2) in triglyceride levels [65].

- We then evaluated in an observational study 91 patients with plasma VL < 50 copies/mL who had been switched from an NRTI, PI or NNRTI-based regimen to a dual raltegravir/etravirine therapy.

Among the 91 patients included, 65 have already completed 6 months of follow-up and 48 have completed 12 months of follow-up. At 6 and 12 months respectively, 89.2% (54/55) and 92.3% (36/39) patients under RAL/ETR had an HIV-RNA plasma VL <50 copies/mL. Five cases of virological failure, defined as 2 consecutive plasma VLs > 50 copies/mL, occurred after a median (IQR) treatment duration of 7 months (IQR, 6-16).

All 5 patients had been previously exposed to NNRTIs and 4/5 patients had previously replicated under an NNRTI containing regimen. Two of these 4 patients showed pre-existing mutations conferring resistance to ETR at the time of raltegravir/etravirine initiation (K103N and Y181C in both cases).

These data underlines the need of ensuring the absence of mutations impacting ETR prior to switch, as RAL functional mono-therapy is hazardous in terms of virological suppression and resistance.

In conclusion, clinical experience concerning the virological safety and tolerability to raltegravir/etravirine combination is encouraging and emphasises the need for further investigation in a clinical trial.

5.5.2 Pharmacologic interactions between raltegravir and etravirine

- Interactions involving both raltegravir and etravirine are well documented. Raltegravir is metabolised through glucuronidation by UDP (Uridine Diphosphate)-glucuronosyltransferase 1A1 (UGT1A1) and has a low potential for drug-drug interactions and does not interfere with the hepatic cytochrome P450-3A4 such as most of the NNRTIs and PIs. Raltegravir is known to interact with atazanavir, an inhibitor of UGT1A1, increasing the plasma concentrations of raltegravir by 40%.

- Etravirine is a substrate of CYP2C19, CYP2C9 and CYP3A4. It moderately inhibits CYP2C19 and CYP2C9 and strongly induces CYP3A4. Etravirine specific interactions are listed in paragraph 10.3.

There is minimal interaction to be expected between etravirine and raltegravir. Etravirine, an inducer of UGT1A1, reduced raltegravir C12 by 34% and AUC (Area Under the Curve) by 10% when given concomitantly in healthy volunteers considered as not clinically relevant [66]. No dose modification is recommended in light of these findings. A retrospective study performed on a pharmacological database between 2011-2012, including 867 patients (of whom 166 were under a RAL/ETR therapy) with 1208 RAL C12h samples collected, found no significant PK interaction between RAL and ETR [67].

- In the ANRS 163 ETRAL trial a sample bank will be constituted in order to monitor raltegravir and etravirine plasma concentrations. At specific points these concentrations will be analysed in correlation with trial end-points.

5.6 Trial hypothesis

Given the potency of raltegravir and etravirine, and although our limited clinical experience, we bring the hypothesis that a dual RAL/ETR regimen will be able to maintain the viral suppression if the two drugs are fully sensitive namely in patients naïve to both raltegravir and etravirine without any mutation that might impair drug's efficacy.

The second hypothesis is that, in a patient population with long-term ART, of at least 45 years of age, the switch to dual raltegravir/etravirine therapy should limit the long-term toxicity induced by NRTI and PI drugs, in particular cardiovascular, bone and renal diseases, without derogating from the key principle of sustained virological control.

ANRS 163 ETRAL trial should assess:

- The virological safety of raltegravir/etravirine association.
- The impact of the discontinuation of NRTIs, PIs on the distribution of adipose tissue, bone mineral density, metabolic parameters and seminal HIV-RNA viral load.

6 OBJECTIVES

6.1 Principal objective

To evaluate over 48 weeks of treatment the capacity to maintain virological success defined as the absence of 2 consecutive plasma viral loads (VL) > 50 copies/mL within 2 to 4 weeks of a dual raltegravir/etravirine regimen in HIV-1 infected patients, of at least 45 years of age, with suppressed plasma viremia switching from a boosted PI-containing regimen.

6.2 Secondary Objectives

6.2.1 Biological efficacy

- To assess the proportion of patients in therapeutic success up to week 48 and week 96
- To assess the proportion of patients with virological success (plasma HIV-RNA ≤ 50 copies/mL) up to week 96
- To assess the proportion of patients with an interruption of therapeutic strategy
- To assess the proportion of patients with low grade virological failure (HIV-RNA plasma VL between 51 and 200 copies/mL) and the proportion of patients with high grade of virological failure defined as HIV-RNA >200 copies/mL at time of virological failure
- Time limit to virological failure
- HIV genotypic resistance profile, in plasma, in case of virological failure
- To determine the factors associated with virological rebound (plasma HIV-RNA > 50 copies/mL)
- Evolution of total cell-associated HIV-DNA from D0 to W48 and W96
- Evolution of CD4+, CD8+ T cells counts and CD4/CD8 ratio at each time point from D0

6.2.2 Tolerability and Metabolic Impact

- Incidence of clinical and biological adverse effects
- Incidence of clinical and biological adverse events (grade 3 or 4)
- Modification of metabolic parameters (fasting triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol and fasting glycemia)
- Evolution of the calibrated Framingham risk score and of the SCORE risk equation including HDL cholesterol (from the European Cardiovascular Society) from D0 to W48 and W96
- Evolution of renal function evaluated using proteinuria and the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration Calculator) formula to estimate the Glomerular Filtration Rate (GFR) from D0 to W96
- Modification of peripheral and central body fat distribution, at W48 and W96 compared to D0 measured by DXA scan (Dual-energy X-Ray Absorptiometry) (DXA scan sub-study, 80 patients)
- Evolution of bone mineral density measured by DXA scans at W48 and W96 compared to D0 (DXA sub-study, 80 patients)
- To assess HIV-RNA viral load and Cmin (Minimal Drug Concentration) of raltegravir and etravirine at W48 in human male genital compartment (Semen sub-study, 20 patients)
- Evolution of the inflammation markers (IL-6hs, sCD14, sCD163, D-Dimers, IP-10, IgG, CRPus and insulin on frozen plasma aliquots from D0 to W48, and W96

- Evaluation of health-related quality of life with a self-assessment questionnaire at D0, W48, W96 and of the compliance with a self-assessment questionnaire at W-6/W-4, W48, W96

6.2.3 Evaluation of the evolution of the cardio-vascular disease-related markers in women according to their ovarian reserve and their menopausal status

- Evolution of the ovarian reserve from D0 to W48 measured by AMH on frozen aliquots
- Evolution of the level of MCP1/CCL2 from D0 to W48 on frozen samples
- Evaluation of the metabolic/inflammatory profile according to sex at inclusion and its evolution up to week 48
- Evaluation of metabolic profile, inflammatory, innate immune activation markers in women according to their status regarding ovarian reserve and menopausal status at inclusion and its evolution up to week 48

7 EXPERIMENTAL DESIGN

7.1 Main study

ANRS 163 ETRAL is a multicentre non-comparative phase II trial evaluating, in fully suppressed HIV-1-infected patients, of at least 45 years of age, with a suppressed viremia, the capacity of a dual raltegravir/etravirine antiretroviral regimen to maintain the virological success defined as two consecutive HIV-RNA plasma viral loads > 50 copies/mL within 2 to 4 weeks. Eligible patients must be under a stable PI-containing ARV regimen for at least 6 months and they must be fully suppressed within the 24 months prior the screening visit (W-6/W-4), as confirmed by 4 documented viral loads (e.g. 2 measurements per year during the past 24 months and not more than 1 HIV-RNA plasma viral load between 51 and 200 copies/mL).

All PI-containing baseline ARV regimens are eligible except those containing raltegravir and/or etravirine.

At Day 0, patients eligible according all criteria detailed in paragraph 8 will be switched to the dual raltegravir (400 mg BID) plus etravirine (200 mg BID) regimen.

Any SAE considered by the investigator and/or the sponsor as potentially related to the trial treatments will be reviewed and evaluated by DSMB.

For all patients, during the 96 first weeks of the trial, a summary of the virological data including HIV-RNA viral loads and virus strains genotypes will be regularly submitted to the DSMB for review.

The immunologic analysis of the evolution of the inflammation markers will be performed on frozen plasma aliquots from whole blood samples collected at specific time points: D0, W48, and W96. The markers of interest are: IL-6hs, sCD14, sCD163, D-Dimers, IP-10, IgG, CRPus and insulin.

7.2 Sub-studies

7.2.1 DXA-scan

After signing a sub-study-specific informed consent form, 80 patients will be included in the DXA-scan sub-study assessing the evolution of bone mineral density (BMD) and of body fat distribution, and evaluating the potential impact of the dual raltegravir/etravirine regimen on these two parameters.

DXA-scans will be performed locally in all participating French sites at D0, W48 and W96 with a time limit up to 7 days before the date of D0 visit and with a time limit up to 10 days before and after the visit date of W48 and W96. The acquired images will be electronically transferred to a central review facility for final evaluation.

7.2.2 Seminal sub-study

This sub-study will be proposed to 20 male patients of the centres located in the region of Ile-de-France (neighbourhood of Paris) to evaluate at W48 the potential suppressive effect of the dual raltegravir/etravirine regimen on the HIV-RNA seminal viral load; and the minimal concentrations (Cmin) of RAL and ETR in the seminal fluid.

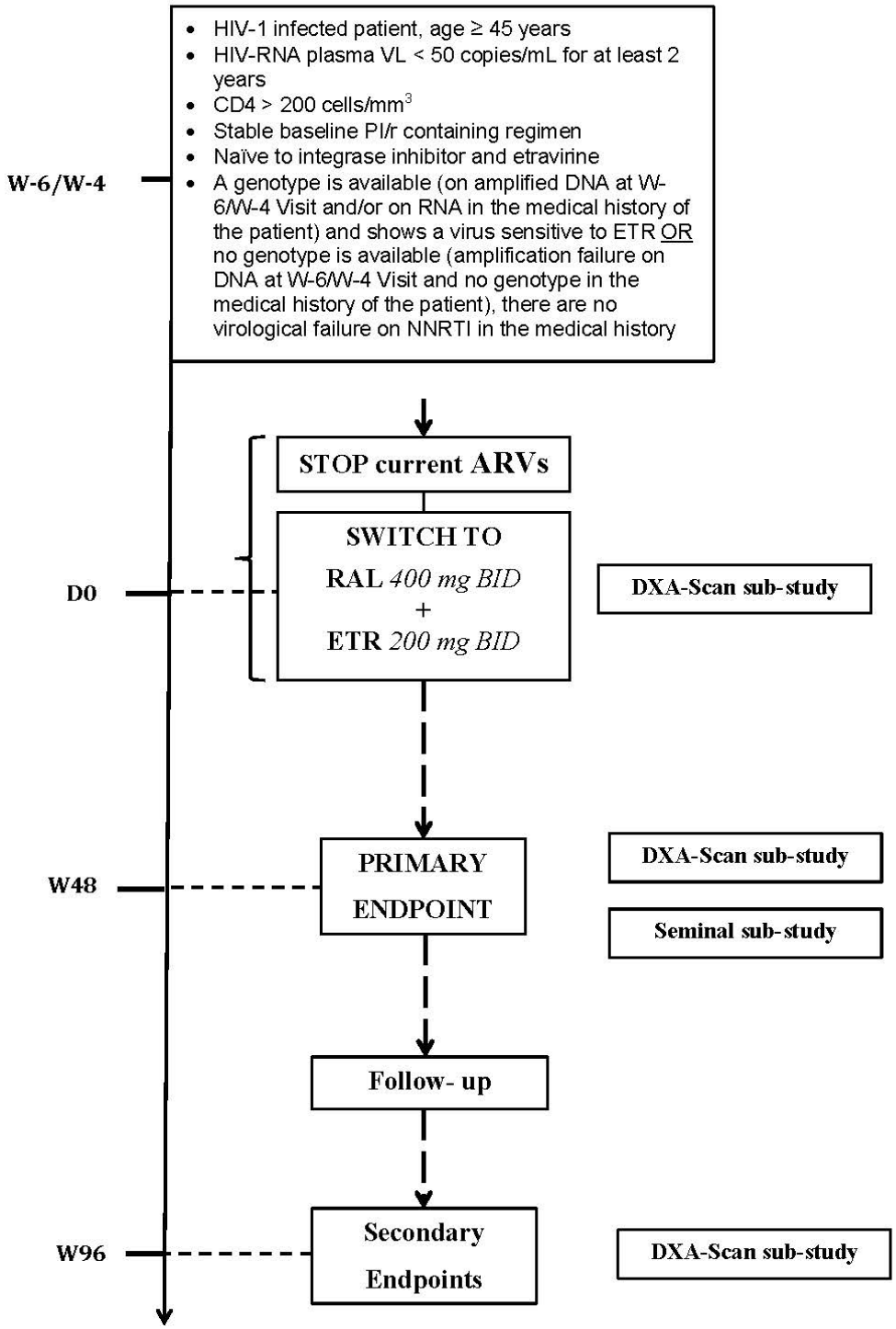
Total sperm samples will be collected at home the day of the patient visit using the dedicated container delivered by the investigator during the previous visit and then transferred to the participating site within the 6 hours following sample collection.

Collected samples will be directly carried by the participant to “Service des maladies infectieuses”, department of the Pitié-Salpêtriere site.

7.2.3 Women substudy

This study will include all women recruited in the ETRAL trial. It will use frozen samples already collected and stored at Tenon Hospital, department of Biochemistry and Hormonology, for additional essays of Anti-Müllerian Hormone and CCL2/MCP1. Il will also use information on menopausal status already collected in the database.

7.3 Study Design



7.4 Estimated Study duration

Inclusion duration:	18 months
Maximum trial duration per patient:	24 months (4 weeks for screening, 96 weeks of trial treatment and 2 weeks post-treatment interruption for safety reasons)
Primary endpoint and analysis:	30 months after trial initiation
End of the trial:	6 months after the last visit of the last patient
Trial duration:	3.5 to 4 years
Expected trial initiation:	1st trimester 2015

8 ELIGIBILITY CRITERIA

8.1 Inclusion criteria

- Documented HIV-1 infection
- Age ≥ 45 years
- Naïve to integrase inhibitor and etravirine
- At least 6 months of stable antiretroviral therapy (ART) including a boosted protease inhibitor, whatever the number of combined drugs
- HIV-RNA plasma VL ≤ 50 copies/mL during the last 24 months prior to screening visit (W-6/W-4), documented by at least 4 time-points with no more than one blip in HIV-RNA plasma viral load between 51 and 200 copies/mL
- HIV-RNA plasma VL ≤ 50 copies/mL at screening visit (W-6/W-4)
- A genotype is available (on amplified DNA at W-6/W-4 Visit and/or on RNA in the medical history of the patient) and shows a virus sensitive to ETR OR no genotype is available (amplification failure on DNA at W-6/W-4 Visit and no genotype in the medical history of the patient), there are no virological failure on NNRTI in the medical history
- CD4+ lymphocytes > 200 cells/mm3
- Creatinine < 2.5 x ULN
- CPK (Creatine Phospho Kinase) < 6 ULN
- AST (Aspartate Aminotransferase), ALT (Alanine Aminotransferase) < 5 ULN
- Hemoglobin > 10 g/dL
- Platelets > 100 000/mm3
- Negative urinary pregnancy test and use of efficient contraception for women of childbearing potential
- For French participants only : subject enrolled in or a beneficiary of a Social Security programme (State Medical Aid or AME is not a Social Security programme), article L1121-11 of the Public heatlh code.)
- Patients with a coverage from a social healthSigned informed consent

8.2 Non-inclusion criteria

- Previous exposure to raltegravir or etravirine
- Presence of any documented integrase inhibitor mutation on DNA genotype at W-6/W-4 and/or on RNA in the medical history of the patient.
- Positive hepatitis B HBsAg or Positive HBc Ac and negative HBs Ac
- HIV-2 infection
- Active viral hepatitis C requiring a specific treatment during the 24 months of the trial
- Patient with a history of non-compliance or irregular follow-up
- Initiation of a concomitant anti-hypercholesterolemia (e.g. statins) or anti-diabetic treatment within the last 3 months prior the screening visit (W-6/W-4)
- Patient using: clopidogrel (Plavix®), prasugrel (Effient®), Ticagrelor (Brilinta®), Ticlopidine (Ticlid®), Flurbiprofen (Antadys® - Cebutid®), Rifampin (Rifampicin® - Rifadin® - RofactMC - Rifater®), Rifapentine (Priftin®), St John's wort, Carbamazepine (Tegretol®), Phenobarbital, Phenytoin (Dilantin®), Avanafil (Stendra™), Triazolam (Halcion®).
- Concomitant treatment using interferon, interleukins or any other immune-therapy or chemotherapy
- Concomitant prophylactic or curative treatment for an opportunistic infection
- All conditions (use of alcohol, drugs, etc.) judged by the investigator to possibly interfere with trial protocol compliance, adherence and/or trial treatment tolerance
- Subjects under "sauvegarde de justice" (judicial protection due to temporarily and slightly diminished mental or physical faculties), or under legal guardianship

- Subjects participating in another clinical trial evaluating different therapies and including an exclusion period that is still in force during the screening phase
- Pregnant women or breastfeeding women

9 STUDY ENDPOINTS

9.1 Primary Endpoint

Proportion of patients remaining, at week 48, on virological success defined as the absence of 2 consecutive HIV-RNA plasma VL > 50 copies/mL within 2 to 4 weeks.

9.2 Secondary Endpoints

Biological efficacy

- Percentage of patients remaining in therapeutic success up to week 48 and week 96 defined as the absence of virological failure and the absence of treatment interruption due to adverse event judged by DSMB as related to the trial treatment or procedure
- Percentage of patients in virological success (plasma HIV-RNA ≤ 50 copies/mL) up to week 96
- Percentage of patients with trial treatment interruption
- Percentage of patients with plasma HIV-RNA VL between 51 and 200 copies/mL and percentage of patients with plasma HIVRNA VL > 200 copies/mL at time of virological failure
- Median time of virological failure (time limit between the date of the study treatment initiation and the date of virological failure)
- Percentage of patients with RAL and/or ETR resistance mutations in case of virological failure and percentage of patients with resistant viruses to all study drug's class in case of virological failure
- Factors associated with the occurrence of plasma HIV-RNA VL> 50 copies/mL (genotype history, pre-cART VL, plasma drug concentration (etravirine, raltegravir) at the virological rebound, viral reservoir measured by HIV-DNA at D0 and adherence assessed with a self-questionnaire)
- Evolution of total cell-associated HIV-DNA from D0 to W48 and W96
- Evolution of CD4+, CD8+ T cells counts and CD4/CD8 ratio at each time point from D0

Tolerability and Metabolic Impact

- Percentage of patients with at least one serious adverse event as judged by DSMB as related to the trial treatment or to the trial strategy
- Percentage of patients with grade 3 or grade 4 clinical and biological adverse events
- Evolution of metabolic parameters (fasting triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol and fasting glycemia)
- Evolution of the calibrated Framingham risk score and of the SCORE risk equation including HDL cholesterol (from the European Cardiovascular Society) from D0 to W48 and W96
- Evolution of renal function measured using proteinuria and the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration Calculator) formula to estimate the Glomerular Filtration Rate (GFR) from D0 to W96
- Evolution of limb lean, limb fat, visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT)., measured by DXA scan (Dual-energy X-Ray Absorptiometry), from D0 to W48 and W96 (DXA scan sub-study, 80 patients)
- Evolution of bone mineral density measured by DXA scans from D0, to W48 and W96 (DXA scan sub-study, 80 patients)
- HIV-RNA viral load and Cmin (Minimal Drug Concentration) of raltegravir and etravirine in seminal fluid at W48 (Seminal sub-study, 20 patients)
- Evolution of the inflammation markers (IL-6hs, sCD14, sCD163, D-Dimers, IP-10, IgG, CRPus and insulin) on frozen plasma aliquots from D0 to W48, and W96
- Evaluation of health-related quality of life with a self-assessment questionnaire from D0 to W48, and W96 and of the compliance with a self-assessment questionnaire at W-6/W-4, W48, and W96
-

Evaluation of metabolic impact according to the ovarian reserve and menopausal status

- between D0 and W48
- Comparison of metabolic (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, non-HDL-cholesterol and triglyceride/HDL-cholesterol), inflammatory and innate immune activation (IL-6hs,

sCD14, sCD163, D-Dimers, IP-10, IgG, CRPus and insulin), fat distribution and bone markers measured by DEXA scan between men and women at D0 et comparison of their evolution at W48

- Comparaison of the metabolic/inflammatory profile in women according to their ovarian reserve and menopausal status at D0 and its evolution up to week 48

10. DRUGS MANAGEMENT

10.1 Study drug

The investigational ARV regimen is defined as raltegravir (RAL, Isentress®) plus etravirine (ETR, Intelence®).

Raltegravir 400 mg tablets will be administered as one 400 mg oral tablet PO twice daily (800 mg per day) after a meal.

Etravirine 200 mg tablets will be administered as one 200 mg oral tablet PO twice daily (400 mg per day) after a meal.

The reference documents for raltegravir and etravirine, follow the recommendations clearly stated in the summary of product characteristics of the respective drugs.

10.2 Study drug circuit

10.2.1 Study drug: delivery

The sponsor is in charge of providing raltegravir and etravirine in association with Merck Sharp & Dohme Ltd and Janssen Cilag Pty Ltd. The Sponsor will contract a specific partner, to manage the trial drugs provided to the patients.

Study drug order to pharmaceutical firms will be done by the sponsor in collaboration with the CMG Inserm UMR S 1136 and the pharmacy of study sites.

The service provider of the trial drug, also called a pharmaceutical provider in this study protocol, will be responsible to receipt study drugs delivered by the pharmaceutical firms, store, and label both raltegravir and etravirine according to GCP (Good Clinical Practice) requirements and to deliver the study drugs ready to use to the pharmacy of the clinical centres. The service provider will also regularly perform quality controls according to GMP (Good Manufacturing Practice) requirements.

10.2.2 Study drug: packaging

Merck Sharp & Dohme Ltd will provide raltegravir in the form of commercial supply Isentress® and Janssen will provide etravirine in the form of commercial supply Intelence®.
Raltegravir (RAL, Isentress®) 400 mg tablets and etravirine (ETR, Intelence®) 200 mg tablets will be packed in their original and respective boxes/bottles.

10.2.3 Study drug: labeling

The sponsor will provide trial specifications to the service provider in charge of drugs labeling within the respect of the Good Manufacturing Practices (according to article 26 to 30 of annex 13 of the European Good Manufacturing Practices of 2009).

The study drug's label will be in agreement with European regulatory requirements (according to article 26 to 30 of annex 13 of the European Good Manufacturing Practices of 2009).

10.2.4 Study drug: dispatching and dispensiation

Study drug dispatching
Pharmaceutical companies will ship the study drugs to the pharmaceutical provider in charge of the delivery to the pharmacy of the clinical centres. Pharmaceutical firms will provide the trial medication to the pharmaceutical provider in several batches which will be defined in the contract.
The CMG Inserm UMR S 1136 will inform the study drug service provider or every patient's inclusion.

A theoretical calendar for every patient's visit will be provided by the CMG Inserm UMR S 1136 to the pharmaceutical provider. This will be realized once the D0 visit is done and the data of the D0 visit are reported into the eCRF by the investigator of the clinical centre.

Study drug: dispensation
Raltegravir and etravirine, will be dispensed by the pharmacist of the trial site upon receipt of a prescription specific to ARNS 163 ETRAL trial filled and signed by the investigator at the name of the patient.

Delivery of raltegravir and etravirine to the patient will occur at the pharmacy on the trial site and have to be dispensed in their original containers. In most cases, one bottle will include enough for one month of therapy.

The patient should return the empty boxes of treatment at each time of delivery in order to measure the adherence.

Pharmacists of trial sites will be in charge of

- Receiving trial medication;
- keeping trial medications in a locked secure storage facility, only accessible to authorized staff;
- A trial medication inventory will be maintained, including materials received and dispensed to patients;
- At the conclusion or termination of the trial, the pharmacist agrees to conduct a final drug supply inventory and to record this on a Drug Accountability Form;
- Deliveries are documented;
- Trial medications are adequately stored;
- Records should include dates, quantities and the unique code numbers assigned to the investigational drugs and the trial subjects.

10.2.5 Study drug: return and destruction

Before IMP(s) (Investigational Medical Product) is returned to or destroyed, documentation of the delivery, use, and destruction or return of unused, used or partially used packages of IMP(s) has to be kept by the pharmacist.

Accountability will include documentation (on a study-specific accountability log) of the numbers of tablets dispensed by the pharmacist, as well as the amount of medication, which is not used and returned. The accountability log will be checked by the Sponsor's study monitor.

Upon completion or termination of the trial, all unused and/or partially used study drugs must be returned to the service provider of the study drug

All study drugs returned to the service provider must be accompanied by appropriate documentation and be clearly identified by protocol number and trial site number on the outermost shipping container. Returned supplies should be in the original containers (eg patient kits). The assigned study monitor should facilitate the return of unused and/or partially used study drugs.

If the study drug is authorized to be destroyed at the site by the Sponsor, it is the pharmacist's responsibility to ensure that arrangements have been made for the disposal. Written authorization should be issued by the Sponsor, procedures for proper disposal should be established according to applicable regulations, guidelines and procedures, and appropriate records of the disposal/study drug destruction should be documented and forwarded to the Sponsor.

10.3 Concomitant treatments

Interactions with Other Drugs
Potential drug-drug and/or drug-food interactions should be taken into consideration when selecting an antiretroviral (ARV) regimen. A thorough review of concomitant medications can help in designing a regimen that minimizes undesirable interactions. In addition, the potential for drug interactions should be assessed when any new drug (including over-the-counter agents), is added to an existing ARV combination. Most drug interactions with ARV drugs are mediated through inhibition or induction of hepatic drug metabolism.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)
All NNRTIs are metabolized in the liver by cytochrome P450 (CYP) 3A isoenzymes. In addition, efavirenz (EFV) and nevirapine (NVP) are substrates of CYP2B6 enzymes, and etravirine (ETR) is a substrate of CYP2C9 and 2C19 enzymes. Concomitantly administered drugs that induce or inhibit these enzymes can alter NNRTI drug concentrations, resulting in virologic failure or adverse effects. All NNRTIs, except rilpivirine (RPV), induce or inhibit CYP isoenzymes. EFV acts as a mixed inducer and inhibitor, but like NVP, it primarily induces CYP3A and 2B6

enzymes. ETR also induces CYP3A but inhibits CYP2C9 and 2C19 enzymes. The inducing effects of NNRTIs can result in sub-therapeutic concentrations of concomitantly administered drugs that are metabolized by CYP enzymes. Examples of such interacting medications include azole antifungals, rifamycins, benzodiazepines, hepatitis C virus (HCV) protease inhibitors, HMG-CoA reductase inhibitors (statins), and methadone.

Integrase Strand Transfer Inhibitors (INSTIs)
Raltegravir (RAL) is primarily eliminated by glucuronidation mediated by the uridine diphosphate (UDP)-glucuronosyltransferase (UGT) 1A1 enzymes. Strong inducers of UGT1A1 enzymes (e.g., rifampin) can significantly reduce the concentration of RAL. Raltegravir does not appear to affect CYP or UGT enzymes or P-glycoprotein-mediated transport.

Drug Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors/ Integrase Inhibitors and Other Drugs (Last updated February 12, 2013; last reviewed February 12, 2013) (Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents - Downloaded from http://aidsinfo.nih.gov/guidelines on 2/16/2014)

10.3.1 Interations and dose recommendations with other medicinal products concomitant

Drug Class/Name	Etravirine (ETR) or raltegravir (RAL)	Effect on NNRTI or INI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticoagulant			
Warfarin	Etravirine	↑ warfarin possible	No dosage adjustment necessary; use with caution. Consider monitoring International Normalized Ratio (INR) level.
Antifungals,			
Voriconazole	Etravirine	voriconazole AUC ↑ 14% ETR AUC ↑ 36%	No dosage adjustment necessary; use with caution. Consider monitoring voriconazole level.
Antimycobacterials			
Clarithromycin	Etravirine	clarithromycin AUC ↓ 39% ETR AUC ↑ 42%	Consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
Rifabutin	Etravirine	rifabutin and metabolite AUC ↓ 17% ETR AUC ↓ 37%	If ETR is used with an RTV-boosted PI, rifabutin should not be co-administered. Dose: rifabutin 300 mg once daily if ETR is not coadministered with an RTV-boosted PI.
Benzodiazepines			
Alprazolam	Etravirine	No data	Monitor for therapeutic effectiveness of alprazolam.
Diazepam	Etravirine	↑ diazepam possible	Decreased dose of diazepam may be necessary.
Midazolam	Etravirine	Significant ↑ midazolam expected	Do not co-administer with oral midazolam. Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.
Cardiac Medications			
Antiarythmic medications	Etravirine	↓ antiarythmic medications possible	No dosage adjustment necessary; use with caution.
Dihydropyridine calcium channel blockers (CCBs)	Etravirine	↓ CCBs possible	Titrate CCB dose based on clinical response.
Diltiazem Verapamil	Etravirine	diltiazem AUC ↓ 69% ↓ verapamil possible	Titrate diltiazem or verapamil dose based on clinical response.
Digoxin	Etravirine	Digoxin AUC ↑ 18%	No dosage adjustment necessary; use with caution.
Corticosteroids			
Dexamethasone	Etravirine	↓ ETR possible	Consider alternative corticosteroid for long-term use. If dexamethasone is used with NNRTI, monitor virologic response.
HMG-CoA Reductase Inhibitors			
Atorvastatin	Etravirine	atorvastatin AUC ↓ 32%–43%	Adjust atorvastatin according to lipid responses, not to exceed the maximum recommended dose.
Fluvastatin	Etravirine	↑ fluvastatin possible	Dose adjustments for fluvastatin may be necessary.
Lovastatin Simvastatin	Etravirine	↓ lovastatin possible ↓ simvastatin possible	Adjust lovastatin or simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If ETR

			or NVP used with RTV-boosted PI, simvastatin and lovastatin should be avoided.
Immunosuppressants			
Cyclosporine Sirolimus Tacrolimus	Etravirine	↓ immunosuppressant possible	Increase in immunosuppressant dose may be necessary. Therapeutic drug monitoring of immunosuppressant is recommended. Consult with specialist as necessary.
Phosphodiesterase Type 5 (PDE5) Inhibitors			
Sildenafil	Etravirine	sildenafil AUC ↓ 57%	May need to increase sildenafil dose based on clinical effect.
Tadalafil	Etravirine	↓ tadalafil possible	May need to increase tadalafil dose based on clinical effect.
Vardenafil	Etravirine	↓ vardenafil possible	May need to increase vardenafil dose based on clinical effect.

10.3.2 Drugs That Should Not Be Used With Antiretroviral Agents as etravirine and raltegravir

	Trade names	DCI	Metabolic pathway	Effects on drug levels
Platelet Aggregation Inhibitors	Plavix®	Clopidogrel	A prodrug, active metabolite CYP**2C19**	Increased activity of Clopidogrel, risk of overdose
	Effient®	Prasugrel	A prodrug, active metabolite CYP**3A4**, CYP2B6, **2C9/19**	Increased activity of Prasugrel, risk of overdose
	Brilinta®	Ticagrelor	Active parent compound CYP**3A4**/5	Decreased activity of Ticagrelor, risk of inefficiency
	Ticlid®	Ticlopidine	Active parent compound CYP1A2, **2C19**, 2D6 +active metabolite CYP2B6	Decreased activity of Ticlopidine, risk of inefficiency
	Antadys® Cebutid®	Flurbiprofen	Active parent compound CYP2C9,UGT (Isozyme)	Possible decrease activity of Flurbiprofen, risk of inefficiency
Anti mycobacterials	Rifampicin® Rifadin® Rofact[MC] Rifater®	Rifampin	/	Rifampin reduces plasma levels of etravirine and Raltegravir.
	Priftin®	Rifapentine	/	Rifapentine reduces plasma levels of Etravirine
Herbs	Millepertuis	St John's wort	/	St John's wort reduces plasma levels of Etravirine
Anticonvulsant	Tegretol®	Carbamazepine	/	Carbazamepine, phenobarbital and phenytoin are expected to decrease plasma concentrations of Etravirine.
		Phenobarbital	/	
	Dilantin®	Phenytoin	/	
Others	Stendra™	Avanafil	/	Co-administration is not recommended
	Halcion®	Triazolam	/	Significant increased triazolam expected

11 STUDY ASSESSMENTS AND CONDUCT

11.1 Schedule of assessments

	W-6/W-4	D0	W2	W4	W12	W24	W36	W48	W64	W80	W96	EOT
Informed Consent Signature	X											
Review eligibility criteria	X	X										
Collection of adverse events		X	X	X	X	X	X	X	X	X	X	X
Quality of life, felt symptoms		X						X			X	X
Adherence evaluation	X							X			X	X
Clinical exam *(blood pressure, heart rate, body temperature, weight and targeted physical examination)*	X[1]	X[2,3,4]	X	X	X	X	X	X[2,3,4]	X	X	X[2, 3, 4]	X[2]
HBV/HCV serology	X											
Urinary pregnancy test If positive: β HCG[5]	X	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]
HIV-RNA plasma Viral Load[7]	X	X		X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]
CD4/CD8 Lymphocytes	X	X			X	X		X		X	X	X
Whole blood cells count	X					X		X		X	X	X
Creatinine, AST, ALT, CPK, bilirubin, urine analysis[9]	X			X	X	X		X		X	X	X
Lipid profile[10], fasting glycemia		X			X	X		X			X	X
Genotypic resistance on blood DNA	X											
DXA-Scan sub-study[11]		X						X			X	
Seminal sub-study[12]								X				
Study drug prescription		X		X	X	X	X	X	X	X		
Sample bank[13]												
Plasma bank: *minimal plasma ARV concentration, virological analysis*		X	X	X	X	X	X	X	X	X	X	X
Whole blood bank: Total cell-associated HIV-DNA		X						X			X	X
Plasma and serum bank: Immunologic analysis of inflammation markers[14]		X						X			X	X

[1] Electrocardiogram (ECG)
[2] Anthropometric measurements (abdominal and waist circumference)
[3] Cardiovasculor risk factors: arterial hypertension, tobacco, alcohol abuse, physical activity, diabetes
[4] Measurement of the systolic blood pressure at D0 W48 W96 according to the recommendations (Pickering et al. Circulation 2005, in Appendix A7)
[5] Only for women of childbearing potential
[6] Only in case of suspicion
[7] Plasma viral loads using a routine technique with a positivity threshold of maximum 50 copies/mL
[8] If HIV-RNA plasma viral loads > 50 copies/mL an additional blood collection have to be performed, within an interval of two to four weeks, to confirm the virological rebound. If the virological failure is confirmed, a resistance genotype and a dosage of ARV drugs concentration in plasma will be performed on the second HIV-RNA plasma VL test. A plasma bank should also be done
[9] Urine analysis: proteinuria, albuminuria, creatininuria, glycosuria
[10] Lipid profile: fasting triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol
[11] DXA-scan sub-study: evolution of the Bone Mineral Density (BMD) and of the body fat distribution in 80 patients
[12] Seminal sub-study in 20 patients. The HIV-RNA viral load and the RAL/ETR Cmin will be measured
[13] Refer to paragraph 12
[14] Immunological analysis of inflammation markers might be performed on frozen plasma aliquots. Markers of interest are: IL-6hs, sCD14, sCD163, D-Dimers, IP-10, IgG, CRPus and insulin

11.2 Study participation

11.2.1 Information

No examinations will be carried out before the patient concerned gave his/her written informed consent. Before any study-related trial procedures, the investigator will:

- Explain the nature, purpose and potential risks of the trial in which patients volunteer to participate and answer all questions regarding this trial,

- Inform patients that their participation is voluntary and that they may withdraw consent to participate at any time without giving any reason; if patients decide not to participate or withdraw from the trial, it will not affect the standard care they will receive to treat their disease,

- Provide to patients the informed consent form in their own language. The patients will be given sufficient time to consider before consenting,

The investigator(s) has both ethical and legal responsibility to ensure that each patient being considered for inclusion in this trial is given a full explanation of the protocol.

11.2.2 Obtaining consent

Once the appropriate essential information has been provided to the patient and fully explained by the investigator (or a qualified designee) and it is felt that the patient understands the implications of participating, the IRB (Institutional Review Board)/IEC-approved written informed consent form shall be signed and dated by both the patient and the person obtaining consent (investigator or designee), and by any other parties required by the IRB/IEC. The patient shall be given a copy of the signed informed consent form; the original shall be kept on file by the investigator. All of the above mentioned activities must be completed prior to the patient's participating in the trial.

After obtaining the informed consent form signed and personally dated by the patients, the investigator must attribute a trial identification code to any patient who has accepted to participate into the trial (see procedure described below).

The inclusion and non-inclusion criteria after signature of the written informed consent must be checked.

Patients that fail screening may be re-screened while keeping their previous identification code.

11.2.3 Patient identification

The investigator will assign an identification code to the patient according to the following procedure.

The patient identification code is composed of:

- Two letters for the country: FR for France, ES for Spain

- The centre number (3 digits)

- The patient order of entry in the trial in this centre (3 digits)

- A four letter code randomly generated and be provided to any participant centres by the CMG Inserm UMR S 1136 before starting the trial

For example, for a patient, screened in France, in centre 060, and screened for inclusion at the second position in this centre with letter code of FRSD, the patient identification code will be: FR-060-002-FRSD.

11.3 Screening visit (W -6/W-4)

This visit will be performed between 4 and 6 weeks before the beginning of trial treatment (RAL/ETR) at D0 Visit.
During this visit, the investigator:

- Collects the fully informed patient's consent,
- Collects the following patient characteristics (Birth date, Sex, Origin and HIV transmission group) and patient's lifestyle (tobacco, drugs and alcohol),
- Collects current/previous ART,

- Interviews the patient to collect the medical history, the potential concomitant pathologies and concomitants treatments,
- Evaluates the patient's adherence using self-questionnaires
- Performs an extensive and detailed anamnesis of the patient's immunovirologic history including a complete chronological list of the viral strains genotypes allowing the exclusion of any virological failure under NNRTI treatment. In addition, the investigator has to perform prior to inclusion a Genotypic resistance on blood DNA showing its full sensibility to ETR and RAL,
- Performs a clinical examination: blood pressure, heart rate, body temperature, targeted physical examination,weight, and height. An ECG will be performed to exclude any concomitant condition that might jeopardize patient's safety and participation,
- Performs urinary pregnancy test for women of childbearing potential,
- Collects urine sample for urine analysis: proteinuria, albuminuria, creatininuria, glycosuria,
- Collects blood samples for the following biological exams:
    - Whole blood cells counts
    - HIV-RNA plasma viral load
    - Genotypic resistance on blood DNA
    - CD4/CD8 lymphocytes count
    - Creatinine, CPK, AST, ALT and bilirubin dosages
    - HBV and HCV serologies
    - ßHCG for women of childbearing potential with positive urinary test

A copy of the biological exams with an anonymized copy of the Patient's Informed Consent Form will be faxed by the investigator to CMG Inserm UMR S 1136 in order for them to validate the inclusion.

The investigator will schedule the D0 visit and the DXA scan of D0 visit (for patients participating in the DXA sub-study). DXA scan might be performed with a time limit up to 7 days before the date of D0 visit.

11.4 Day 0 visit (inclusion)

The designated D0 Visit (Day 0) is the date planned for the first prescription and, a fortiori, the first administration of trial treatment (RAL/ETR).

During this visit, the investigator:

- Realizes a clinical examination (blood pressure, heart rate, body temperature, targeted physical examination, weight) and anthropometric measurements (specific circumferences: abdomen (perimeter at the umbilicus) and hips (bi-trochanterian perimeter)). Cardiovascular risk factors (arterial hypertension, tobacco, alcohol abuse, physical activity, diabetes) and the measurement of the systolic blood pressure (refer to appendix 7) will be recorded.
- Checks the presence of intercurrent pathologies and the treatments intake
- Evaluates the patient's quality of life and felt symptoms using self-questionnaires
- Performs urinary pregnancy test for women of childbearing potential, in case of suspicion
- Collects blood samples for the following biological exams:
    - HIV-RNA plasma viral load
    - CD4/CD8 lymphocytes count
    - Lipids (fasting triglycerides, total cholesterol, HDL-Cholesterol, and LDL-cholesterol) and fasting glycemia
    - Sample bank (plasma,serum and whole blood bank)
- DXA-Scan will be performed for patients participating in this sub-study (DXA scan might be performed up to 7 days before D0 visit).

A copy of the biological exams will be faxed by the investigator to CMG Inserm UMR S 1136.

The investigator will give the first prescription of trial treatment (RAL/ETR) and schedule the W2 visit.

11.5 Follow-up visits

After the D0 visit, 9 visits are scheduled in the clinical centres, W2, W4, W12, W24, W36, W48, W64, W80 and W96 or End of treatment (EOT). EOT visit will be performed in case of giving up or premature stop of trial

treatment. Assessments and procedures will be performed according to schedules reported in the table (schedule of assessment). A copy of all biological exams will be faxed by the investigator to CMG Inserm UMR S 1136.

11.5.1 Visits W2 to W80

- **W2 Visit:** the investigator will realize a clinical examination (blood pressure, heart rate, body temperature, targeted physical examination, weight), check the presence of intercurrent pathologies and the treatments intake. Urinary pregnancy test for women of childbearing potential will be performed, in case of suspicion. Blood samples will be collected for sample bank (plasma bank).
  The investigator will schedule the W4 visit.

- **W4 Visit:** the investigator will realize a clinical examination (blood pressure, heart rate, body temperature, targeted physical examination, weight), check the presence of intercurrent pathologies and the treatments intake. Urinary pregnancy test for women of childbearing potential will be performed, in case of suspicion. Plasma HIV-1 RNA viral load, Creatinine, CPK, AST, ALT and bilirubin dosages will be realized in the local laboratory. Blood samples will be collected for sample bank (plasma bank). Urine sample for proteinuria, albuminuria, creatininuria, glycosuria analysis (in the local laboratory) will be collected.
  The investigator will give the prescription of trial treatment (RAL/ETR) and schedule the W12 visit.

- **W12 Visit:** the investigator will realize a clinical examination (blood pressure, heart rate, body temperature, targeted physical examination, weight), check the presence of intercurrent pathologies and the treatments intake. Urinary pregnancy test for women of childbearing potential will be performed, in case of suspicion. Plasma HIV-1 RNA viral load, CD4/CD8 count, metabolic parameters (fasting triglycerides, total cholesterol, HDL-Cholesterol, and LDL-cholesterol), fasting glycemia, Creatinine, CPK, AST, ALT and bilirubin dosages will be realized in the local laboratory. Urine sample for proteinuria, albuminuria, creatininuria, glycosuria analysis (in the local laboratory) will be collected. Blood samples will be collected for sample bank (plasma bank).
  The investigator will give the prescription of trial treatment (RAL/ETR) and schedule the W24 visit.

- **W24 Visit:** the investigator will realize a clinical examination (blood pressure, heart rate, body temperature, targeted physical examination, weight), check the presence of intercurrent pathologies and the treatments intake. Urinary pregnancy test for women of childbearing potential will be performed, in case of suspicion. Plasma HIV-1 RNA viral load, CD4/CD8 count, whole blood cells count, metabolic parameters (fasting triglycerides, total cholesterol, HDL-Cholesterol, and LDL-cholesterol), fasting glycemia, Creatinine, CPK, AST, ALT, bilirubin dosages and urine analysis (proteinuria, albuminuria, creatininuria, glycosuria) will be realized in the local laboratory. Blood samples will be collected for sample bank (plasma bank). The investigator will give the prescription of trial treatment (RAL/ETR) and schedule the W36 visit.

- **W36 Visit:** the investigator will realize a clinical examination (blood pressure, heart rate, body temperature, targeted physical examination, weight), check the presence of intercurrent pathologies and the treatments intake. Urinary pregnancy test for women of childbearing potential will be performed, in case of suspicion. Plasma HIV-1 RNA viral load will be realized in the local laboratory. Blood samples will be collected for sample bank (plasma bank).
  The investigator will give the prescription of trial treatment (RAL/ETR), schedule the W48 visit and the DXA scan (for patients participating in the DXA sub-study). DXA scan might be performed with a time limit up to 10 days before and after the visit date of W48.

  The investigator will deliver the dedicated container for patients participating in the seminal sub-study to collect the sperm within the 6 hours prior the W48 visit.

- **W48 Visit:** the investigator will realize a clinical examination (blood pressure, heart rate, body temperature, targeted physical examination, weight) check the presence of intercurrent pathologies and the treatments intake. Anthropometric measurements (specific circumferences: abdomen (perimeter at the umbilicus) and hips (bi-trochanterian perimeter)),cardiovascular risk factors (arterial hypertensions, tobacco, alcohol abuse, physical activity, diabetes), measurement of the systolic blood pressure (refer to appendix 7) will be recorded . Urinary pregnancy test for women of childbearing potential will be performed, in case of suspicion. Plasma HIV-1 RNA viral load, CD4/CD8 count, whole blood cells count, metabolic parameters (fasting triglycerides, total cholesterol, HDL-Cholesterol, and LDL-cholesterol), fasting glycemia, Creatinine, CPK, AST, ALT, bilirubin dosages, urine analysis (proteinuria, albuminuria, creatininuria, glycosuria) will be realized in the local laboratory. Blood samples will be collected for sample bank (plasma, serum and whole

blood bank), The patient's quality of life, felt symptoms, and adherence will be collected using self-questionnaires.

Patients participating to the DXA-Scan sub-study will perform their second scans. DXA scan might be performed with a time limit up to 10 days before and after the visit date of W48.

At W48, patients participating to the seminal sub-study will bring the total sperm sample collected within the 6 hours prior the visit using the dedicated container delivered by the investigator at W36.

The investigator will give the prescription of trial treatment (RAL/ETR) and schedule the W64 visit.

- **W64 Visit:** the investigator will realize a clinical examination (blood pressure, heart rate, body temperature, targeted physical examination, weight), check the presence of intercurrent pathologies and the treatments intake. Urinary pregnancy test for women of childbearing potential will be performed, in case of suspicion. Plasma HIV-1 RNA viral will be realized in the local laboratory. Blood samples will be collected for sample bank (plasma bank).
  The investigator will give the prescription of trial treatment (RAL/ETR) and schedule the W80 visit.

- **W80 Visit:** the investigator will realize a clinical examination (blood pressure, heart rate, body temperature, targeted physical examination, weight), check the presence of intercurrent pathologies and the treatments intake. Urinary pregnancy test for women of childbearing potential will be performed, in case of suspicion. Plasma HIV-1 RNA viral load, CD4/CD8 count, whole blood cells count, Creatinine, CPK, AST, ALT, bilirubin dosages and urine analysis (proteinuria, albuminuria, creatininuria, glycosuria) will be realized in the local laboratory. Blood samples will be collected for sample bank (plasma bank).
  The investigator will give the prescription of trial treatment (RAL/ETR), schedule the W96 visit and the DXA scan (for patients participating in the DXA sub-study). DXA scan might be performed with a time limit up to 10 days before and after the visit date of W96.

11.5.2 Last visit of follow-up

The last visit of follow-up for each patient will be the week 96 visit if the patient completes the trial or the EOT visit in case of giving up or premature stop. Patients who stop the trial treatment will continue to be followed according to the trial calendar until the week 96.

- **W96 Visit:** the investigator will realize a clinical examination (blood pressure, heart rate, body temperature, targeted physical examination, weight), anthropometric measurements (specific circumferences: abdomen (perimeter at the umbilicus) and hips (bi-trochanterian perimeter), check the presence of intercurrent pathologies and the treatments intake. Cardiovascular risk factors (arterial hypertensions, tobacco, alcohol abuse, physical activity, diabetes) and the measurement of the systolic blood pressure (refer to appendix 7) will be recorded. Urinary pregnancy test for women of childbearing potential will be performed, in case of suspicion. Plasma HIV-1 RNA viral load, CD4/CD8 count, whole blood cells count, metabolic parameters (fasting triglycerides, total cholesterol, HDL-Cholesterol, and LDL-cholesterol), fasting glycemia, Creatinine, CPK, AST, ALT, bilirubin dosages, urine analysis (proteinuria, albuminuria, creatininuria, glycosuria) will be realized in the local laboratory. Blood samples will be collected for sample bank (plasma, serum and whole blood bank). The patient's quality of life, felt symptoms and adherence will be collected using self-questionnaires.

  Patients participating to the DXA-Scan sub-study will perform their third scans. DXA scan might be performed with a time limit up to 10 days before and after the visit date of W96.

- **EOT Visit (End of treatment):** this visit will be realized only in case of giving up or premature stop of trial treatment.

  At this visit, the investigator will realize a clinical examination (blood pressure, heart rate, body temperature, targeted physical examination, weight), anthropometric measurements (abdominal and waist circumference),check the presence of intercurrent pathologies and the treatments intake. Urinary pregnancy test for women of childbearing potential will be performed, in case of suspicion. Plasma HIV-1 RNA viral, CD4/CD8 count, whole blood cells count, metabolic parameters (fasting triglycerides, total cholesterol, HDL-Cholesterol, and LDL-cholesterol), fasting glycemia, Creatinine, CPK, AST, ALT, bilirubin dosages, and urine analysis (proteinuria, albuminuria, creatininuria, glycosuria) will be realized in the local laboratory. Blood samples will be collected for sample bank (plasma, serum and whole blood bank).

  The patient's quality of life, felt symptoms and adherence will be collected using self-questionnaires.

11.6 Study end

The end of the trial occurs when the last patient still being followed realizes the week 96 visit, abandons or withdraws consent plus 6 months. At the end of the trial (six months after the last visit of the last patient), for each participant, according to the trial results, the investigator will decide to maintain or change the trial treatment. The patients will be followed with the best clinical practices. In case of premature stop of the trial, the investigator will follow the scientific committee recommendation. All patients will be informed of the trial results.

11.7 Premature and definitive stop of the study treatment

"Stop of treatment" is when the patient is not taking RAL and/or ETR.
All patients who discontinue trial medication will be followed up and requested to attend for trial visits up until week 96, even if they stop taking trial medication.
Reasons of a premature stop can be:

- Wish of the patient,
- Intolerance or occurrence of an adverse event,
- New or worsening of an intercurrent pathology,
- Death of the patient,
- Virological failure defined as two successive HIV-RNA plasma viral loads > 50 copies/mL within 2 to 4 weeks,
- Pregnancy,
- All medical event that induce an interruption of the treatment,
- Major violation of the protocol,
- Non- adherence of the treatment resulting in danger for the health of the patient,
- Necessity for the patient to be treated by a non-authorized treatment in the protocol,
- Motivated investigator's decision for any other reason than those listed above.

"Premature stop" is considered as a deviation to the protocol if it is not due to a reason cited above. Any event resulting in premature stop should be reported within the two working days of the decision to discontinue in the eCRF using the dedicated form. The reason and date of the treatment discontinuation will have to be documented. The CMG project manager will receive an automatic alert email. Patients who stop the trial treatment will continue to be followed according to the trial calendar.

The investigator must collect the information for the primary end points at the time of the premature stop of trial treatment (EOT visit).

11.8 Lost to follow-up

A patient is considered lost to follow-up when he/she is not coming to more than 2 consecutives visits of the protocol. Three documented attempts should be made to contact the patient via telephone and one registered letter (letter which requires signature upon receipt) should be sent to the patient prior to assigning the patient as lost to follow-up. Patients who cannot be contacted on or before the last scheduled visit prior to the week 96 and who do not have a known reason for discontinuation (eg, withdrew consent, giving up, etc.) will be classified as "lost to follow-up".
The CMG UMR S 1136 should be informed as soon as possible using the dedicated form in the eCRF. The CMG project manager will receive an automatic alert email.

11.9 Withdrawal of the consent and giving up

Patients who want to giving up or withdraw their consent as they are allowed to do at any time, are no more followed in the context of the protocol but will be followed with the best clinical practices.

11.9.1 Consent withdrawal

In case of a withdrawal of the consent, the investigator must inform the CMG UMR S 1136 to have the procedure to follow. The patient's data will be removed (from the date of the consent's withdrawal) from the database according to the law (loi n°78-17 du 6 janvier 1978 modifiée, article 38) and the biological samples will be destroyed.

Any consent withdrawal has to be confirmed to the Methodology Centre by using the dedicated form in the eCRF within the two working days, and date of withdrawal.

Subjects withdrawing from the trial may be replaced if considered necessary by the Coordinating investigator.

11.9.2 Giving up

Patients give up the trial when they refuse to continue the follow-up of the trial. The investigator must identify the reason and collect the information for the primary end points at the time of the giving up (EOT visit). The CMG UMR S 1136 should be informed within the two working days using the dedicated form in the eCRF. The reason and date of discontinuation have to be documented. The CMG project manager will receive an automatic alert email.
They will be followed with the best clinical practices.

11.10 Protocol deviations

According to Good Clinical Practises sponsor and investigators should not use systems of prospectively approving protocol deviations, in order to effectively widen the scope of a protocol.

Protocol deviations have to be fully argumented and documented. Are defined as major protocol deviations the following violations related to: regulatory aspects of the research, eligibility criteria, the primary evaluation criteria, the investigational treatment. The whole protocol deviations will be listed and submitted to both Trial Scientific Committee, Data Safety Monitoring Board and to the sponsor. According to the deviation, the end of participation of the patient concerned may be considered

11.11 Trial-specific rules for treatment management

11.11.1 Virological failure

A virological failure is defined as two consecutive HIV-RNA plasma viral loads > 50 copies/mL within an interval of two to four weeks. During the course of the trial, the onset of an HIV-RNA plasma VL > 50 copies/mL will automatically conduct to schedule an additional blood collection within an interval of two to four weeks o confirm the rebound of the HIV-RNA plasma VL. If the virological failure is confirmed, a resistance genotype and a dosage of ARV drugs concentration in plasma will be performed on the second HIV-RNA plasma VL test A plasma bank should also be done.

- If the HIV-RNA plasma VL rebound is not confirmed by the second test, the trial treatment will be maintained without any specific adaptation.
- If the HIV-RNA plasma VL rebound is confirmed by the second test the baseline ARV regimen will be immediately reintroduced. If needed, treatment will be subsequently adapted according resistance genotype.

In order to ensure real-time virological safety for patients included, the Data Safety Monitoring Board will be informed every time 2 virological failures are confirmed by two consecutive plasma viral load tests > 50 copies/mL within 2 to 4weeks. (see 10.2.2)

11.11.2 Potential risks of study drug and the research and management guidelines

In case of grade 3/4 intolerance related to raltegravir and/or etravirine, one or both drugs should be interrupted and the baseline ARV regimen might be reintroduced once the event is resolved or once the related clinical and/or biological symptoms are enough improved.

No raltegravir and/or etravirine dosage adaptation will be authorized. Upon investigator's opinion, an additional clinical visit might be scheduled within 2 to 4 weeks following the onset of the event to control the symptoms evolution.

In case of raltegravir and/or etravirine treatment related grade 1/2 adverse event, a symptomatic treatment can be proposed.

Particular attention to the following symptoms (see below), related to raltegravir and/or etravirine, will be requested. In case of grade 3/4 (please refer to Appendix A6 for a definition) suspected treatment will be discontinued:
- Skin reaction and severe hypersensitivity (such as: Stevens-Johnson syndrome, erythema multiforme (EM)
- Psychiatric effects (such as: depression, suicide attempt, suicidal behavior and suicidal thoughts)
- Metabolism disorder (such as: diabetes,hyperglycemia, hyperlipidemia)
- Heart conditions (such as: myocardial infarction)

11.11.3 Management of lipid metabolism impairment

In case of mild increase of the lipid parameters, a dietary regime will be proposed. Concomitant lipid-lowering treatments with fibrates or statins are needed. They will have to be prescribed according the guidelines, taking into account the potential interactions with cytochrome P450 based enzymes.

11.11.4 Management of glycaemia impairment

In case of onset of hyperglycaemia or diabetes, an appropriate treatment should be proposed with a dietary regime, physical exercise and anti-diabetic drugs if needed.

11.11.5 Management of pregnancy

In case of suspicion of pregnancy during the trial, a pregnancy test should be performed immediately. Pregnancy must be notified to the sponsor and the methodology centre (see section 13.2.4).

If a female participant becomes pregnant, all study drugs that are not recommended during pregnancy based on the latest SmPC (Summary of the Product Characteristics) must be discontinued. Women should receive regimens that are authorised during pregnancy.

12 BIOLOGICAL SAMPLES AND STORAGE

12.1 Schedule of sample's collection

	W-6/W-4	D0	W2	W4	W12	W24	W36	W48	W64	W80	W96	EOT	In case of virological failure	Volume collected	Aliquots to be prepared	Location of sample's analysis
HBV/HCV serology	√													**2 tubes of 3mL**	According to the local virology laboratory procedures	Local virology laboratory
Genotypic resistance on blood DNA	√													**1 tube of 7mL**		
HIV-RNA plasma Viral Load	√	√		√	√	√	√	√	√	√	√	√		**1 tube of 7mL**		
Urinary pregnancy test If positive: β HCG	√	√	√	√	√	√	√	√	√	√	√	√		***I***		
Urine analysis	√			√	√	√		√		√	√	√		***I***		
Whole blood cells count	√					√		√		√	√	√		**1 tube of 3mL**		
CD4/CD8 Lymphocytes	√	√			√	√		√		√	√	√		**1 tube of 3mL**		
Creatinine, AST, ALT, CPK, Bilirubin	√			√	√	√		√		√	√	√		**1 tube of 3mL**		
Lipid profilefasting glyceemia		√		√	√	√		√			√	√		**3 tubes of 3mL**		
Concentrations of ARVs in Plasma/ Genotypic resistance on blood RNA													√	**2 EDTA tubes of 7mL**	3-4 aliquots of 1.2mL of EDTA plasma	
Seminal sub-study								√						***I***		Pr Vincent CALVEZ/ Dr Anne-Geneviève MARCELIN, *Service de Virologie - Groupe Hospitalier Pitié-Salpêtrière*
Sample bank centralized and stored at Biobank																
Plasma bank		√	√	√	√	√	√	√	√	√	√	√		**3 EDTA tubes of 7mL**	6-7 aliquots of 1.2mL of EDTA plasma	1 aliquot of 1.2 mL to measure ARVs concentration in Plasma → Dr Gilles PEYTAVIN, *Laboratoire de Pharmacologie Clinique - Hôpital Bichat-C. Bernard*
Concentrations of ARVs in Plasma/ Genotypic resistance on blood RNA													√	**1 EDTA tube of 7mL**	3-4 aliquots of 1mL EDTA plasma	Dr Gilles PEYTAVIN and Pr Vincent CALVEZ/ Dr Anne-Geneviève MARCELIN, *Laboratoire de Pharmacologie Clinique - Hôpital Bichat-C.Bernard* Service *de Virologie -Groupe Hospitalier Pitié-Salpêtrière*
Immunologic analysis of inflammation markers		√						√			√	√		**1 EDTA tube of 7mL**	3-4 aliquots of 1mL EDTA plasma	Pr Jacqueline CAPEAU, *CDR Saint-Antoine Faculté de Médecine et Université Pierre et Marie Curiesite Saint-Antoine*
														1 citrate tube of 5mL	2 aliquots of 1mL citrate plasma	
														1 dry tube of 5mL	2-3 aliquots of 1mL of serum	
Total cell-associated HIV-DNA quantification		√						√			√	√		**1 EDTA tube of 7mL**	3 aliquots of 2mL of whole blood sample	Pr Vincent CALVEZ/ Dr Anne-Geneviève MARCELIN, *Service de Virologie - Groupe Hospitalier Pitié-Salpêtrière*
Total blood volume	**29**	**67**	**21**	**40**	**43**	**46**	**28**	**70**	**28**	**37**	**70**	**53**	**21**			

collected (mL)													

12.2 Blood samples preparation for HIV-DNA quantification and plasma storage

The blood samples collected during the patients' visits as defined above will be transferred to the virology laboratories of the participating sites using EDTA (Ethylene Di-Amine Tetra-Acetate) tubes (3,4,5 tubes of 7 mL according to the visit) with an additional citrate and dry tube (1 tube of 5 mL each) according to the visit.

A trial-specific form inside the eCRF will ensure the traceability of the collected samples from the clinical site to the virology laboratory mentioning:

- Patient's name
- Patient's identification code
- Site's number
- Date and number of the patient's visit

Plasma and serum bank preparation and storage:

- At each time point, 6-7 plasma aliquots of 1,2 mL (EDTA tube) will be precisely measured. Additional 3-4 plasma aliquots of 1 mL (EDTA tube), 2 aliquots of 1mL (citrate tube), 2-3 aliquots of 1mL of serum (dry tube), depending the visit, will be prepared.
- The plasma aliquots will be stored in 2 mL NUNC- vials
- The vials will be identified using anonymized labels mentioning only patients' identification codes, sites numbers, number and dates of each visits
- Prepared samples will be cryopreserved at -80°C

Preparation of whole blood samples for total cell-associated HIV-DNA quantification:

- Whole blood samples will be slowly and gently blended for homogeneity
- 3 whole blood aliquots of 2mL will be precisely measured
- The plasma aliquots will be stored in 2 mL NUNC vials
- The vials will be identified using anonymized labels mentioning only patients' identification codes, sites numbers, number and dates of each visits
- Prepared samples will be cryopreserved at -80°C

12.3 Evaluated parameters

12.3.1 Evaluation of the glucid and lipid metabolism

The evolution of the glucid and lipid metabolism will be evaluated by measuring the fasting glycemia, triglycerides, total-cholesterol, LDL-cholesterol and HDL-cholesterol. At visit at which these parameters will be measured, the median values and the proportion of patients above the upper normal will be reported and analyzed.

12.3.2 Evaluation of the cardiovascular risk

For all included patients, the cardiovascular risk will be evaluated at Day 0, week 48 and week 96 using the Framingham equation adapted for France and the SCORE equation proposed by the European Society of Cardiology for countries with a low risk of cardiovascular event. The variables needed for the equations are: Age, sex, blood pressure, tobacco, total- and HDL-cholesterol, and diabetic defined by the fasting glycemia value or any anti-diabetic treatment. This evaluation supposes a standardization of the blood pressure measurements between the participating sites. The measurements have to be performed according to the "Recommendations for Blood Pressure Measurements in Humans and Experimented Animals" (Pickering et al. Circulation 2005).

12.3.3. Evaluation of the HIV reservoir in the blood

The quantification of total cell-associated HIV-DNA will be performed using the consensual real-time PCR method developed and implemented by the ANRS AC11 Quantification Group (limit of detection: 5 HIV-DNA copies/150 000 cells).

12.3.4. Minimal concentrations of ARVs in the plasma

At each visit, for all patients, a specific blood sample will be drawn and frozen to measure the minimal concentrations of all antiretroviral drugs including raltegravir and etravirine. The precise date and hour of each blood collection will be strictly reported in the eCRF. The minimal concentrations of ARVs will be measuredin case of virological failure in local laboratory and at the end of the study (plasma bank).

12.4 Centralization of samples in Inserm-ANRS Biobank

12.4.1 Centralization at CRB CHU Bordeaux-Pellegrin (France)

Blood samples are collected at the trial site. The trial site is responsible for cytopreservation, separation and storage of all samples collected at the trial site as prescribed by the protocol.
The samples which have to be transported to central laboratories or to a central biobank, are stored at the trial site until shipment. The handling and shipment of these samples is detailed in a separate document (trial specific SOP (Standard Operating Procedure)). Blood samples will be centralized in the Biobank at CRB (CHU Bordeaux-Pellegrin, France).
All laboratories involved shall use the human materials sampled in the trial only in accordance with the agreed protocol, the international Good Clinical Practice principles as laid down by the ICH Harmonised.
Tripartite Guidelines for Good Clinical Practice (ICH GCP), the EU Clinical Study Directive and relevant other legislation or regulatory requirements as may be required in the country.
The CMG project manager shall supply trial sites with guidance on handling and storage of the materials, and other related relevant information.
All proposals for additional laboratory assessments that are not specified in this protocol must be submitted to the Study Steering Committee and approved prior to their implementation.

12.4.2 Samples access

Samples centralized at CRB should exclusively be used to:

- confirm the results obtained during the research authorized by the Scientific Committee,
- perform studies already planned according to the protocol,
- further studies not initially foreseen in the protocol and in accordance with procedures established by the Scientific Committee. For studies outside the field of investigation specified in the participants' information consent, an Ethics Committee approval and if appropriate, a new consent will be required.

These samples will be used according to procedures set up by INSERM SC10-US019. Before extraction of samples for analysis, sampling, recipients and deadlines will have been decided by the Scientific Committee.
At the end of the trial, six months after the last visit of the last participant, biological samples will be included in the Inserm-ANRS biobank, authorized for their total or partial transfer for scientific use, except in case of disagreement by each participant. Samples will no longer be available to the the scientific committee, but remain under the responsibility of the Inserm-ANRS. Strict adherence to the participants' rights to refuse further use of this biobank is guaranteed.

13 TRIAL SAFETY

13.1 Definitions

13.1.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or a clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with the treatment or the research.

13.1.2 Adverse Reaction (AR)

All untoward and unintended responses to an investigational medicinal product related to any dose administered or to the research (e.g. trial procedures, trial treatments).

13.1.3 Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

Any untoward medical occurrence or effect that at any dose:
- results in death;
- is life-threatening (means that the subject was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- requires hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is a grade 3 or 4 clinical or biological adverse event;
- is an important medical event that, when based upon appropriate medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above in the definition for a serious adverse event;
  Examples of such events include allergic bronchospasm requiring intensive treatment at an emergency room or at home, blood dyscrasias, convulsions those do not result in inpatient hospitalization, development of drug dependency or drug abuse, or suspected transmission of an infectious agent via a medicinal product…

EXCEPTIONS: SAE not requiring immediate reporting to the sponsor
• Hospitalizations or prolongation of existing hospitalizations that are not considered as serious:
- outpatient care: the patient has been formally admitted to a hospital for medical reasons with no seriousness criteria (described above) and does not require overnight hospitalization;
- elective or previously scheduled surgery or medical treatment;
- hospitalization for social or administrative reasons;
- pre-specified trial hospitalization for observation.

• Pre-existing biological abnormalities or diseases or conditions present or detected prior to start of study drug administration that do not worsen.

13.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

An adverse reaction, the nature, the outcome or severity of which is not consistent with the applicable product Reference Safety Information (Summary of the Product Characteristics, SmPC, for the study drugs) or the applicable trial procedures information noted in the protocol.

13.1.5 New fact

Any safety data that could modify significantly the evaluation of the benefit/risk ratio of the study drug or the clinical trial, likely to affect the safety of participants or that could modify the study drug administration, the trial documentation or the conduct of the trial.
Examples: a serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial, a significant hazard to the subject population such as lack of efficacy of an investigational medicinal product used for the treatment of a life-threatening disease, recommendations of the DSMB, if any, where relevant for the safety of subjects.

13.2 Responsibilities of the investigator

13.2.1 AE notification

Grade 1 and 2 clinical and biological events and all other AE/AR have to be reported in corresponding sheet of the eCRF (AE form) with the intensity and causal relationship, except those detected prior to start of study drug administration. If a clinical or biological event is present at inclusion, only its aggravation will be notified.

13.2.2 SAE notification

- ***What needs to be notified?***

The investigator has to notify to the sponsor all Serious Adverse Events (SAE) except those that the protocol identifies as not requiring immediate reporting (see section 13.1.3).

The investigator should collect all relevant documentation related to the SAE/SAR (e.g. hospitalization report, laboratories results…) and send it to the sponsor, without omitting to make it anonymous and note the identification number of the participant in the trial.

The investigator must follow the participant until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilized. Follow-up should continue after completion of protocol treatment if requested.

- ***Reporting time frames***

SAE requiring reporting and all relevant documentation related to these SAE have to be sent by the investigator to the sponsor, immediately, and no later than 24 hours after being made aware of it.

The investigator ensures that all relevant information is forwarded to the sponsor within 8 days after the initial notification.

All SAE must be reported since the subject signed the informed consent to the clinical trial and during the follow-up scheduled by the trial.
Serious adverse events occurring to a subject after the treatment of that subject has ended should be reported to the sponsor if the investigator becomes aware of them. The investigator does not need to actively monitor subjects for adverse events once the trial has ended, unless provided otherwise in the protocol.

- ***How to report?***

The initial report should be notified as a detailed, written report, using "SAE initial notification form".
The initial report must include the minimum information following: the identifiable coded subject, the identifiable reporter, one suspect medicinal product and one AE.

The initial report shall be followed by complementary detailed, written reports using "SAE complementary notification form".

Notification via eCRF:
All SAE/SAR should be recorded in corresponding form of the eCRF.
When the eCRF SAE notification form is completed, dated and signed by the investigator, an automatic email is sent immediately to the Inserm-ANRS Clinical research safety office and to the Clinical project manager of the CMG Inserm UMR S 1136.

Backup circuit when eCRF is unavailable:
The investigator must report all SAE/SAR using the CRF SAE printed form to the CMG Inserm UMR S 1136, by fax: + 33 (0)1 42 16 42 61 (67) or by email: lbeniguel@ccde.chups.jussieu.fr, mesteban@ccde.chups.jussieu.fr, nessouf@ccde.chups.jussieu.fr

Then the CMG Inserm UMR S 1136 will send, within one business day, the CRF SAE printed form to the Inserm-ANRS Clinical research safety office, by fax: + 33 (0)1 53 94 60 02 or by email: pharmacovigilance@anrs.fr.
If an SAE is declared by paper circuit, it is the responsibility of the site to re-enter the form in the eCRF.

Relevant documentation related to the SAE (e.g. hospitalization report, laboratories results…):
The investigator sends all relevant anonymised documentation related to the SAE to the CMG Inserm UMR S 1136, by fax: + 33 (0)1 42 16 42 61 (67) or by email: lprely@ccde.chups.jussieu.fr/staibi@ccde.chups.jussieu.fr
Then the CMG Inserm UMR S 1136 will send, immediately, all documentation to the Inserm-ANRS Clinical research safety office, by fax: + 33 53 94 60 02 or by email: pharmacovigilance@anrs.fr.

13.2.3 SAE evaluation

The adverse event

The investigator should assess, if possible, the diagnosis of all SAE/SAR. Diagnosis, or if not available, syndrome should be reported whenever possible.
Date of "event onset" on SAE notification form should be earlier (or the same day) than date of seriousness.
When medical or surgical procedures (e.g.: surgery, endoscopy, tooth extraction, transfusion) occurred; the condition that leads to the procedure should be notified.

The severity

The severity (i.e. intensity) of all AEs/ARs (serious and non-serious) should be graded using the appropriate table "ANRS scale to grade the severity of adverse events in adults, Version 1.0, November, 2008" (see appendix A6) and reported by the investigator in the corresponding form of the eCRF.

The seriousness

The judgment as to whether the event is serious is usually made by the reporting investigator (see section 13.1.3 for serious criteria).
Deaths must be reported for subjects as the outcome of an adverse event and not as an adverse event itself if the cause is known. If the cause is unknown, the death should be reported as "unknown cause of death".

The causality

The investigator must assess the causality of all AEs/ARs (serious and non-serious) in relation to the study drug, concomitant medication and the research (e.g. trial procedures).

All SAE for which the investigator or the sponsor considers that a causal relationship is a reasonable possibility are considered as suspected SAR.

The relationship of an adverse event to treatment will be assessed as follows:

Relationship	Description	Event type
Definitely	There is a plausible time relationship between the study drug administration and the (S)AE. The (S)AE cannot be explained by another cause (concurrent disease, other drug or chemicals). Dechallange (the event responds to withdrawal of the study drug), if performed, is positive. Rechallange (the event recurs with readministration of the study drug), if feasible, is positive. The (S)AE shows a pattern consistent with previous knowledge of the medication or medication class.	(S)AR
Probable	There is a reasonable time relationship between the study drug administration and the (S)AE. The event responds to dechallenge. Rechallenge is not required. The (S)AE is more likely explained by the study drug than by another cause	(S)AR

	(concurrent disease, other drug or chemicals).	
Possible	There is a reasonable time relationship between the study drug administration and the (S)AE. The (S)AE could also be explained by another cause (concurrent disease, other drug or chemicals). Dechallenge is lacking or unclear.	(S)AR
Unlikely	There is an improbable time relationship to study drug administration. Other drugs, chemicals or underlying disease provide plausible explanations.	(S)AE
Unrelated	There is an incompatible time relationship to study drug administration. There is another obvious cause of the (S)AE.	(S)AE

The expectedness

Assessment on expectedness is usually done by the sponsor.
The expectedness of a SAR is assessed in the light of the RSI (SmPC of study drug).

The adverse event outcome

The adverse event outcome at the time of reporting should be provided on the initial SAE notification form.
Any change in the initial outcome (e.g. resolved, back to previous status, worsening…) should be reported using complementary reporting form(s). As long as the adverse event is not resolved, any new worsening will be reported using complementary forms of the corresponding initial SAE.

13.2.4 Pregnancy notification

Women of childbearing potential (WOCBP) who are sexually active and not sterile must use an effective method of birth control during the course of the trial, in a manner such that risk of failure is minimized. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy.

Before enrolling women of childbearing potential in this clinical trial, investigators must review guidelines about trial participation for WOCBP. The topics should generally include:

- General information
- Informed consent form
- Pregnancy prevention information
- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Guidelines for the follow-up of a reported pregnancy.

Prior to trial enrolment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The patient must sign an informed consent form stating that the above-mentioned risk factors and the consequences were discussed with her.

During the trial, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle).

The investigator has to notify to the sponsor, immediately and no later than 48 hours after being made aware of it, any pregnancy and its outcome, concerning either the **enrolled woman** or the **wife of an enrolled man**.
If pregnancy concerns the wife of enrolled man, the investigator must obtain her consent for information on pregnancy.

The initial report should be notified as a detailed, written report, using the "Initial pregnancy notification form" and specifying estimated date of delivery, obstetrician contact and name of maternity hospital.

The investigator has to follow the subject until the end of the pregnancy (including perinatal and neonatal outcome) or its interruption and to notify the outcome to the sponsor using the “Final pregnancy notification form”.

The investigator will report to the sponsor any safety data occurring to infants if he becomes aware of them, for a minimum of six months.
Follow-up of pregnant participant continues until the end of the trial.
Any exceptions, related to the indication of maternal treatment, should be discussed between the investigator, the coordinating investigator, the sponsor and if necessary a specialist in terato-vigilance.

Warning:

- The medical surveillance of the women and their children should be reinforced: a particular attention must be given on serious pathology occurring during pregnancy abnormalities. A SAE initial report form should be filled if any **anomaly or birth defect** is detected.
- All **voluntary interruption of pregnancy**, **therapeutic interruption of pregnancy** or miscarriage needed a hospitalization is considered as a SAE/SAR and should be notify as mentioned in section 13.2.2. SAE notification.

Notification via eCRF:
All pregnancies should be recorded in corresponding form of the eCRF.
When the eCRF pregnancy notification form is completed, dated and signed by the investigator, an automatic email is sent immediately to the Inserm-ANRS Clinical research safety office and to the Clinical project manager of the CMG Inserm UMR S 1136.

Backup circuit when eCRF is unavailable:
The investigator must report all pregnancy using the CRF pregnancy printed form to the CMG Inserm UMR S 1136, by fax: + 33 (0)1 42 16 42 61 (67) or by email: lprely@ccde.chups.jussieu.fr/staibi@ccde.chups.jussieu.fr
Then the CMG Inserm UMR S 1136 will send, within one business day, the CRF pregnancy printed form to the Inserm-ANRS Clinical research safety office, by fax: + 33 (0)153 94 60 02 or by email: pharmacovigilance@anrs.fr.
If an SAE is declared by paper circuit, it is the responsibility of the site to re-enter the form in the eCRF.

13.3 Responsibilities of the sponsor

13.3.1 Recording and assessment of SAE

The sponsor shall keep detailed records of all SAE which are reported to him by investigators.

The sponsor is also responsible for the assessment of the causality of the SAE in relation to the study drug, concomitant medication (e.g. drug-drug interaction) and the research.

In the absence of information on causality from the reporting investigator, the sponsor should consult the reporting investigator and encourage him to express an opinion on this aspect.

The causality assessment given by the investigator should not be downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, the opinion of both the investigator and the sponsor should be provided in the report to the national competent authority and the Ethics Committee.

All SAE for which the investigator or the sponsor considers that a causal relationship is a reasonable possibility are considered as suspected SAR.

The expectedness of the SAR shall be determined by the sponsor.
The sponsor assesses if the SAE is expected or not using the applicable Reference Safety Information (Summary of the Product Characteristics, SmPC, of study drug).
If information on expectedness has been made available by the reporting investigator, this should be taken into consideration by the sponsor.

13.3.2 Reporting of safety data to the national competent authority and the Ethics Committee

➢ ***SUSAR reporting***

All Suspected Unexpected Adverse Reactions (SUSARs) have to be reported, within the legal timeframe, by the Inserm-ANRS Clinical research safety office to the national competent authority of the Member State concerned, directly or indirectly through EudraVigilance Clinical Trial Module (EVCTM):
- direct reporting: the sponsor reports the SUSAR directly as an individual case safety report (ICSR) to the national competent authority of the relevant Member State;
- indirect reporting: the sponsor reports the SUSAR as an ICSR through EVCTM to the national competent authority of the relevant Member State.

The Inserm-ANRS Clinical research safety office should also report to the concerned Ethics Committee, all SUSAR occurred in the territory of that Member State.

The timelines for expedited initial reporting (day 0) starts as soon as the information containing the minimum reporting criteria has been received by the sponsor.
For fatal and life-threatening SUSAR, the sponsor should report at least the minimum information as soon as possible and in any case no later than 7 calendar days after being made aware of the case. Relevant complementary information should be collected and notified within 8 extra-days.
SUSAR which are not fatal and not life-threatening are to be reported within 15 calendar days.

➢ ***New fact reporting***

The sponsor should inform the national competent authority and the Ethics Committee of safety data that may be relevant in terms of subject safety, or safety issues which might alter the current benefit-risk assessment of the trial immediately and no later than 15 calendar days after being made aware of it.
When a new fact likely to affect the safety of subjects occurs in the trial, the sponsor must implement urgent safety measures.

➢ ***Annual safety reporting***

Once a year throughout the clinical trial, the sponsor should submit to the national competent authority and the concerned Ethics Committee, an annual safety report, the Development Safety Update Report (DSUR - guideline ICH Topic E2F).

The DSUR should be submitted no later than 60 calendar days from the date of the sponsor's first authorization to conduct the clinical trial in any country.

The RSI in effect at the start of the reporting period serves as RSI during the reporting period. The DSUR should clearly indicate the version number and date of the applicable RSI used for this purpose. If there are significant changes to the RSI during the reporting period, they should be listed in the DSUR. Despite the change to the RSI, the RSI in effect at the start of the reporting period serves as RSI during the reporting period.

The DSUR is prepared in collaboration between the Inserm-ANRS Clinical research safety office and the Clinical project manager of the CMG Inserm UMR S 1136, and includes:
- a line-listing of all suspected serious adverse reactions which have occurred over this period (expected and unexpected SAR);
- a cumulative summary tabulation of the all expected and unexpected SAR by System Organ Class (SOC) name;
- a cumulative summary tabulation of all SAE by SOC name;
- a line-listing of deaths;
- DSMB opinion and Steering committee report;
- a concise, critical analysis of the subjects' safety.

The DSUR may be submitted to the coordinating investigator for approval.

14 TRIAL SURVEY

14.1 Scientific Committee (SC)

14.1.1 Composition

The Scientific Committee will be composed of the following members:

-voting members: Pr Christine Katlama (President), Jacques Reynes, Dr Marc-Antoine Valantin, Dominique Costagliola, Pr Jacqueline Capeau, Dr Sami Kolta, Pr Vincent Calvez, Dr Anne-Geneviève Marcelin, Cathia Soulié, Gilles Peytavin, Lambert Assoumou, Lydie Béniguel, Dr Esteban Martinez, Ventzislava Petrov-Sanchez.

- Non-voting members: Clément Guiheneuf, Alpha Diallo or Séverine Gibowski (Representatives of the Inserm-ANRS Clinical research safety office), Fanny Cardon, Josiane Ako, Jérémy Lafable and representatives of Pharmaceutical firms (Merck Sharp & Dohme and Janssen pharmaceutica NV).

14.1.2 Frequency of meetings

The first meeting of the Scientific Committee should be organized prior to the start of the research, and if possible before initiating regulatory procedures to validate all scientific, ethical and logistical aspects of the trial. The subsequent meetings are scheduled twice a year until the end of the research according to the specificities and the progress of the project. Extraordinary meetings may be decided by the chairperson of the Scientific Committee upon request from the Sponsor, or from one or several members of the Scientific Committee. The request motivated in writing shall be diffused for information to all members of the Scientific Committee.

14.1.3 Role

The Scientific Committee's missions are:
- approval of DSMB composition,
- to ask theCMG for information regarding the progress of the research project, any potential issue and available results,
- to ensure compliance with ethics requirements,
- to perform the scientific follow-up of the research: maintain the relevance of the research objectives and the permanent validity of the methods implemented to meet them,
- to make all important decisions at the demand of the Coordinating Investigator or the DSMB regarding the good conduct of the research in compliance with the protocol, any procedure specific to the research and Good Clinical Practices,
- to decide on all relevant modification of the protocol required to achieve the research project (including recruitment facilitating measures, protocol amendments before regulatory submissions, addition or closure of participating sites),
- to provide information to all investigators and other participants in the research,
- to ensure that rules related to data and biological samples access are followed,
- to ensure that rules related to the communication and publication of research results are fulfilled.

Meeting minutes are drafted following each meeting by the CMG Inserm UMR S 1136, together with the president of the Scientific Committee (at least an exhaustive list of the issues discussed and the decisions made as well as the list of the points raised). The minutes are submitted for review and modifications to the members of the Scientific Committee present at the meeting. The minutes are then validated by the president of the Scientific Committee. It is then distributed to the Scientific Committee members and to the persons invited to the meeting, as well as to the Head of the relevant Inserm-ANRS HIV clinical research department, to the Head of the Inserm-ANRS Clinical research safety office. The minutes are definitely adopted at the beginning of the following meeting of the Scientific Committee.

14.2 Data Safety Monitoring Board (DSMB)

14.2.1 Composition

The DSMB will consist of Isabelle Charreau (statistician, Inserm SC10 - US019, Villejuif, France), Dr. Laurence Bocket (clinician and virologist, Centre Hospitalier Régional Universitaire de Lille, France), Dr.

Cédric Arvieux, (clinician, Unité de Maladies Infectieuses CHU de Rennes, France), Dr. David Rey **(**clinician, Hôpitaux Universitaires de Strasbourg, France), and one representative of the TRT-5 (French organization focused on HIV clinical research and HIV treatment).

14.2.2 Frequency of meetings

The first DSMB meeting will occur:

- Within the first three months following the first patient inclusion.
- In order to ensure real-time virological safety for patients included, the Data Safety Monitoring Board will be convoked every time 2 virological failures are confirmed by two consecutive plasma viral load tests > 50 copies/mL within 2 to 4 weeks.
- Then, during the course of the trial, the frequency of the DSMB meetings will have to meet at least once a year. At any time, an extraordinary meeting might be required upon the advice of the Scientific Committee, of the Sponsor, of the Coordinating Investigator, of the Centre of Methodology or by any investigator.
- Additionally, whenever deemed necessary, DSMB expert members or the sponsor can request an additional meeting to discuss specific issues.

14.2.3 Role

The role of the DSMB is to review the progress of the trial and the accumulating data to detect evidence of early safety issues for the enrolled subjects. The DSMB will give recommendation regarding modification to the ongoing conduct of the trial.

The DSMB will monitor the virological safety. Every 2 episodes of virological failures, a complete report will be sent to the DSMB for review.

The DSMB will review and validate any adverse event leading to the trial treatment discontinuation in order to establish whether the adverse event is related to the trial treatment or procedure. This evaluation should not downgrade the causality assessment given by the investigator and the sponsor.

Recommendation regarding trial termination should be done if eight virological failures occur or if a high level of adverse events leading trial treatment discontinuation was judged by the DSMB as related to trial treatment. The DSMB will report its recommendations to the sponsor and the Scientific Committee, for taking a decision about trial termination.

14.3 Methodology and study management Centre (CMG Inserm UMR S 1136)

A methodology and study management centre (CMG Inserm UMR S 1136) will be assigned by the sponsor in order to ensure good clinical practices.

14.3.1 Composition

The members will be chosen among the participating researchers in the current trial and include at least, the following members:

Methodologists: Dominique COSTAGLIOLA and Lambert ASSOUMOU

Project Manager / Clinical Trial Monitors: Lydie BENIGUEL, Josiane AKO and Jérémy LAFABLE

Statistician: Clément GUIHENEUF

14.3.2 Role

CMG Inserm UMR S 1136 is located in Paris. His objective is to ensure the quality of the trial and to discuss and analyze all the relevant clinical and scientific aspects.

The CMG Inserm UMR S 1136 prepares the implementation of the research, coordinates the logistics, data management and statistical analysis.

The CMG Inserm UMR S 1136 is responsible for the quality of data and computer databases.

It prepares the research status and files for the pooled analysis for the Scientific Committee. It informs the Scientific Committee of the conduct of the research, prepares the general meetings of investigators' meetings.

15 CONTROL AND DATA MANAGEMENT

The CMG Inserm UMR S 1136 will be responsible for the data management of the trial. It will be responsible to design and develop an eCRF for data management. The Clinsight software will be used for the management of the data. The eCRF will be developed from the model of the exercise book of observation made by the UMR S 1136 and validated by the Coordinating Investigator and the sponsor. Access to the eCRF will be limited to the trial participants. A specific profile will be assigned to the participants according to their role in the trial. An identifier and password will be provided to the participants by the CMG Inserm UMR S 1136 (must be changed at the first connection).

15.1 Data transfer to CMG Inserm UMR S 1136

The site principal investigator will be responsible for the completion of the eCRF according to SOP. eCRF will be completed according to the source records by the investigator or an appointed representing. Data will be recorded onto the eCRF, which will provide the majority of source data for the trial. There will be some additional source data in the clinical notes, such as medical history related to eligibility, dates of visits, results of pregnancy tests, and details of clinical management (description of adverse events and concomitant medication).

Data will be collected and validated under the responsibility of the principal investigator of each site.

Staff at the clinical centres will be responsible for:

- Entering relevant information in the clinical notes, and holding a record for each participant which includes the eCRF.
- The accurate completion of the eCRF.
- The prompt return of the copy of biological results (CD4, Viral load, biological results of the screening visit, reports for specific diagnosis of primary endpoint infections as specified in the eCRF) to CMG Inserm UMR S 1136.
- Notification of SAEs in the eCRF as soon as they become aware of the event.

At the end of the trial every eCRF pages must be filled, locked by the investigator or its representative, monitored by the project manager of CMG Inserm UMR S 1136 and signed by the investigator who followed the patient.

Every data for each patient will be printed in PDF and stored onto a CD (Compact Disc) and given to the principal investigator of the site by the CMG Inserm UMR S 1136.

15.2 Data control

15.2.1 Electronic control of the data

The data manager or their deputy will review all data entered in the eCRF, as they arise. Queries raised will be directed to the investigators at the relevant clinical site using the dedicate tool of the eCRF or during a monitoring visit. Prior to analysis, the safety data will be checked, AEs validated and data extracted in order for the trial statisticians to run the analysis and prepare the tables.

15.2.2 Data control in the clinical site

Before starting the trial, the CMG Inserm UMR S 1136 will establish the monitoring plan that will be sent to the trial sponsor (Inserm-ANRS). The monitoring plan may be amended during the trial based on the dynamic of inclusions.

15.2.3 Participants in charge of study monitoring

Monitoring will be done by the CMG project manager from CMG Inserm UMR S 1136 mandated by the sponsor in accordance with the regulations and recommendations of Good Clinical Practice. At any time, the CRA or project manager in charge of the trial can be contacted for any questions regarding the protocol and its practical application.

15.2.4 Monitoring of the trial

An investigator meeting with at least one representative in each participating centre will be held before starting the trial. Staff from CMG Inserm UMR S 1136 in charge of trial monitoring will visit the clinical centres. The first visit will be to open the centre. This opening visit will be held before any screening in the centre. During this visit, the CMG project manager will give to investigators all documents needed for starting the trial: Protocol, Manual for the use eCRF, and all procedures. Participants (clinical centres and laboratories members) in each centre must be present during the opening visit.

All monitoring visits will be done in the centres with at least one patient included and will take place according to the monitoring plan established by the CMG Inserm UMR S 1136. The first monitoring visit will take place within the first three months after the first inclusion in the centre.

the CMG Inserm UMR S 1136 projet manager in charge of the monitoring is responsible for to validate data entered in the eCRF against the clinical records. The site principal investigator and participants, by giving consent, agree that the CMG Inserm UMR S 1136 may consult and/or copy source records (clinical notes and laboratory values) in order to do this. Such information will be treated as strictly confidential and will in no circumstances be made publicly available. The monitoring will adhere to ICH GCP guidelines.

The volume of data that will be collected allows us to plan only a control of 100% of the baseline data and 100% of the data used as endpoints in 100% of patients.

However, particular attention will be paid to the following data:

- Signed consent
- Documentation of any existing conditions or past conditions relevant to eligibility
- Dates of visits
- Laboratory results
- Grade 3 or 4 AEs and any events leading to trial treatment discontinuation
- Date of trial treatment discontinuation, date of giving up, and date of consent withdrawal

A Closing visit will take place in each of the centres in which at least one patient has been selected at the end of the trial.

15.3 Auditing

An audit can be performed at any time by persons representing the sponsor and independent from the research. Its objectives are to ensure the quality and follow-up of the research, data consistency and local regulations in force.

The sponsor's as well as the investigational products' suppliers' Quality Assurance Units (or representatives) may conduct audits at the trial site(s). Audits will include, but are not limited to, drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The investigator agrees to participate with audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may also inspect the investigator during or after the trial. The investigator should contact the sponsor immediately if this occurs, and must fully cooperate with the inspections conducted at a reasonable time in a reasonable manner.

16 STATISTICAL CONSIDERATIONS

16.1 Patients sample calculation

ANRS 163 ETRAL is a non-comparative phase II trial evaluating in HIV-1-infected patients, of at least 45 years of age, switching from a virologically suppressive boosted PI-containing regimen the capacity of a dual raltegravir/etravirine regimen to maintain the virological success as defined by the absence of 2 consecutive HIV-RNA plasma VL > 50 copies/mL within 2 to 4 weeks.

Raltegravir/etravirine will be considered acceptable if the percentage of patients in virological success at week 48 is significantly above 90 %.

Assuming a 95 % virological success rate, by including **160 individuals** and considering the strategy to be acceptable if no more than 8 individuals have virological failure; we will have a 95 % probability to discard a

combination for which efficacy is smaller than 90 % and we will select with a power of 80 % the strategy for which the efficacy is above or equal to 95 %.

16.2 Statistical analysis

16.2.1 Criteria for evaluation

All enrolled patients receiving at least one day of trial treatment will be included in the intent-to-treat (ITT) population. Patients who withdrew their consent will be excluded in the ITT population. The per-protocol population will include all patients from the ITT population except those who did not fulfil the inclusion criteria or discontinued trial treatment without virologic failure or adverse event as judged by the DSMB as related to trial treatment or procedure.

16.2.2 Statistical methods

The primary endpoint is the virological success up to week 48 defined by the absence of 2 consecutive HIV-RNA plasma VL > 50 copies/mL within 2 to 4 weeks.

The therapeutic success is defined by the absence of virological failure and the absence of treatment interruption due to adverse event judged by DSMB as related to the trial treatment or procedure up to week 96.

In particular:

- Patients with 2 or more consecutive missing HIV-1 RNA plasma viral load values or lost to follow up will be considered as patients with treatment failure (failing patients).
- Patients who discontinue the treatment due to adverse event judged by DSMB as related to the trial treatment or procedure will be considered as failing patients.
- Patients who discontinued the treatment due to adverse event judged by DSMB as NOT related to the trial treatment or procedure will not be considered as failing patients.
- Patients who gave up will not be considered as failing patients.
- Patients who discontinued the trial treatment for any reason other than a virological failure or adverse event judged by DSMB as related to the trial treatment will not be considered as failing patients.
- Patients with a missing HIV-1 RNA value between 2 documented HIV-1 RNA plasma viral loads ≤ 50 copies/mL will not be considered as failing patients.

Analysis of the primary endpoint will be performed on both ITT and per protocol populations. The 95% two-sided confidence interval of the percentage of patients in therapeutic success will be calculated and raltegravir/etravirine will be considered as an acceptable strategy if the lower bound is greater than 90%.

The changes in continuous endpoints will be compared in the ITT population (LOCF of other imputation method to be defined in the statistical analysis plan) using a two-sided non-parametric paired Wilcoxon test with a 5 % type I error. We will use percentage and 95 % two-sided confidence interval to describe the qualitative endpoints, their change over time will be tested a McNemar test with a 5 % type I error.

The adverse events leading to a trial treatment discontinuation and the number of patients who discontinued the trial treatment, as well as the number and nature of grade 3 and 4 adverse events will be described.

16.2.3 Statistical analysis plan

The number of included patients and the flowchart of the trial will be presented.
The baseline patients' eligibility and characteristics of the ITT population will be described. Quantitative variables will be described by their means, standard deviations, medians, IQR, minimums and maximums. For qualitative variables, figures and percentages per class will be presented or method will be given. All protocol deviations and their reasons will be described.

A detailed statistical analysis plan will be written prior to any analysis of the trial results.

16.2.4 Software programs used

The analyzes are performed with the software <SAS® /logiciel SPSS®/logiciel STATA® > (version n° 9.4 and later versions).

17 PUBLICATION

The results of the trial (positive or negative) must be made publicly available. The President of the Scientific Committee (Pr Christine Katlama) is responsible for publication of the trial results.
All publications shall include a list of participants (the investigators mentioned above), and if there are named authors, these should include the main persons responsible for the trial including the Study coordinator (Christine Katlama, Jacques Reynes) and the Methodology and Study Management Coordinator (Dominique Costagliola) and its results.
If there are no named authors (i.e. group authorship) then a writing committee is identified that would usually include these people.
The principles of generally accepted specifications for authorship shall be followed in the appointing of authors and co-authors. All contributors to a specific publication (abstracts or original studies) have a true opportunity for full evaluation of the final text before submission to a scientific meeting or an editor.
Inserm-ANRS will review any abstract, poster, communication or publication written on this trial.
The results from different centres are analysed together and published as soon as possible. Individual clinicians must not publish data concerning their patients that are directly relevant to questions posed by the trial until the report of the overall results of the trial has been published.
The trial identifier that has been allocated to this trial (ANRS 163 ETRAL), as well as the name of the sponsor, Inserm – ANRS, should be attached to any publications resulting from this trial.
The sponsor agrees to include in all scientific publication-type communications and in all submissions to scientific conferences or to the media the following type of notice: “Trial conducted with the support of Merck and Janssen”.
The members of the Scientific Committee and DSMB are to be listed with their affiliations in the Acknowledgements/Appendix of the main publication.
Any publication has to be reviewed by ANRS 163 ETRAL Scientific Committee.

18 ETHICS AND REGULATORY ISSUES

18.1 Ethical and regulatory aspects

Before the initiation of this trial, regulatory approval by the National Competent Authorities and local Ethical Committees or Institutional Review Boards is obtained for conduct of the trial (see appendices A2 and A3).
The trial only starts after written approval from an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) that operates according to ICH GCP guidelines. The written IEC/IRB approval and the names and qualifications of members of the IEC/IRB must be made available to the legal sponsor before the trial can start. The sponsor or its delegate is, together with the investigator, responsible for submission to and communication with the IEC/IRB as well as for obtaining approval of all subsequent major changes, in compliance with local law.
The investigator should conduct the trial in in accordance with this protocol, the declaration of Helsinki (version 2013) and the ICH GCP guidelines. .

18.2 Participant consent (cf. information note and consent)

Each participant’s consent to participate in the trial should be obtained after a full explanation has been given about the trial. The right of the patient to refuse to participate in the trial without giving reasons must be respected. The patient must remain free to withdraw at any time from the protocol and follow-up without giving reasons and without prejudicing his/her further care.
Consent from the patient participating to the trial has to be signed BEFORE any related trial procedures. If consent is given, the patient and the investigator write both their name in all letters and date and sign.
The consent form will consist of three sheets.
The first sheet will be kept by the investigator for at least 15 years.
The second sheet on which the names and signature of the patient are hidden will be faxed to CMG Inserm UMR S 1136 at the screening date.
The last sheet attached to the information note is intended to the patient. If the patient refuses to take his copy, the investigator must report this information in the eCRF and in the patient's source document. The patient's consent must be sealed in an individual envelope signed by the principal investigator or its

representative and must be kept in the investigator's document ANRS 163 - ETRAL Version n° 1.0 dated 10/03/2014appendix A5.
For any amendment to the Protocol that modifies the care of the participant, a new information note must be given to the participant and a new consent form must be collected based on the same procedure described above.

18.3 Data confidentiality

Individual subject medical information, obtained as result of this trial is considered confidential and disclosure to third parties is prohibited. Such medical information may be given to the subject's physician or to other appropriate medical personnel responsible for the subject's well being.
Data generated as a result of this trial are anonymised and are to be available for inspection on request by the participating physicians, the sponsor's monitor, the IEC/IRB and the regulatory health authorities, including external site audits and inspections.
During the trial, data that will be collected for any patients in the trial must never clearly mentioned any information (names, address, etc...) which could allow to identify him easily. For this reason, each patient will be assigned an identification code in the trial (*cf patient identification*).

18.4 Data collection

During each patient visit to the clinic/hospital, a clinician participating in the trial will record progress notes to document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revised consents;
- Demographic data (date of birth, sex, ethnic group);
- Details related to the inclusion criteria;
- Medical history and physical examination details;
- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General subject status remarks, including any significant medical findings. The severity, frequency, and duration of any adverse experiences and the investigator's assessment of relationship to study drug must also be recorded;
- Any changes in concomitant medications or dosages;
- Results of relevant examinations;
- Laboratory print-outs;
- A general reference to the procedures completed;

Information from the trial progress and other source documents have to be promptly entered into the eCRF for each patient. The reported information in the eCRF and the name of the person who completed the eCRF will be automatically stored and dated.

Any information changes in the eCRF will be saved with the name of the person who made the correction to assure a data tracking.

18.5 Amendment policy

The investigator will not make any changes to this protocol without prior written consent from the sponsor and subsequent approval by the IRB/IEC.
Any permanent change to the protocol, whether it be an overall change or a change for specific trial centre(s), must be handled as a protocol amendment. Any amendment to the protocol that appears indicated as the trial progresses will be fully discussed by the investigator(s) and the sponsor.
A "substantial amendment" is defined as an amendment to the terms of the IEC/IRB application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial,
- the scientific value of the trial,
- the conduct or management of the trial, or
- the quality or safety of any intervention used in the trial.

If agreement is reached regarding the need for an amendment, it will be written by the sponsor. The written amendment must be submitted to the chairman of the IRB/IEC identified with this responsibility.
Except for "non-substantial amendments", investigators must await IRB/IEC approval of protocol amendments before implementing the change(s).

Non-substantial amendments are only notified to the accredited IEC/IRB and competent authority, and are recorded and filed by the sponsor.
Examples of non-substantial amendments are typing errors and administrative changes like changes in names, telephone numbers and other contact details of involved persons mentioned in the submitted trial documentation.

When, in the judgment of the chairman of the local IRB/IEC, the investigators and/or the sponsor, the amendment to the protocol substantially alters the trial design and/or increases the potential risk to the subject, the currently approved written informed consent will require similar modification. In such cases, repeat informed consent will be obtained from subjects enrolled in the trial before expecting continued participation.

18.6 Insurance

Inserm-ANRS will provide insurance (HDI Gerling, tours opus 12, 77 Esplanade de la Défense 92914 PARIS LA DEFENSE) for individual patient's for the period of the trial (see Appendix A3) from France and Spain and covering its civil liability in conformance with applicable legal and regulatory requirements.
Each clinical centre will be responsible for ensuring that cover is in place for harm due to clinical negligence caused by their employees to a trial participant.

18.7 Redaction of the final report

The final report of the research and its summary will be prepared by the CMG Inserm UMR S 1136, the sponsor Inserm-ANRS and the coordinating investigator.
These documents should be prepared in accordance with the recommendations of the International Conference on Harmonization (International Conference for Harmonization - ICH Topic E3 - Structure and Content of Clinical Study Reports CPMP/ICH/137/95).
The final report should be established within the year following the end of the trial and will be addressed to the competent authorities by the sponsor (Inserm - ANRS).

18.8 Archiving

The trial documentation includes the following documents:
- Trial protocol (and amendments)
- Subject Information documents (including Informed Consent)
- SAE report forms
- eCRF
- Questionnaires
- Investigator's File
- Trial contracts

In order to start the trial, the investigator is required to have the following documentation available:
- Signed investigator statement for this protocol,
- Signed trial contracts,
- IEC approval letter, stating the sponsor's name, trial number, as well as all documents reviewed and should include a list of members present at the meeting,
- Recent CVs of investigators and sub investigators (signed and dated),
- Signature sheet, documenting delegation of tasks and names and initials of the investigator team,
- Regulatory approval,
- Laboratory normal ranges and quality certificates and/or accreditations.

At the end of the trial every eCRF pages must be filled, locked by the investigator or its representative, monitored by the CMG Inserm UMR S 1136 project manager and signed by the investigator who followed the patient.
Every data for each patient will be printed in PDF and stored onto a CD (Compact Disc) and given to the principal investigator of the site by the CMG Inserm UMR S 1136.
The investigator archives all trial data (subject ID code list, source data, CD storing the eCRF, and Investigator File) and relevant correspondence in a secure location. These documents are to be kept on file for at least 15 years after completion of the trial or another time period as specified by local laws.
Consents for the sponsor will be sealed in an inviolable envelope signed by the principal investigator or its representative.
On each consent form will be reported the patient anonymous code.

After this 15 years' period, trial documents can be discarded by the trial site after sponsor's written approval.

19 DATA ACCESS

All material collected under the protocol, that is to say, the research data and biological samples is placed at the beginning of the research under the responsibility of the CMG Inserm UMR S 1136. It remains under its responsibility throughout the research and beyond in case of research data, after dissolution of the Scientific Committee, unless otherwise decided by the sponsor.

20 INVESTIGATOR DUTIES

In accordance with good clinical practices and to ensure the quality of research, each investigator will:

- Respect the rights of participants and ensure their safety and well-being,
- Ensure that the whole team and himself remain available,
- Ensure that its recruitment possibilities are compatible with the conduct of research,
- Take responsibility for organizing the technical structures for the implementation of circuits specific research (consultations, samples) and archiving of documents during the duration of the research and for fifteen (15) years after the end of the research,
- Collect and store the written consent of the participants in a safe place,
- Ensure compliance with the protocol and to ensure the quality of data in the eCRF: Biological results should be submitted to the CMG UMR S 1136 within a maximum of ten (10) days after the visit of the participant,
- Immediately inform the CMG UMR S 1136 if serious adverse events occur during the research, as described in the protocol (see chapter safety)
- Allow regular monitoring of research by a representative of the CMG Inserm UMR S 1136 and access to the source documents for validation of data reported in the eCRFs.

  At any time, the CMG Inserm UMR S 1136 project manager or coordinating investigator can be contacted for any questions regarding the protocol, its application in practice or actions to take with certain events,
- Accept any audit of research by the sponsor directly or with his authorization by other organizations,
- Accept the inspection of research by health authorities.

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APPENDICES

Appendices A

Appendix A1: ***Ethical Committee or Institutional Review Board Approval***

Appendix A2: ***National Competent Authorities authorization***

Appendix A3: ***Insurance***

Appendix A4: ***Declaration of Helsinki (Version 2013)***

Appendix A5: ***Information and consent (in french)***

Appendix A6: ***ANRS scale to grade the severity of adverse events in adults***

Appendix A7: ***Recommendations for blood pressure measurement in humans and experimental animals***

Appendix A8: ***Women substudy***

Appendices B (separate appendices)

Appendix B1: ***Investigator's sites***

Appendix A1: ***Ethical Committee or Institutional Review Board Approval***

CPP - Ile-de-France VI
Groupe Hospitalier Pitié-Salpêtrière

CPP n° 26-14
EudraCT : 2014-000828-24

A Paris, le 18 avril 2014

Le comité a été saisi le : 10 mars 2014

d'une demande d'avis pour le projet de recherche intitulé :

« A non-comparative phase II trial evaluating the capacity of the dual combination raltegravir/etravirine to maintain virological success in HIV-1 infected patients of at least 45 years of age with an HIV-RNA plasma viremia below 50 copies/mL under a current boosted protease inhibitor containing regimen » Protocol 163 ETRAL

. Protocole 163 ETRAL du 7/3/14
. Note d'information et formulaire de consentement du 7/3/14
. Liste des investigateurs du 7/3/14

dont le promoteur est : **Inserm - ANRS**

dont le coordinateur est : **Professeur C. KATLAMA**

Le comité a examiné les informations relatives à ce projet lors de sa séance du :

16 avril 2014

Ont participé à la délibération :

Nathalie BRION - Thérapeute (S)
Laurent CAPELLE - Neurochirurgien (T)
Christophe DEMONFAUCON - Représentant des associations agréées de malades (T)
Micheline DENANCE - Représentante des associations agréées d'usagers du système de santé (S)
Marie-Hélène FIEVET - Pharmacien hospitalier (T)
Anne-Marie FONCELLE - Qualifiée en matière juridique (S)
Clarisse GOUDIN - Qualifiée en matière juridique (S)
Gilles HUBERFELD - Neurologue (S)
Nathalie JOUNIAUX-DELBEZ - Psychologue hospitalier (S)
Christiane LOOTENS - Représentante des associations agréées de malades (S)
Marie-Cécile MASURE - Psychologue hospitalier (T)
Anne-Laure MORIN - Qualifiée en matière juridique (T)
Thang NGUYEN - Médecin généraliste (T)
Sophie TEZENAS DU MONTCEL - Biostatisticien (T)
Dominique VARIN - Médecin généraliste (S)

LE COMITE A ADOPTE LA DELIBERATION SUIVANTE : AVIS FAVORABLE

. Motivation : Le comité a estimé que le rapport bénéfice/risque est acceptable pour les sujets participant à la recherche.

. Conformément à l'article R. 1123-28 du code de la santé publique, le présent avis devient caduque si la recherche n'a pas débuté dans un délai d'un an.

Le Président du CPP
Docteur Laurent CAPELLE

CPP IDF VI 47, Boulevard de l'Hôpital 75013 PARIS
Tél:0142161683 Fax:0142162715

CPP - Ile-de-France VI
Groupe Hospitalier Pitié-Salpêtrière

Projet de recherche enregistré
Sous le n° 26-14
EudraCT : 2014-000828-24

A Paris, le 15 mai 2015

Documents soumis à l'approbation du comité :
. **Protocole 163 ETRAL du 18/3/15**
. **Note d'information et formulaire de consentement du 18/3/15**

Le comité a été saisi le : 24 mars 2015

d'une demande d'avis pour les documents ci-dessus référencés relatifs au protocole intitulé :

« A non-comparative phase II trial evaluating the capacity of the dual combination raltegravir/etravirine to maintain virological success in HIV-1 infected patients of at least 45 years of age with an HIV-RNA plasma viremia below 50 copies/mL under a current boosted protease inhibitor containing regimen » Protocol 163 ETRAL

dont le promoteur est : **Inserm - ANRS**

dont le coordinateur est : **Professeur C. KATLAMA**

Le comité a examiné les informations relatives à ce projet lors de sa séance du :

13 mai 2015

Ont participé à la délibération :
Odile BALAND - Infirmière (T)
Magali BOUVIER - Qualifiée en matière juridique (T)
Laurent CAPELLE - Neurochirurgien (T)
Christophe DEMONFAUCON - Représentant des associations agréées de malades (T)
Micheline DENANCE - Représentante des associations agréées d'usagers du système de santé (S)
Marie-Hélène FIEVET - Pharmacien hospitalier (T)
Anne-Marie FONCELLE - Qualifiée en matière juridique (S)
Marie GICQUEL-BENADE - Travailleur social (T)
Clarisse GOUDIN - Qualifiée en matière juridique (S)
Gilles HUBERFELD - Neurologue (S)
Nathalie JOUNIAUX-DELBEZ - Psychologue hospitalier (S)
Annie LE FRANC - Représentante des associations agréées de malades (T)
Christiane LOOTENS - Représentante des associations agréées de malades (S)
Marie-Cécile MASURE - Psychologue hospitalier (T)
Michèle MEUNIER-ROTIVAL - Chercheur en génétique (S)
Thang NGUYEN - Médecin généraliste (T)
Sophie TEZENAS DU MONTCEL - Biostatisticien (T)

LE COMITE A ADOPTE LA DELIBERATION SUIVANTE : AVIS FAVORABLE

Le Président du CPP
Docteur Laurent CAPELLE

CPP IDF VI 47, Boulevard de l'Hôpital 75013 PARIS
Tél : 01 42 16 16 83 Fax : 01 42 16 27 15

CPP - Ile-de-France VI
Groupe Hospitalier Pitié-Salpêtrière

Projet de recherche enregistré
Sous le n° 26-14
EudraCT : 2014-000828-24

A Paris, le 6 mars 2018

Documents soumis à l'approbation du comité :
. Amendement n°2 du 19/1/18
. Liste des investigateurs du 24/1/18

Le comité a été saisi le : 31 janvier 2018

d'une demande d'avis pour les documents ci-dessus référencés relatifs au protocole intitulé :
« A non-comparative phase II trial evaluating the capacity of the dual combination raltegravir/etravirine to maintain virological success in HIV-1 infected patients of at least 45 years of age with an HIV-RNA plasma viremia below 50 copies/mL under a current boosted protease inhibitor containing regimen » Protocol 163 ETRAL

dont le promoteur est : **Inserm - ANRS**

dont le coordinateur est : **Professeur C. KATLAMA**

Le comité a examiné les informations relatives à ce projet lors de sa séance du :

21 février 2018

Ont participé à la délibération :
Kevin BIHAN - Pharmacien hospitalier (S)
Nathalie BRION - Thérapeute (T)
Laurent CAPELLE - Neurochirurgien (T)
Christophe DEMONFAUCON - Représentant des associations agréées de malades (T)
Micheline DENANCE - Représentante des associations agréées d'usagers du système de santé (S)
Jacqueline DUNO - Qualifiée en matière juridique (S)
Marie-Hélène FIEVET - Pharmacien hospitalier (T)
Cloé GIQUEL - Qualifiée en matière juridique (S)
Nathalie JOUNIAUX-DELBEZ - Psychologue hospitalier (S)
Annie LE FRANC - Représentante des associations agréées de malades (T)
Christiane LOOTENS - Représentante des associations agréées de malades (S)
Marie-Cécile MASURE - Psychologue hospitalier (T)
Michèle MEUNIER-ROTIVAL - Chercheur en génétique (T)
Marie-Caroline MEYOHAS - Qualifiée en matière éthique (T)
Anne-Laure MORIN - Qualifiée en matière juridique (T)
Sabine PLANCOULAINE - Biostatisticien (S)
Martyna TOMCZYK - Qualifiée en matière éthique (S)

LE COMITE A ADOPTE LA DELIBERATION SUIVANTE : AVIS FAVORABLE

Le Président du CPP
Professeur Nathalie BRION

CPP IDF VI 47, Boulevard de l'Hôpital 75013 PARIS
Tél : 01 42 16 16 83 Fax : 01 42 16 27 15

Appendix A2: ***National Competent Authorities authorization***

ANSM/INFHEP 04-04-14 11:39 Pg: 1/1

ansm
Agence nationale de sécurité du médicament et des produits de santé

AUTORISATION D'ESSAI CLINIQUE DE MEDICAMENT A USAGE HUMAIN

Nombre de pages : 1
(incluant la page de garde)

Envoi par Télécopie

Date : 04 AVR. 2014

Identifiants de l'essai clinique					
Titre	A non-comparative phase II trial evaluating the capacity of the dual combination raltegravir/etravirine to maintain virological success in HIV-1 infected patients of at least 45 years of age with an HIV-RNA plasma viremia below 50 copies/mL under a current boosted protease inhibitor containing regimen.				
Promoteur	Inserm-ANRS			Réf. CPP	
Réf. Promoteur	ANRS163 (ETRAL)	N° EudraCT	2014-000828-24	Réf. ANSM	140304A-41

Expéditeur
ANSM / Direction Produit INFHEP / Equipe maladies infectieuses
Dossier suivi par : Stéphanie Vallet Tél : 33 (0) 1 55 87 36 57 / Fax : 33 (0) 1 55 87 34 02

Destinataire (demandeur : nom / société / tél.)	
Anne-Laure ARGOUD ANRS 331 44236027	
Fax	331 53 94 60 02

CPP destinataire en copie	Ile-de-France VI (Paris-La-Pitié)	Fax	01.42.16.27.15	Code 30

Vu le code de la santé publique et notamment ses articles L. 1123-8, L. 1123-12 et vu le dossier de demande d'autorisation d'essai clinique adressé à l'Agence nationale de sécurité du médicament et des produits de santé (ANSM) ;

L'autorisation mentionnée à l'article L. 1123-8 du code de la santé publique est accordée pour l'essai clinique cité en objet. Cette autorisation est valable pour toute la durée de l'essai à compter de la date de la présente décision.

Toutefois, conformément à l'article R. 1123-33 du code de la santé publique, la présente autorisation devient caduque si la recherche n'a pas débuté dans un délai d'un an.

La directrice
Direction des médicaments anti-infectieux, en hépato-gastro-entérologie, en dermatologie et des maladies métaboliques rares

Caroline SEMAILLE

Je vous demande de transmettre toute demande d'informations complémentaires concernant ce dossier par courriel adressé à la boite : aec-essaisclinigues@ansm.sante.fr . Je vous précise qu'il vous est possible d'utiliser à cet effet le système de messagerie électronique sécurisée Eudralink. Lors de l'envoi de ces dossiers, je vous demande de veiller à reporter dans l'objet du message les mentions suivantes :
- pour les MS transmises à l'ANSM pour information : **MSI/ Réf ANSM du dossier**
- pour les MS soumises pour autorisation ou pour les dossiers mixtes (comportant des modifications soumises pour autorisation et d'autres pour information) : **MSA/ Réf ANSM du dossier**

Si vous ne recevez pas toutes les pages de cette télécopie, veuillez contacter le secrétariat de la Direction Produit INFHEP / Equipe maladies infectieuses au : 33 (0) 1 55 87 34 04.

143/147, bd Anatole France - F-93285 Saint-Denis cedex - tél. +33 (0)1 55 87 30 00 - www.ansm.sante.fr Page 1 sur 1

ansm
Agence nationale de sécurité du médicament et des produits de santé

AUTORISATION DE MODIFICATION (S) SUBSTANTIELLE (S) D'ESSAI(S) CLINIQUE(S) DE MEDICAMENT A USAGE HUMAIN (AMS)

Nombre de pages : 1
(incluant la page de garde)

Envoi par Télécopie

Date : 27 AVR. 2015

Identifiants de la (des) modification(s) et du (des) essai(s) concerné(s)

Promoteur	Inserm-ANRS		
Réf. Essai(s)		Réf. Modification(s)	
N° EudraCT	Réf. ANSM	Réf. ANSM	Réf. Promoteur (item E.1 du formulaire de demande d'AMS)
2014-000828-24	140304A-41	140304M-4101	ANRS 163 ETRAL version 2.0 du 18/03/2015

Expéditeur

ANSM / Direction Produit INFHEP / Equipe maladies infectieuses

Dossier suivi par : Armelle Tourbez / Joanna Guirao
Tél : 33 (0) 1 55 87 37 41 / Fax : 33 (0) 1 55 87 34 02

Destinataire (demandeur : nom / société / tél.)

Anne-Laure ARGOUD
ANRS
331 44236027

Fax **01 53 94 60 02**

Vu le code de la santé publique et notamment l'article L. 1123-9 et vu la ou les autorisations d'essais cliniques délivrées par l'Agence nationale de sécurité du médicament et des produits de santé (ANSM) pour le ou les essais cliniques ci-dessus référencés ;

Vu le dossier de demande d'autorisation de modification(s) substantielle(s) adressé à l'ANSM ;

L'autorisation mentionnée à l'article L. 1123-9 du code de la santé publique est accordée pour la (les) modification(s) substantielle(s) identifiée ci-dessus, pour les aspects relevant de la compétence de l'ANSM.

Le chef produits maladies infectieuses
Direction des médicaments anti-infectieux, en hépato-gastro-entérologie, en dermatologie et maladies métaboliques rares

Nathalie MORGENSZTEJN

Je vous demande de transmettre toute demande d'informations complémentaires concernant ce dossier par courriel adressé à la boite : **ams-essaiscliniques@ansm.sante.fr** . A cet égard, je vous précise qu'il vous est possible d'utiliser le système de messagerie électronique sécurisée Eudralink. Je vous demande alors de veiller à reporter dans l'objet du message uniquement les mentions suivantes :

- pour les MS transmises à l'ANSM pour information : **MSI / Réf ANSM du dossier** ;
- pour les MS soumises pour autorisation ou pour les dossiers mixtes (comportant des modifications soumises pour autorisation et d'autres pour information) : **MSA / Réf ANSM du dossier** .

Si vous ne recevez pas toutes les pages de cette télécopie, veuillez contacter le secrétariat de la Direction Produit INFHEP / Equipe maladies infectieuses au : 33 (0) 1 55 87 34 04.

Appendix A3: ***Insurance***

Biomedicinsure
COURTIER EN ASSURANCES
Parc d'Innovation Bretagne sud
C.P. 142 - 56038 VANNES CEDEX
Tel. +33(0)2 97 69 19 19
Fax +33(0)2 97 69 11 11
biomail@biomedic-insure.com

HDI GERLING

ATTESTATION D'ASSURANCE
RESPONSABILITE CIVILE
PROMOTEUR DE RECHERCHE BIOMEDICALE

CONTRAT n°
0100846414031 - 140009 - 10998

Nous, soussignés HDI-GERLING - TOUR OPUS 12, 77, Esplanade de la Défense 92914 PARIS LA DEFENSE agissant en qualité d'assureur, attestons par la présente que :

INSERM-ANRS
101 rue de Tolbiac
75013 PARIS

a souscrit un contrat de Responsabilité Civile sous le numéro ci-dessus référencé.

Ce contrat est conforme aux dispositions légales et réglementaires Françaises sur les recherches biomédicales et notamment aux dispositions de la loi 88.1138 du 20/12/1988, modifiée par les textes subséquents: loi 90.86 du 23/01/1990, décret 91-440 du 14/05/1991, loi 94.630 du 25/07/1994, décret 97-888 du 01/10/1997, décret 2002-722 du 03/05/2002, loi 2004.806 du 09/08/2004, décret 2006-477 du 26/04/2006.

Description précise de la recherche assurée :

Essai pilote de phase II non comparatif évaluant la capacité de la combinaison raltégravir+étravirine à maintenir le succès virologique chez des patients infectés par le VIH-1, âgés d'au moins 45 ans, avec une charge virale plasmatique inférieure à 50 copies/mL sous un traitement antirétroviral comportant un inhibiteur de protéase boosté.
Protocole n° ANRS 163 ETRAL

La garantie est conforme à l'obligation d'assurance instituée par les textes de la loi précitée, article L 1121-10 du Code de la Santé Publique, à la charge du promoteur, tant pour sa responsabilité que pour celle des intervenants.

La garantie prévue au contrat restera acquise à l'Assuré en cas de modification affectant la prise d'effet du protocole.

La présente attestation est valable pour la durée de la recherche concernée et sa présentation vaut présomption de garantie à la charge de l'assureur.

Fait le 10 mars 2014

Biomedicinsure
COURTIER EN ASSURANCES

Le Courtier
BIOMEDIC INSURE
Parc d'Innovation Bretagne sud
C.P. 142 - 56038 VANNES CEDEX
Jean-Pierre DANIEL
Fax +33(0)2 97 69 11 11
biomail@biomedic-insure.com

L'Assureur
HDI-GERLING INDUSTRIES
HDI-Gerling Industrie Versicherung AG
Capital 125.000.000 EUR
TOUR OPUS 12 - LA DEFENSE 9
77, Esplanade du Général de Gaulle
F 92914 PARIS LA DEFENSE CEDEX
Tél. : +33 1 44 05 56 00 - Fax : +33 1 44 05 56 66

HDI Gerling Industries Versicherungs-AG
Direction pour la France
TOUR OPUS 12 – LA DEFENSE 9
77, Esplanade du Général de Gaulle
F 92914 PARIS LA DEFENSE CEDEX
Téléphone : +33 (0) 1 44 05 56 00
Télécopie : +33 (0) 1 44 05 56 66
Web : www.hdi-gerling.com

75/2014
Entreprise privée régie par le Code des Assurances
R.C.S. Nanterre 478 913 882

Siège social : HDI-Gerling Industrie Allgemeine Versicherungs-AG,
Capital : 125 000 000€
Riethorst 2 - 30659 Hannover
Téléphone : 00 49 511 3747-0
Télécopie : 00 49 511 3747 2525

Appendix A4: ***Declaration of Helsinki (Version 2013)***

WMA Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

4.1.1 Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

4.1.2 General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive,

diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

4.1.3 Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

4.1.4 Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

4.1.5 Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

4.1.6 Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

4.1.7 Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

4.1.8 Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician

must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

4.1.9 Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

4.1.10 Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

4.1.11 Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

4.1.12 Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

France REcherche Nord & sud Sida-hiv Hépatites
Agence autonome de l'Inserm

ANRS 163 ETRAL Trial

Information notice

Non-comparative phase II pilot trial to evaluate the ability of a combination of raltegravir + etravirine to maintain virological success in HIV-1-infected patients of at least 45 years of age with a plasma viral load of less than 50 copies/mL on antiretroviral therapy including a boosted protease inhibitor.

Version 2.0, dated 03/18/2015, approved by the CPP on 05/15/2015

Coordinating Investigator:

Prof. Christine Katlama, Pitié-Salpêtrière Hospital, Paris.

Scientific Director:

Prof. Jacques Reynes, Montpellier University Hospital.

Trial Sponsor:

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

- This notice is designed to help you decide whether or not to participate in the trial described below.
- You are free to answer yes or no to the question asked: do you want to participate in the trial?
- You have the right to take as much time as you need to think about it, to discuss this trial and to ask anyone you want whatever you want to know about it.
- If you do not wish to participate, you will still continue to receive the best possible care
- You can change your mind at any time and ask to withdraw from the trial. You will continue to benefit from the best care that your doctor can offer you. We ask only that you inform your doctor of your decision as soon as possible.

The words underlined in the text are explained in the glossary.

Glossary

Biobank: A bank of biological samples kept for research purposes.

Data: Information collected as part of the trial.

Right of access: The right to see the data concerning you.

Anonymized data: Your name and surname are removed from all medical records and replaced with a code. Only the doctor and people with a right of access to the medical data are aware of the link between your identity and this code.

Right of opposition: The right to oppose the transmission of your data by the investigating doctor to the sponsor. The exercise of this right terminates your participation in the trial.

Right of rectification: The right to request that the correction of your data in the event of an error.

Samples: Samples taken from people participating in the trial (e.g. blood, cells, etc.). In general, the samples are stored in a **Biobank** centralized at the ANRS.

Consent form: A document in which you declare that you have read the terms of participation in the trial and give your consent to participate.

Coordinating investigator: The doctor supervising the running of the trial at the various participating centers.

Investigating doctor of the trial (or investigator): The doctor following you in the framework of the trial. He/she may be your regular doctor, or another doctor involved in the trial.

Bone densitometry: A painless radiological examination measuring the mineral content of the bone, and the percentage of fat and lean mass in the limbs and trunk.

Pre-inclusion: The time point at which all conditions are met for your participation in the trial.

Sponsor: The organization legally and financially responsible for the trial.

Substudy: A study carried out only on some of the people participating in the trial.

Adipose tissue: A tissue that contains fat.

Integrase inhibitor: A molecule that blocks a viral enzyme, integrase, which allows the virus to enter the cell's nucleus to multiply.

Non-nucleoside reverse transcriptase inhibitor: A molecule that blocks a viral enzyme, reverse transcriptase, the role of which is to convert the viral genome into DNA that can integrate into the genome of the host cell.

In this notice you will find:

You will find a consent form on the last page: this signed document attests to your willingness to participate in the trial and contains the contact details of the investigating doctor of the trial, whom you can contact if necessary.

To whom it may concern,

The investigating doctor of the ANRS 163 ETRAL trial would like to invite you to participate in this trial.

You have been on antiretroviral therapy including at least one boosted protease inhibition for the treatment of HIV infection for at least six months. This treatment makes it possible to control your viral load, that is, it prevents the multiplication of the virus in the blood (resulting in what we call an "undetectable plasma viral load"). This treatment also increases the number of CD4 cells in the blood, improves survival, and slows disease progression.

Despite the considerable clinical progress achieved in patients whose virus is under control, vascular (angina pectoris or myocardial infarction), lipid (increases in cholesterol and triglyceride levels), renal (a decrease in the filtration rate of the kidney), or bone (decrease in bone density) complications may emerge over time. They are related to the persistent inflammation due to HIV, and to certain molecules used in antiretroviral treatments, such as, nucleoside or nucleotide analogs (tenofovir (Viréad®, Truvada®) or abacavir (Ziagen®, Kivexa®)) and protease inhibitors (atazanavir (Réyataz®), darunavir (Prézista®) lopinavir / r (Kalétra®)). The frequency of these events also increases with age and increasing patient life expectancy. Today, almost 40% of patients treated in French hospitals at least 50 years old. A comparison between HIV-positive and HIV-negative patients has shown that the frequency of complications is higher in HIV-positive patients and that these complications occur earlier.

Some of the most recent classes of antiretroviral therapy or drugs are both effective against HIV and have little effect on lipid balance, bones, or adipose tissue.

We are inviting you to participate in a trial evaluating a new strategy combining two powerful antiretroviral drugs that are well known and have been marketed for several years:

- Raltegravir (or Isentress®), which has been available since 2008, belongs to the new class of integrase inhibitors (integrase allows the virus to enter the nucleus of the cell to multiply).
- Etravirine (or Intelence®), which belongs to the second generation of non-nucleoside reverse transcriptase inhibitors, blocks a viral enzyme, reverse transcriptase, which converts the viral genome into DNA capable of integrating into the genome of the host cell (see the *Trial treatments* section).

1. Objectives of the trial

The objective of the trial is to determine whether this new combination of two antiretroviral molecules — raltegravir (Isentress®) and etravirine (Intelence®) — makes it possible to maintain an undetectable HIV viral load while reducing potential side effects, such as cardiovascular, bone, kidney, or adipose tissue distribution disorders.

This trial includes two substudies to evaluate the following parameters:

- The DXA substudy: changes in the distribution of adipose tissue in the body and in bone mineral density. This substudy will involve a painless radiological examination for measuring the mineral content of the bone, and the percentage of fat and lean mass in the limbs and trunk, which will be performed at regular intervals (day (D) 0, week (W) 48, W96) for 80 participants.

- The semen substudy: measurements of HIV RNA viral load and the residual concentrations of raltegravir (Isentress®) and etravirine (Intelence®) in a sample of sperm fluid collected at W48 from 20 male participants.

2. The conditions for participation in the trial

If you decide to participate in this trial, a first visit, the "pre-inclusion visit", will take place 2 to 4 weeks before the start of the trial. During this visit, the doctor will assess your state of health: clinical examination, weight, height; blood and urine samples will also be collected. Your doctor will ask you about your medical history, to check that you are eligible to participate in the trial.

The principal conditions for participation in this trial are as follows. You must:

- Be at least 45 years old
- Be infected with HIV-1
- Have been on stable antiretroviral treatment for at least six months
- Have a CD4 lymphocyte count above 200/mm^3
- Have had an undetectable viral load (i.e. less than 50 copies/mL) for at least 24 months
- Have never been treated with raltegravir (Isentress®) and etravirine (Intelence®)
- Not take prohibited drugs during the trial (see the list in the *Trial treatments* section)
- Accept the constraints imposed by the trial (see the paragraph *What are the constraints linked to participation in the trial?* section)
- Be affiliated to or be a beneficiary of a social security regime (State Medical Aid or AME is not a social security regime)
- Have signed the consent form: this form must be signed before any examination (e.g. blood test, scan, etc.) is carried out as part of the trial
- Not participate in another trial at the same time as this one

The following situations are incompatible with participation in the trial:

- Being pregnant or breastfeeding
- Having chronic hepatitis B or C (treated during the 24 months of the trial)
- Anti-hypercholesterolemia and/or anti-diabetic treatment initiated in the 3 months preceding your participation in the trial

If, after checking these conditions, the investigator decides that you cannot participate in this trial, he/she will decide, with you, which treatment is best suited to your situation.

3. Schema for the trial

Once the eligibility criteria have been verified, you can start the trial.

All participants will replace their usual antiretroviral therapy with raltegravir (Isentress®) plus etravirine (Intelence®).

Therefore, all trial participants will receive the same treatment: raltegravir (Isentress®) and etravirine (Intelence®).

The duration of participation in the trial is 96 weeks (approximately two years).

The maximum total duration of the trial is estimated at four years, including the time required to include all the trial participants.

We to include 160 participants from several hospitals in France and Spain.

4. Trial treatments

Raltegravir (Isentress®): what you should know

Raltegravir (Isentress®), developed by the Merck Sharp & Dohme Ltd laboratory, has been marketed in France since January 2008.

Raltegravir (Isentress®) blocks the action of an enzyme (protein) called "integrase". It is produced in the form of tablets and must be taken at a dose of 1 tablet twice daily (i.e. 2 tablets per day).

The tolerance of raltegravir (Isentress®) is generally good. However, like most treatments, it can cause certain adverse effects, the main ones being:

- Diarrhea, nausea (feeling sick) and headache (may affect more than 1 in 10 people)
- Insomnia (difficulty sleeping), dizziness, bloating, stomachache, flatulence (gas), vomiting, rash, weakness, fatigue (may affect 1 to 10 users in 100)
- **Contact your doctor immediately if you develop a cutaneous (skin) reaction**. Skin reactions and life-threatening severe allergic reactions have been reported in some people receiving this medicine.
- **Inform your doctor if you have a history of depression or psychiatric illness**. Depression, including suicidal thoughts and behavior, has been reported in some people taking this medication, especially those with a history of depression or psychiatric illness.

Etravirine (Intelence®): what you should know

Etravirine (Intelence®), developed by Janssen Cilag Laboratories, has been marketed in France since August 2008.

It is produced in the form of tablets and must be taken at a dose of 1 tablet twice daily (i.e. 2 tablets per day).
Etravirine is a non-nucleotide reverse transcriptase inhibitor.
Tolerance to etravirine is generally good, but like most treatments, it can have certain adverse effects, the main ones being:
- Skin rashes that are usually mild to moderate. However, a very serious and potentially life-threatening rash has been reported in rare cases. **It is therefore important that you contact your doctor immediately if you develop a rash.**
- Nausea, stomach problems (diarrhea, stomachache, indigestion), headache, dizziness, tiredness (may affect less than 1 in 10 people).

- Risk of myocardial infarction (frequency: less than 1 in 10 people).

Doses of raltegravir (Isentress®) and etravirine (Intelence®):

The table below specifies the dose and number of doses of the treatments that you will take as part of this trial:

Who?	Medicine	Form	Morning	Evening	How to take it
All participants	Raltegravir 400 mg (Isentress®),	Pink oval tablets	1	1	After a meal
	Etravirine 200 mg (Intelence®),	White oval tablets	1	1	After a meal

If you want more information about these treatments, do not hesitate to talk to your doctor.

Tell your doctor before taking other medicines during the trial:

It is important to tell your doctor about the medicines that you take or wish to take (with or without a prescription) during the trial.

The following drugs are **formally contraindicated** and must not be taken in combination with the trial treatments because they may interact with or limit the efficacy of the anti-HIV treatments:

- **Antiplatelet agents:** Clopidogrel (Plavix®), prasugrel (Effient®), ticagrelor (Brilique®), ticlopidine (Ticlid®), flurbiprofene (Antadys® - Cebutid®).
- **Anti-infection agents:** Rifampicine (Rifampicine® - Rifadin® - RofactMC - Rifater®), rifapentine (Priftin®).
- **Certain herbal medicines containing St. John's Wort.**
- **Anti-epileptic agents:** Carbamazepine (Tegretol®), phenobarbital, phenytoine (Dilantin®).
- **Other drugs:** Avanafil (Stendra™), triazolam (Halcion®).

If you have any questions about these medicines, do not hesitate to talk to your doctor.

5. Sexuality, contraception, and pregnancy

It is very important to use a condom during sex, because treatment for HIV does not always prevent the transmission of HIV and other sexually transmitted infections.

Raltegravir (Isentress®) and etravirine (Intelence®) have not been evaluated in pregnant women. Their effects on the unborn child are not known. It is therefore important not to take any risks and not to become pregnant during the trial. You should discuss the contraceptive method best suited to your situation with your doctor. If you, nevertheless, discover that you are pregnant during the trial, you should immediately tell your doctor.

6. What are the constraints linked to participation in the trial?

During this trial, medical examinations will be slightly more frequent than during your usual follow-up. You should expect:

- A pre-inclusion visit and 10 follow-up visits during the two years of participation.
- Blood tests at each visit and questionnaires to be completed at certain visits.

If you agree to take part in one or both of the two proposed substudies, you must also be available for the examinations or blood tests for these substudies: bone densitometry (a painless radiological examination that measures the mineral content of bone and the percentages of fat and lean mass in the limbs and trunk) and sperm collection.

For your safety and for the success of the trial, it is important to follow the visit schedule as closely as possible. Given the importance of keeping to the timetable for the trial, the medical team in charge of your follow-up in the trial will do their utmost to facilitate this. You will be in contact with the clinical research team of your center, who will give you your schedule and all the telephone numbers that might prove useful for the smooth running of your participation. If you cannot come for a consultation or provide a sample, remember to tell your doctor.

Your agreement to participate in this trial implies that you accept the constraints imposed by the scheduled examinations.

Do not hesitate to ask the investigating doctor all the necessary questions on this subject. If you wish, he/she can give you information about your follow-up in the trial at each consultation.

7. The progress and timetable of the trial

If you agree to participate in the trial, you will sign a consent form before the first examination related to the trial. You will have a total of 11 visits spread over the two years of your participation in the trial:

"Pre-inclusion" visit: the investigating doctor will ask you about your medical history and perform a clinical examination and blood tests to make sure that you can participate in the trial.

If all the conditions for participation are met:

Visit D0: corresponds to the first dose of raltegravir (Isentress®) and etravirine (Intelence®). This visit takes place 2 to 4 weeks after the pre-inclusion visit.

There will be 9 other visits: W2, W4, W12, W24, W36, W48, W64, W80, and W96 (see the trial calendar).

During these visits, the investigating doctor will take blood samples for routine blood tests, such as blood sugar, the measurement of viral load (measurement of the amount of virus in the blood), or counts of CD4 lymphocytes. Other blood samples will be used to carry out more specific blood tests, such as determinations of the amount of the trial drugs in your blood.

Some samples/blood samples will be analyzed immediately, and others will be kept for analysis at the end of the trial.

You will be asked for a urine sample at visits W-6/W-4, W4, W12, W24, W48, W80, and W96, to check for protein or glucose (sugar) in your urine, these substances normally being present in only very small amounts.

Blood samples for storage will be sent to the French Blood Establishment (EFS) in Beynost (France) to constitute a biobank. Each sample will be labeled and numbered anonymously (your name will not be indicated).

The samples from the biobank can be used for additional studies. If these additional studies involve genetic testing, you will be asked for consent for such testing.

You can specify in your consent that you do not wish your samples to be kept in the biobank for use in future research.

Substudies

If you are volunteering for the DXA substudy, to evaluate changes in the distribution of fat in your body and changes in bone mineral density, bone densitometry will be performed on D0 and at W48 and W96 (80 participants).

Patients wishing to participate in the semen substudy, which aims to measure the viral load of HIV and the residual concentration of raltegravir (Isentress®) and etravirine (Intelence®) in sperm fluid, will provide a sperm sample at W48 (20 participants).

The questionnaires and self-administered questionnaires to be completed during the trial

- “Quality of life” and “compliance” self-administered questionnaires: These are anonymized questionnaires, on paper, that you will complete on your own. At no time will we be able to intervene your responses. The self-administered "compliance" questionnaire will tell us whether you are taking your treatments as prescribed by your doctor. If this is not the case, your doctor will try to understand why and work with you to try to find a solution.

Trial Calendar

	Pre-inclusion* (W-6/W-4 to W-2)	D: Start of treatment	W2	W4	W12	W24	W36	W48	W64	W80	W96	In case of virological failure
Signature of consent form												
Clinical examination												
Quality of life self-administered questionnaires												
Compliance questionnaire												
Come to the consultation after a period of at least 12 h without eating												
Pregnancy test (1)												
Urine sample												
DXA / Bone densitometry (substudy)												
Sperm sample (substudy)												
Amount of blood for the ETRAL trial (without storage in the biobank)	29 mL (7 tubes)	22 mL (6 tubes)	0 mL	19 mL (5 tubes)	22 mL (6 tubes)	25 mL (7 tubes)	7 mL (1 tubes)	25mL (7 tubes)	7 mL (1 tubes)	16 mL (4 tubes)	25 mL (7 tubes)	14 mL (2 tubes)

Additional blood for the biobank	0 mL	45 mL (7 tubes)	21 mL (3 tubes)	21 mL (3 tubes)	21 mL (3 tubes)	21 mL (3 tubes)	21 mL (3 tubes)	45 mL (7 tubes)	21 mL (3 tubes)	21 mL (3 tubes)	45 mL (7 tubes)	7 mL (1 tubes)
Total amount of blood collected (mL)	29 mL (7 tubes)	67 mL (13 tubes)	21 mL (3 tubes)	40 mL (8 tubes)	43 mL (9 tubes)	46 mL (10 tubes)	28 mL (4 tubes)	70 mL (14 tubes)	28 mL (4 tubes)	37 mL (7 tubes)	70 mL (14 tubes)	21 mL (3 tubes)

**Pre-inclusion: takes place 2 to 4 weeks before the start of treatment. W: week*

(1) The pregnancy test is carried out only for women of childbearing age at W-6/W-4 and then at subsequent visits if pregnancy is suspected.

8. Expected benefits and possible risks

Expected benefits

- The antiretroviral drugs that you will receive as part of the ANRS 163 ETRAL trial have shown, separately, to have virological efficacy, with raltegravir (Isentress®) having a lesser effect on lipid profile and bones.

You will benefit from participation if the trial shows that the raltegravir (Isentress®) + etravirine (Intelence®) combination controls viral replication, is well tolerated, and reduces the frequency of complications associated with HIV infection and your previous treatment.

- You will benefit from more frequent monitoring and more detailed examinations.
- You will be involved in research, the results of which may be of benefit to other people.

Possible risks

- Raltegravir (Isentress®) and etravirine (Intelence®) can cause known (as described in the *Trial treatments* section) or unknown adverse effects.
- The trial treatment should control viral replication and ireduce the complications of HIV infection and your previous treatment. However, there is a risk of replication. You will be monitored closely to detect any rise in HIV viral load.
- Blood tests may cause bruising at site of puncture, on the day of the examination and on the following two to three days.

9. Monitoring

During the trial if, for example, your health deteriorates and other treatments are preferable, or if justified by adverse effects, you can decide, with your doctor, to stop the trial treatment at any time, while continuing your monitoring.

Throughout the trial, scientific committees will monitor the study for adverse effects or failures of raltegravir (Isentress®) and etravirine (Intelence®). These committees ensure the safety of those involved in the trial and oversee the running of the trial. If necessary, for safety reasons, for example, they can decide to end the trial or to modify the way in which it is performed.

10. Alternatives

You should know that your participation in the trial is free and voluntary. You can decide to refuse to participate in the trial and remain on your current treatment. Your decision to agree or refuse to participate in this trial will not change the quality of your medical care.

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

Raltegravir (Isentress®) and etravirine (Intelence®) are already sold in France. If the final results of the trial are conclusive, your doctor may wish to consider continuing with this combination. At the end of the trial, participants will be able to discuss their results and their experience of participation in the trial.

The overall results of the trial will be communicated to the participants after the trial has ended.

12. What are your rights?

Do not forget that you can:

- Take as long as you need to think before deciding to participate in this trial
- Leave the trial at any time, without giving a reason, by simply telling your doctor
- Find out about your health
- Be informed of any serious events occurring during the trial
- Be informed of your results and of the overall results of the trial
- Check and correct data concerning you
- Oppose the transmission of data concerning you
- Obtain compensation in the event of harm

Your data:

As part of the trial in which you are being asked to participate by the National Agency for Research on AIDS and Viral Hepatitis (ANRS), your personal data will be processed as part of the analysis of the results of the trial with respect to its objectives, which have been presented to you.

To this end, the medical data concerning you and the data relating to your lifestyle, and, insofar as these data are necessary for the trial, your ethnic origins, and sex life, will be transmitted to the sponsor of the trial or to individuals or companies acting on the sponsor's behalf, in France or abroad.

These data will be identified by a code number. These data may also be transmitted to French or foreign health authorities (Medicines Agency, etc.) or to other ANRS partners, under conditions of confidentiality.

In accordance with the provisions of the law relating to data processing and freedoms, you have the right of access and rectification. You also have the right to oppose the transmission of data covered by professional secrecy that may be used in the context of this trial and be processed. The exercise of this right will terminate your participation in the trial.

You can also access all of your medical data directly or through a doctor of your choice, in accordance with the provisions of article L 1111-7 of the French Public Health Code.

If you have any questions about these rights, you can contact the doctor following you during the trial. If desired, information about the trial and your participation will be shared with your general practitioner.

This trial received was approved by the Personal Protection Committee (CPP) on 04/16/2014 and authorized by the ANSM on 04/04/2014.

The sponsor of this trial, Inserm-ANRS, has taken out civil liability insurance in the event of harm, in accordance with the provisions of the French Public Health Code, with HDI Gerling (Tours opus 12, 77 Esplanade de la Défense 92914 PARIS LA DEFENSE) .

The French Public Health Code also guarantees compensation to anyone suffering harm due to participation in research.

13. Information about the fate of your samples at the end of the trial

To whom it may concern,

As specified in the information notice specific to the ANRS 163 ETRAL trial, in which you are invited to participate, blood samples, urine samples, and (possibly) a semen sample will be taken.
If the blood and semen samples are not completely used up at the end of this trial, they may be used for scientific research on HIV unless you object.
The remaining samples:

- Will be stored at the EFS (French Blood Establishment - Beynost site), under the control of its logistics management, on behalf of the ANRS, and under the scientific responsibility of the common service 10-US019 of Inserm (Paul Brousse Hospital, Villejuif)
- May be supplied free of charge, and under certain conditions, to other national or international private or public research groups, under conditions guaranteeing the confidentiality of your data
- May not, in any case, be used for the examination of genetic characteristics without new written consent from you.

You may freely, and at any time, object to this further use for research purposes, by contacting the investigating doctor of the trial.
Your decision will have no consequences for your participation in the ANRS 163 ETRAL trial or your medical care.

Name, address, and contact details.

.....

....
.....

In accordance with the law, no remuneration can be paid to you.

The transferred samples cannot be sold.

For sample management, the EFS uses a computer file authorized by the French National Commission for Data Protection (CNIL). This file contains anonymized data for the identification of samples.

ANRS 163 ETRAL Trial **Consent Form**

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Country Center No. Patient No. Letter code

Version 2.0 of 03/18/2015, approved by the CPP on 05/15/2015

Sponsor: Inserm-ANRS **Coordinating investigator: Prof. Christine Katlama**

Ms, Mr .....*(first and last name)*

I certify:

having received information notice version 2.0 dated 03/18/2015, that I have had the opportunity to ask all the questions I wished on the nature, objectives, potential risks, and constraints relating to my participation in this trial, and that I have had sufficient time to reflect between receiving this information and giving my consent.

I understand the constraints (more frequent visits, numerous blood samples) and the benefits linked to my participation in this trial, which will last approximately 2 years.

I understand that I am free to discontinue my participation in this trial at any time, without having to explain why, but I will do my best to inform the doctor. This will not affect the quality of my subsequent care.

I have been reassured that the decisions that are necessary for my health will be made at all times, in accordance with the state of knowledge on HIV.

I have noted that blood samples and a semen sample (if I participate in the semen substudy) will be taken during the trial and stored anonymously. They will make it possible to carry out the planned analyses for this trial.

I accept that the data recorded during this trial will be collected, processed, and computerized. I understand that the right of access laid down in the modified law of January 6, 1978 relating to data processing, files, and freedoms, can be exercised at any time, through the doctor following me in the trial, and that I can exercise my right of rectification and opposition.

I accept that the scientists involved in this trial, and the individuals authorized by the health authorities in France and abroad, may have access to the information, under strict conditions of confidentiality.

My consent in no way relieves the organizers of the trial of their responsibilities. I retain all my statutory rights.

At the end of the trial, I may be informed of the overall results through the investigating doctor of the trial.

I have been informed by the explanatory notice that my blood and/or semen samples may be used at the end of the trial for other research on HIV infection, **unless I oppose this**.

☐ **I authorize the storage of my blood samples for future research.**	☐ **I oppose the storage of my blood samples for future research. They will be destroyed at the end of the trial.**
☐ I agree to participate in the DXA substudy "Distribution of fat mass and bone mineral density"	
☐ I agree to participate in the seminal sub-study "Measurement of RNA-HIV viral load in semen"	
☐ **I authorize the storage of my sperm samples for further research.**	☐ **I oppose the storage of my sperm samples for future research.**

I freely agree to participate in this test under the conditions specified in the information notice

Participant's signature

Date └─┴─┘ └─┴─┘ └─┴─┴─┴─┘

ANRS 163 ETRAL Trial **Consent Form**

code Country Center No. Patient No. Letter

I, the undersigned, Dr/Pr ……..
certify that I have communicated to the participant all the useful information relating to this trial, that I have answered his questions and obtained his consent.

Date

Write or place a label
Name of the unit:
Address:
Telephone:

Doctor's signature

INVESTIGATOR COPY (a copy is made for the sponsor)

Version 2.0 dated 03/18/2015, approved by the CPP on 05/15/2015

Sponsor: Inserm-ANRS **Coordinating investigator: Prof. Christine Katlama**

Ms, Mr *(first and last name)*

I certify:

having received information notice version 2.0 dated 03/18/2015, that I have had the opportunity to ask all the questions I wished on the nature, objectives, potential risks, and constraints relating to my participation in this trial, and that I have had sufficient time to reflect between receiving this information and giving my consent.

I understand the constraints (more frequent visits, numerous blood samples) and the benefits linked to my participation in this trial, which will last approximately 2 years.

I understand that I am free to discontinue my participation in this trial at any time, without having to explain why, but I will do my best to inform the doctor. This will not affect the quality of my subsequent care.

I have been reassured that the decisions that are necessary for my health will be made at all times, in accordance with the state of knowledge on HIV.

I have noted that blood samples and a semen sample (if I participate in the semen substudy) will be taken during the trial and stored anonymously. They will make it possible to carry out the planned analyses for this trial.

I accept that the data recorded during this trial will be collected, processed, and computerized. I understand that the right of access laid down in the modified law of January 6, 1978 relating to data processing, files, and freedoms, can be exercised at any time, through the doctor following me in the trial, and that I can exercise my right of rectification and opposition.

I accept that the scientists involved in this trial, and the individuals authorized by the health authorities in France and abroad, may have access to the information, under strict conditions of confidentiality.

My consent in no way relieves the organizers of the trial of their responsibilities. I retain all my statutory rights.

At the end of the trial, I may be informed of the overall results through the investigating doctor of the trial.

I have been informed by the explanatory notice that my blood and/or semen samples may be used at the end of the trial for other research on HIV infection, **unless I oppose this**.

ANRS 163 ETRAL Trial **Consent Form**

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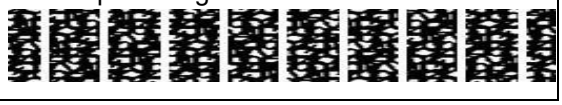
Country Center No. Patient No. Letter

code

I freely agree to participate in this trial under the conditions specified in the information notice

Participant's signature



Date └─┴─┘ └─┴─┘ └─┴─┴─┴─┘

I, the undersigned, Dr/Pr ……..
certify that I have communicated to the participant all the useful information relating to this trial, that I have answered his/her questions and obtained his/her consent.

Date └─┴─┘ └─┴─┘ └─┴─┴─┴─┘

Write or place a label
Name of the unit:
Address:
Telephone:

Doctor's signature

CMG Inserm UMR S 1136 COPY

Version 2.0 dated 03/18/2015, approved by the CPP on 05/15/2015

Sponsor: Inserm-ANRS **Coordinating investigator: Prof. Christine Katlama**

Ms, Mr .....*(first and last name)*

I certify:

having received information notice version 2.0 dated 03/18/2015, that I have had the opportunity to ask all the questions I wished on the nature, objectives, potential risks, and constraints relating to my participation in this trial, and that I have had sufficient time to reflect between receiving this information and giving my consent.

I understand the constraints (more frequent visits, numerous blood samples) and the benefits linked to my participation in this trial, which will last approximately 2 years.

I understand that I am free to discontinue my participation in this trial at any time, without having to explain why, but I will do my best to inform the doctor. This will not affect the quality of my subsequent care.

I have been reassured that the decisions that are necessary for my health will be made at all times, in accordance with the state of knowledge on HIV.

I have noted that blood samples and a semen sample (if I participate in the semen substudy) will be taken during the trial and stored anonymously. They will make it possible to carry out the planned analyses for this trial.

I accept that the data recorded during this trial will be collected, processed, and computerized. I understand that the right of access laid down in the modified law of January 6, 1978 relating to data processing, files, and freedoms, can be exercised at any time, through the doctor following me in the trial, and that I can exercise my right of rectification and opposition.

ANRS 163 ETRAL Trial

Consent Form

└─┴─┘ └─┴─┴─┘ └─┴─┴─┘ └─┴─┴─┴─┘

Country Center No. Patient No. Letter code

I accept that the scientists involved in this trial, and the individuals authorized by the health authorities in France and abroad, may have access to the information, under strict conditions of confidentiality.

My consent in no way relieves the organizers of the trial of their responsibilities. I retain all my statutory rights.

At the end of the trial, I may be informed of the overall results through the investigating doctor of the trial.

I have been informed by the explanatory notice that my blood and/or semen samples may be used at the end of the trial for other research on HIV infection, **unless I oppose this**.

☐ **I authorize the storage of my blood samples for future research.**	☐ **I oppose the storage of my blood samples for future research. They will be destroyed at the end of the trial.**
☐ I agree to participate in the DXA substudy "Distribution of fat mass and bone mineral density"	
☐ I agree to participate in the semen substudy "Measurement of HIV-RNA viral load in semen"	
☐ **I authorize the storage of my sperm samples for further research.**	☐ **I oppose the storage of my sperm samples for future research. They will be destroyed at the end of the trial.**

I freely agree to participate in this trial under the conditions specified in the information notice

Participant's signature

Date └─┴─┘ └─┴─┘ └─┴─┴─┴─┘

I, the undersigned, Dr/Prof. ……..
certify that I have communicated to the participant all the useful information relating to this trial, that I have answered his/her questions and obtained his/her consent.

Date └─┴─┘ └─┴─┘ └─┴─┴─┴─┘

Write or place a label
Name of the unit:
Address:
Telephone:

Doctor's signature

PATIENT'S COPY (attached to the notice)

*Appendix A6: **ANRS scale to grade the severity of adverse events in adults***

A.N.R.S

ANRS scale to grade the severity of adverse events in adults

Version n° 1.0 4 November 2008

This severity scale is a working guide intended to harmonise evaluation and grading practices for symptomatology in ANRS biomedical research protocols.

In practice, the items evaluated are grouped according to the system taking the form of a non-exhaustive symptomatic table (and not a classification of pathologies). Our choices focus on the most frequently observed clinical and biological signs or those whose monitoring is essential to ensure the protection of the subjects participating in the research.

For abnormalities NOT found elsewhere on the Table, refer to the scale below to estimate grade of severity:

GRADE 1	***Mild***	Mild or transient discomfort, without limitation of normal daily activities; no medical intervention or corrective treatment required.
GRADE 2	***Moderate***	Mild to moderate limitation of normal daily activities; minimal medical intervention or corrective treatment required.
GRADE 3	***Severe***	Marked limitation of normal daily activities; medical intervention and corrective treatment required, possible hospitalisation.
GRADE 4	***Life-threatening***	Severe limitation of normal daily activities; medical intervention and corrective treatment required, almost always in a hospital setting.

Abbreviations used in the table:

ULN	:	Upper Limit of Normal
RBC	:	Red Blood Cells
FEV1	:	Forced Expiratory Volume in one second
EMG	:	Electromyogram
Prothrombin Time (%)	:	Corresponds to Quick time (sec)
aPTT	:	activated Partial Thromboplastin Time

Please note that this scale was devised for use in HIV, HCV or HBV related pathologies.

ANRS scale to grade the severity of adverse events in adults (version n° 1.0 4 November 2008)

GRADES		GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe	GRADE 4 Life-threatening
HAEMATOLOGY					
1	Haemoglobin (g/dl)	8.0 – 9.4	7.0 – 7.99	6.5 – 6.99	< 6.5
2	Leucocytes (/mm^3)	3 000 – 3 900	2 000 – 2 999	1 000 – 1 999	< 1 000
3	Neutrophils (/mm^3)	1 000 – 1 500	750 – 999	500 – 749	< 500
4	Platelets (/mm^3)	75 000 – 99 000	50 000 – 74 999	20 000 – 49 999	<20 000 or generalized petechiae
5	Prothrombin Time (%)	/	45 – ≤ 70	20 – < 45	< 20
6	aPTT	1.0 – 1.66 x ULN	> 1.66 – 2.33 x ULN	> 2.33 – 3.0 x ULN	> 3.0 x ULN
BIOCHEMISTRY					
Hepatic and pancreatic biochemistry					
7	AST (SGOT) (UI/l)	1.25 – 2.50 x ULN	> 2.50 – 5.0 x ULN	> 5.00 – 10.0 x ULN	> 10.0 x ULN
8	ALT (SGPT) (UI/l)	1.25 – 2.50 x ULN	> 2.50 – 5.0 x ULN	> 5.00 – 10.0 x ULN	> 10.0 x ULN
9	GAMMA GT (UI/l)	1.25 – 2.50 x ULN	> 2.50 – 5.0 x ULN	> 5.00 – 10.0 x ULN	> 10.0 x ULN
10	Alkaline phosphatase (UI/l)	1.25 – 2.50 x ULN	> 2.50 – 5.0 x ULN	> 5.00 – 10.0 x ULN	> 10.0 x ULN
11	Hyperbilirubinaemia (µmol/l)	1.25 – 2.50 x ULN	> 2.50 – 5.0 x ULN	> 5.00 – 10.0 x ULN	> 10.0x ULN
12	Amylasaemia (UI/l) / Lipasaemia (UI/l)/ Pancreatitis	≥1.25 – 2.50 x ULN	> 2.50 – 5.0 x ULN	> 3.0 x ULN with acute abdominal pain and/or imaging indicating acute pancreatitis.	> 3.0 x ULN with abdominal pain and signs of shock.
13	CPK (UI/l)	1.25 – 2.50 x ULN	> 2.50 – 5.0 x ULN	> 5.00 – 10.0 x ULN	> 10.0 x ULN
Lipid status					
14	Hypertriglyceridaemia (mmol/l)	/	4.50 – 8.59	8.60 – 13.70	> 13.70
15	Hypercholesterolaemia (mmol/l)	>ULN –7.75	>7.75 – 10.34	>10.34 – 12.92	>12.92

ANRS scale to grade the severity of adverse events in adults (version n° 1.0 4 November 2008)

GRADES		GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe	GRADE 4 Life-threatening
Electrolytes / Evaluation of renal function / Metabolism					
16	Hyponatraemia (mEq/l)	130 – 135	123 – 129	116 – 122	<116
17	Hypernatraemia (mEq/l)	146 – 150	151 – 157	158 – 165	>165
18	Hypokalaemia (mEq/l)	3.2 – 3.4	2.8 – 3.1	2.5 – 2.7	<2.5
19	Hyperkalaemia (mEq/l)	5.6 – 6.0	6.1 – 6.5	6.6 – 7.0	>7.0
20	Bicarbonate (mEq/l or mmol/l)	20.0 – 24.0	15.0 – 19.99	10.0 – 14.99	< 10.0
21	Creatininaemia (µmol/l)	1.0 – 1.50 x ULN	> 1.50 – 3.0 x ULN	> 3.0 – 6.0 x ULN	6.0 x ULN or dialysis required
22	Blood Urea Nitrogen (UI/l)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
23	Hypocalcaemia (mmol/l)	1.95 – 2.10	1.75 – 1.94	1.50 – 1.74	< 1.50
24	Hypercalcaemia (mmol/l)	2.65 – 2.87	2.88 – 3.13	3.14 – 3.38	> 3.38
25	Hypophosphataemia (mg/dl)	2.0 – 2.4	1.5 – 1.9	1.0 – 1.4	<1.0
26	Hyperuricaemia (µmol/l)	1.25 – 2.0 x ULN	> 2.0 – 5.0 x ULN	> 5.0 – 10.0 x ULN	> 10.0 x ULN
27	Hypoglycaemia (mmol/l)	3.1 – 3.6	2.2 – 3.0	1.7 – 2.1	< 1.7
28	Hyperglycaemia (mmol/l)	6.1 – 7.0	> 7.0 – 16.5	> 16.5 without ketosis.	See diabetes Item no. 52 (grade 4)
29	Hyperlactataemia (mmol/l) (venous blood sample)	2.0 – 2.99*	3.0 – 3.99**	4.0 – 4.99**	≥ 5.0***
Urinalysis					
30	Proteinuria (dipstick)	+	++	≥ +++	Nephrotic syndrome
31	Haematuria.	≥ 80 RBC/µl (dipstick).	≥ 200 RBC/µl (dipstick).	Macroscopic with or without clots.	Obstructive or requiring a blood transfusion.

* Lactataemia – GRADE 1: a confirmatory test is necessary within 8 to 10 days

** Lactataemia – GRADE 2, 3: a confirmatory test is necessary within 24 hours.

*** *Lactataemia – GRADE 4: a confirmation test is necessary immediately.*

ANRS scale to grade the severity of adverse events in adults (version n° 1.0 4 November 2008)

GRADES		GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe	GRADE 4 Life-threatening
Gastro-intestinal/hepatic/pancreatic abnormalities					
32	Nausea.	Transient, normal diet.	Restricted diet for less than 3 days.	Restricted diet for more than 3 days.	Liquid only diet. Hospitalization required.
33	Vomiting.	Transient: 2 – 3 episodes / day or duration ≤ 1 week.	Repeated: 4 – 5 episodes / day or duration > 1 week.	Solid/liquid vomiting for 24 h. Orthostatic hypotension. Perfusion required.	Hospitalization for hypovolemic shock.
34	Diarrhoea.	Transient, 3 – 4 stools / day, diarrhoea ≤ 1 week.	Persistent, 5-7 stools / day, diarrhoea > 1 week.	> 7 stools/day or requiring perfusion. Bloody stools.	Hospitalization, Hypovolemic shock, perfusion.
35	Constipation.	/	Moderate abdominal pain, 78 h without stools. Treatment required.	Meteorism. Requiring disimpaction or hospital treatment.	Meteorism with vomiting or occlusion.
36	Dysphagia.	Mild discomfort when swallowing.	Difficulty in swallowing but food intake possible.	Inability to swallow solids.	Inability to swallow liquids, perfusion required.
37	Oesophagitis.	Pyrosis occurring less than once a week	Pyrosis occurring at least once a week but relieved by PPIs*	Pyrosis occurring at least once a week but not relieved by PPIs*	Food intolerance and vomiting

**PPIs: proton pump inhibitors*

GRADES		GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe	GRADE 4 Life-threatening
Respiratory abnormalities					
38	Bronchospasm.	Transient, no treatment, FEV1 70 % - < 80 %.	Permanent, Improvement under bronchodilation FEV1 50 % - < 70 %.	Persistent under bronchodilation. FEV1 25 % - < 50 %.	Cyanosis, FEV1 < 25 % intubation.
39	Dyspnoea	Dyspnoea upon exertion.	Dyspnoea during normal daily activities.	Dyspnoea at rest.	Dyspnoea requiring respiratory assistance.
Muscular abnormalities					
40	Myalgia (excluding injection site).	Mild myalgia for less than 4 weeks. Not requiring analgesic treatment.	*Presence of one of the following symptoms:* 1 – Mild to moderate myalgia for more than 4 weeks and/or which may require treatment with level 1* analgesics. 2 – Predominance of difficulties upon exertion (difficulty in climbing stairs or rising from a sitting position). Can walk without assistance. Optional confirmation through the identification of biological (CPK), electromyographical (EMG) or histological (muscular biopsy) abnormalities.	*Presence of one of the following symptoms*: 1 – Moderate to severe myalgia for more than 4 weeks requiring treatment with level I/II* analgesics. 2 – Assistance required for walking and normal daily activities. Paraclinical confirmation recommended (CPK, EMG and/or muscular biopsy).	*Presence of one of the following symptoms*: 1 – Severe myalgia not related to exertion requiring treatment with level II/III* analgesics. 2 – Muscular weakness making walking impossible without assistance. 3 – Acute rhabdomyolysis with muscular necrosis and oedema. 4 – Acute rhabdomyolysis with electrolytic disturbances and renal insufficiency. Paraclinical confirmation required (biology, EMG and/or muscular biopsy).

** Level I analgesics* : *Peripheral analgesics (paracetamol and/or salicylics or non-steroid anti-inflammatory drugs) ;*
** Level II analgesics* : *Weak opiates (codeine, dextropropoxyphene), morphinic agonists-antagonists (buprenorphine, nalbuphine) ;*
** Level III analgesics* : Morphine.

GRADES		GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe	GRADE 4 Life-threatening
Cardiovascular abnormalities					
41	Arterial hypertension.	Transient or permanent. Increased blood pressure ≤ 20 mmHg and systolic BP 140-159 or diastolic BP 90-99.	Permanent. Increased blood pressure > 20 mmHg and systolic BP 160-179 or diastolic BP 100-109.	Permanent. Systolic BP ≥ 180 or diastolic BP > 110	Malignant or accelerated arterial hypertension.
42	Orthostatic hypotension.	Decreased systolic blood pressure ≤ 20 mmHg in orthostatic position. No treatment.	Decreased systolic blood pressure > 20 mmHg, durable but corrected with liquid intake per os.	Perfusion required.	Hypovolemic shock requiring hospitalization.
43	Ventricular cardiac rhythm disorders.	/	Isolated ventricular extrasystoles, no treatment, symptomatic or asymptomatic.	Recurrent, persistent or symptomatic cardiac rhythm disorders. Treatment required.	Dysrhythmia requiring hospitalization.
44	Prolongation of the QT interval.	/	Man: >450 and < 500 ms Woman: >470 and <500 ms	>500ms	>500 ms with clinical symptoms (ventricular rhythm disorders, syncope, torsade de pointes)
45	Cardiac ischaemia.	/	Atypical pain under exploration.	Appearance of angina upon exertion, controlled with treatment.	Myocardial infarction, unstable angina, preinfarction syndrome.
46	Pericarditis.	Chance discovery of a small effusion during ultrasound scan	Moderate effusion with few symptoms. No treatment or intervention deemed necessary for the time being.	Moderate or significant symptomatic effusion but without tamponade. Treatment required and hospitalization to be considered.	Tamponade. Hospitalization and intervention required.
47	Stroke.	/	/	Transient Ischemic Attack (regressive focal neurological syndrome within 24 h).	Cerebrovascular accident non-regressive within 24 h.
48	Peripheral arterial embolism.	/	/	/	Peripheral arterial embolism. Hospitalization. Adapted treatment.
49	Deep vein thrombosis and/or pulmonary	/	/	Deep vein thrombosis. Anticoagulant treatment. Hospitalization to be considered.	Pulmonary embolism. Adequate hospitalization and treatment.

	embolism.				

GRADES		GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe	GRADE 4 Life-threatening
Endocrine abnormalities					
50	Hyperthyroidism.	Infraclinical hyperthyroidism. Low TSH. Normal free T3 and T4.	Moderate, non-complicated thyrotoxicosis. Treatment required.	Malignant exophtalmia. Cardiac arrhythmia. Myopathy.	Thyrotoxic crisis and/or cardiac insufficiency.
51	Hypothyroidism.	Infraclinical hypothyroidism. Increased TSH but <12 mU/l. Normal free T4.	Simple hypothyroidism without complications. Treatment required.	Severe hypothyroidism with multiple clinical symptoms. Urgent treatment. Hospitalization to be considered.	Myxoedematous coma.
52	Diabetes/hyperglycaemia.	Moderate fasting hyperglycaemia between 6.1 and 7 mmol/l. No immediate treatment required.	Fasting glycaemia: > 7 mmol/l. Special diet required, possibly supplemented with oral antidiabetics.	Fasting glycaemia:>16.5 mmol/l on an empty stomach, with or without clinical symptoms. Insulin therapy required.	Ketoacidosis or hyperosmolarity (>27.8 mmol/l without acidosis).
Cutaneous abnormalities					
53	Cutaneous and/or mucosal eruptions.	Erythaema, Moderate pruritis.	Extended maculopapular eruption, with or without pruritis.	Extended papulovesicular or oozing eruption. Palpable purpura (suggestive of vasculitis). Polymorphous erythaema. Small-size cutaneous or mucous ulcerations.	Any blistering cutaneous and/or mucosal lesions (Lyell or Stevens-Johnson). Febrile erythrodermia, whether or not associated with other signs indicative of hypersensitivity. Cutaneous necrosis requiring surgical excision.
54	Symptoms of immediate hypersensitivity, with or without cutaneous symptoms.	/	Acute localised urticaria.	Giant urticaria, Quincke's oedema.	Anaphylactic shock.

GRADES		GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe	GRADE 4 Life-threatening
Neurological abnormalities					
55	Wakefulness / sleep disorders.	Minor attention and concentration impairment.	Diurnal somnolence and/or difficulty falling asleep and/or night time awakening, mental activity decreased, obnubilation.	Sleep-wake cycle modification or insomnia requiring treatment or change in dream content. Obvious confusional syndrome with temporal disorientation.	Sleep-wake cycle disorganisation not responding to treatment. Dreamlike confusional syndrome, coma and/or convulsion.
56	Psychiatric disorders.	Minor anxiety.	Anxiety requiring treatment or moderate depression.	Major anxiety or confirmed depressive episode requiring treatment.	Acute psychosis requiring hospitalization, including suicidal ideation, manic state, hallucinatory delusion.
57	Cephalalgia.	Intermittent, no treatment.	Requiring level I* analgesics.	Requiring at least level II* analgesics.	Not responsive to level III* analgesics.
58	Paraesthesia.	Paraesthesia, mild pain, no treatment.	Paresthesia, permanent pain of moderate intensity, requiring level I* analgesics.	Paraesthesia, permanent pain of severe intensity, requiring at least level II* analgesics.	Unbearable pain resulting in disability, restricted activity despite administration of level III* analgesics.
59	Motor deficiency.	Subjective feeling of weakness without objective impairment, no reflex changes.	Distal motor deficiency, moderate functional impairment or reflex changes.	Marked motor deficiency interfering with normal daily activities.	Confined to bed or a wheelchair because of motor deficiency.
60	Difficulty controlling movement.	Occasional clumsiness, mild coordination difficulties.	Tremor or dyskinaesia or dysmetria, or dysarthria, moderate limitation of normal daily activities.	Upper or lower limbs ataxia or abnormal movements, limitation of normal daily activities.	Inability to stand up. Total dependence.
61	Sensory loss.	Mild sensory loss, regardless of mode and distribution (focal or symmetric).	Moderate sensory loss.	Severe sensory loss.	Extensive sensory loss involving the trunk and four limbs.

** Level I analgesics : Peripheral analgesics (paracetamol and/or salicylics or non-steroid anti-inflammatory drugs) ;*
** Level II analgesics : Weak opiates (codeine, dextropropoxyphene), morphinic agonists-antagonists (buprenorphine, nalbuphine) ;*
** Level III analgesics :* Morphine.

ANRS scale to grade the severity of adverse events in adults (version n° 1.0 4 November 2008)

GRADES		GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe	GRADE 4 Life-threatening
Miscellaneous					
62	Fever (oral temperature, °C) for more than 12 h.	37.7 – 38.9	39 – 39.5	39.6 – 40.5	> 40.5
63	Renal colic.	Spontaneous regression of symptoms. Pain not requiring treatment.	Colic requiring medical treatment.	Obstructive syndrome, does not disappear spontaneously.	/
64	Fatigue.	Normal daily activities reduced by less than 25% for less than 48 h.	Normal daily activities reduced by 25 – 50 % for more than 48 h.	Normal daily activities reduced by more than 50%, cannot work for more than 48 h.	Unable to care for self. Assistance required for normal daily activities.
65	Arthritis / Arthralgia.	Arthralgia.	Arthralgia, with or without articular effusion or with moderate functional impairment.	Marked arthritis with or without effusion or with severe functional impairment.	/
66	Ocular disorders.	Conjunctival hyperaemia.	Moderate pain. Conjunctivitis.	Decreased visual acuity. Uveitis. Severe pain. Glaucoma.	/

ANRS Vaccine trials
ANRS scale to grade the severity of adverse events in adults (version n° 1.0 4 November 2008)

GRADES		GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe	GRADE 4 Life-threatening
1	Erythaema, oedema, nodule (induration).	< 15 x 15 cm.	≥ 15 x 15 cm.	Ulceration or superinfection or superficial phlebitis.	Skin necrosis
2	Pain, functional impairment.	Mild, no limitation of movements.	Pain inducing partial mobility impairment.	Pain inducing functional impotence.	/

Appendix A7: ***Recommendations for blood pressure measurement in humans and experimental animals***

AHA Scientific Statement

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RECOMMENDATIONS FOR BLOOD PRESSURE MEASUREMENT IN HUMANS AND EXPERIMENTAL ANIMALS

Part 1: Blood Pressure Measurement in Humans: A Statement for Professionals From the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research

Thomas G. Pickering, MD, DPhil; John E. Hall, PhD; Lawrence J. Appel, MD; Bonita E. Falkner, MD; John Graves, MD; Martha N. Hill, RN, PhD; Daniel W. Jones, MD; Theodore Kurtz, MD; Sheldon G. Sheps, MD; Edward J. Roccella, PhD, MPH

Abstract

Accurate measurement of blood pressure is essential to classify individuals, to ascertain blood pressure– related risk, and to guide management. The auscultatory technique with a trained observer and mercury sphygmomanometer continues to be the method of choice for measurement in the office, using the first and fifth phases of the Korotkoff sounds, including in pregnant women. The use of mercury is declining, and alternatives are needed. Aneroid devices are suitable, but they require frequent calibration. Hybrid devices that use electronic transducers instead of mercury have promise. The oscillometric method can be used for office measurement, but only devices independently validated according to standard protocols should be used, and individual calibration is recommended. They have the advantage of being able to take multiple measurements. Proper training of observers, positioning of the patient, and selection of cuff size are all essential. It is increasingly recognized that office measurements correlate poorly with blood pressure measured in other settings, and that they can be supplemented by self-measured readings taken with validated devices at home. There is increasing evidence that home readings predict cardiovascular events and are particularly useful for monitoring the effects of treatment. Twenty-four-hour ambulatory monitoring gives a better prediction of risk than office measurements and is useful for diagnosing white-coat hypertension. There is increasing evidence that a failure of blood pressure to fall during the night may be associated with increased risk. In obese patients and children, the use of an appropriate cuff size is of paramount importance.

Key Words: hypertension ; ambulatory monitoring ; self-measurement

Ten years have passed since the last version of the American Heart Association (AHA) blood pressure measurement recommendations, during which time there have been major changes in the ways by which blood pressure is measured in clinical practice and research; hence, this document is a radical revision of previous versions. Blood pressure determination continues to be one of the most important measurements in all of clinical medicine and is still one of the most inaccurately performed. Hypertension is a major risk factor for coronary heart disease, stroke, and renal failure, and affects approximately one-third of the American population. The latest version of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) recommendations has drawn attention to the condition of " prehypertension," that is, people with blood pressures at the high end of the normal range, which applies to another one-quarter of the adult population. The target blood pressure for patients using antihypertensive treatment has recently been lowered for those with diabetes or renal disease.[1] Thus, it is becoming increasingly important to be able detect small differences in blood pressure.

The gold standard for clinical blood pressure measurement has always been readings taken by a trained health care provider using a mercury sphygmomanometer and the Korotkoff sound technique, but there is increasing evidence that this procedure may lead to the misclassification of large numbers of individuals as hypertensive and also to a failure to diagnose blood pressure that may be normal in the clinic setting but elevated at other times in some individuals. There are 3 main reasons for this: (1) inaccuracies in the methods, some of which are avoidable; (2) the inherent variability of blood pressure; and (3) the tendency for blood pressure to increase in the presence of a physician (the so-called white coat effect).

Numerous surveys have shown that physicians and other health care providers rarely follow established guidelines for blood pressure measurement; however, when they do, the readings correlate much more closely with more objective measures of blood pressure than the usual clinic readings. It is generally agreed that conventional clinic readings, when made correctly, are a surrogate marker for a patient' s true blood pressure, which is conceived as the average level over prolonged periods of time, and which is thought to be the most important component of blood pressure in determining its adverse effects. Usual clinic readings give a very poor estimate of this, not only because of poor technique but also because they typically only consist of 1 or 2 individual measurements, and the beat-to-beat blood pressure variability is such that a small number of readings can only give a crude estimate of the average level.

There are potentially 3 measures of blood pressure that could contribute to the adverse effects of hypertension. The first is the average level, the second is the diurnal variation, and the third is the short-term variability. At the present time, the measure of blood pressure that is most clearly related to morbid events is the average level, although there is also evidence accumulating that suggests that hypertensive patients whose pressure remains high at night (nondippers) are at greater risk for cardiovascular morbidity than dippers.[2] Less information is available for defining the clinical significance of blood pressure variability, although it has been suggested that it is a risk factor for cardiovascular morbidity.

The recognition of these limitations of the traditional clinic readings has led to 2 parallel developments: first, increasing use of measurements made out of the clinic, which avoids the unrepresentative nature of the clinic setting and also allows for increased numbers of readings to be taken; and second, the increased use of automated devices, which are being used both in and out of the office setting. This decreased reliance on traditional readings has been accelerated by the fact that mercury is being banned in many countries, although there is still uncertainty

regarding what will replace it. The leading contenders are aneroid and oscillometric devices, both of which are being used with increasing frequency but have not been accepted as being as accurate as mercury.

Epidemiology of Hypertension

1.1.1 Overview

Blood pressure is a powerful, consistent, and independent risk factor for cardiovascular disease and renal disease. According to the National Health And Nutrition Examination Survey (NHANES), at least 65 million adult Americans, or nearly one-third of the US adult population, have hypertension, defined as a systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, and/or current use of antihypertensive medication.[3] Another one-quarter of US adults have blood pressure in the " prehypertension" range, a systolic blood pressure of 120 to 139 mm Hg or diastolic blood pressure of 80 to 89 mm Hg, ie, a level above normal yet below the hypertensive range.[4] The prevalence of hypertension rises progressively with age, such that more than half of all Americans aged 65 years or older have hypertension.

Data from numerous observational epidemiological studies provide persuasive evidence of the direct relationship between blood pressure and cardiovascular disease. In a recent meta-analysis that aggregated data across 61 prospective observational studies that together enrolled 958 074 adults,[5] there were strong, direct relationships between average blood pressure and vascular mortality. These relationships were evident in middle-aged and older-aged individuals. Importantly, there was no evidence of a blood pressure threshold, that is, cardiovascular mortality increased progressively throughout the range of blood pressure, including the prehypertensive range. It has been estimated that ≈ 15% of blood pressure– related deaths from coronary heart disease occur in individuals with blood pressure in the prehypertensive range.[6]

Individual trials and meta-analyses of clinical trials have conclusively documented that antihypertensive drug therapy reduces the risk of cardiovascular events in hypertensive individuals. Such evidence provides strong evidence for current efforts to identify and treat individuals with hypertension and for parallel efforts to identify individuals with prehypertension, who are at risk for hypertension and blood pressure– related morbidity.

1.1.2 Systolic, Diastolic, and Pulse Pressure

Several dimensions of blood pressure are associated with an increased risk of vascular disease. Clinic-based measurements that predict vascular disease include systolic and diastolic blood pressure, as well as mean arterial pressure and pulse pressure. Several studies have attempted to tease apart the relative importance of these measurements.[7,8] Despite evolving interest in pulse pressure, the best available evidence still supports the use of systolic and diastolic blood pressures as a means to classify individuals.

1.1.3 Importance of Blood Pressure Variability

It has been suggested that blood pressure variability may be an independent risk factor for cardiovascular morbidity, on the grounds that biological materials are more susceptible to damage by changes of pressure than steady-state levels. There are many different ways of expressing blood pressure variability, ranging from beat-to-beat changes[9] to long-term changes between office visits.[10] Although there have been some studies supporting a pathological role of increased variability,[10,11] it remains unclear to what extent such adverse effects are a manifestation of more extensive target organ damage impairing the baroreflex regulation of blood pressure (and hence increasing blood pressure variability) as opposed to a direct effect of the variability itself.

“ Labile hypertension” is a term that has been used in the past to describe blood pressure that is unusually variable, but the wider use of out-of-office monitoring has shown that lability of blood pressure is the rule rather than the exception.

Classification/Subtypes of Hypertension

1.1.4 Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure Classification

The health risks attributable to increasing blood pressure in adults are continuous, beginning at 115/75 mm Hg.[12] Definitions have been established based on these risks and on the demonstrated net health benefits of blood pressure reduction. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[1] (JNC 7) has continued the definition of hypertension beginning at 140/90 mm Hg for adults aged 18 or older. The classification is based on the average of ≥ 2 seated blood pressure measurements, properly measured with well-maintained equipment, at each of ≥ 2 visits to the office or clinic. Hypertension has been divided into stages 1 and 2, as shown in Table 1. JNC 7 has defined normal blood pressure as <120 and <80. The intervening levels, 120 to 139 and 80 to 89 mm Hg, are now defined as prehypertension, a group that has increasing health risks and from which definite hypertension progresses.

TABLE 1. Classification of Hypertension (JNC-7)

BP Classification	SBP mm Hg*	DBP mm Hg*
Normal	<120	<80
Prehypertensive	120-139	80-89
Stage 1 hypertension	140-159	90-99
Stage 2 hypertension	≥160	1≥100
*Classification determined by higher BP category.		
BP indicates blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.		

Current recommendations from World Health Organizations, International Society of Hypertension, and European Society of Hypertension/European Society of Cardiology continue to divide stage 2 hypertension, with stage 3 beginning at ≥ 180 and ≥ 110.[13] They also refer to <120/<80 as optimal, 120 to 129/80 to 84 as normal, and 130 to 139/85 to 89 as high normal. Classification determined by self-measurement or ambulatory assessment is provided in those sections of this statement.

1.1.5 Isolated Systolic Hypertension

As adults age, systolic blood pressure tends to rise and diastolic tends to fall. When the average systolic blood pressure is ≥ 140 and diastolic blood pressure is <90, the patient is classified as having isolated systolic hypertension. The increased pulse pressure (systolic– diastolic) and systolic pressure predict risk and determine treatment.[14]

1.1.6 Isolated Systolic Hypertension of the Young

In older children and young adults, often males, the combination of rapid growth in height and very elastic arteries accentuates the normal amplification of the pressure wave between the aorta and brachial artery, resulting in a high systolic pressure in the brachial artery but normal diastolic and mean pressures. The aortic systolic pressure is normal, however. This can be suspected from pulse wave analysis or intra-aortic blood pressure measurements.[15]

1.1.7 Isolated Diastolic Hypertension

More commonly seen in some younger adults, isolated diastolic hypertension is defined as a systolic pressure <140 and a diastolic ≥ 90. Although diastolic pressure is generally thought to be the best predictor of risk in patients younger than 50,[16] some prospective studies of isolated diastolic hypertension have indicated that the prognosis may be benign.[17] This topic remains controversial, however.

1.1.8 White-Coat Hypertension or Isolated Office Hypertension

In ≈ 15% to 20% of people with stage 1 hypertension, blood pressure may only be elevated persistently in the presence of a health care worker, particularly a physician. When measured elsewhere, including while at work, the blood pressure is not elevated. When this phenomenon is detected in patients not taking medications, it is referred to as white-coat hypertension (WCH). The commonly used definition is a persistently elevated average office blood pressure of >140/90 and an average awake ambulatory reading of <135/85 mm Hg.[18] Although it can occur at any age, it is more common in older men and women. The phenomenon responsible for WCH is commonly referred to as the white coat effect and is defined as the difference between the office and daytime ambulatory blood pressure; it is present in the majority of hypertensive patients. Its magnitude can be reduced (but not eliminated) by the use of stationary oscillometric devices that automatically determine and analyze a series of blood pressures over 15 to 20 minutes with the patient in a quiet environment in the office or clinic. Other health risk factors are often present and should be treated accordingly. Its prognosis is discussed further in the section on Prognostic Significance in Ambulatory Blood Pressure Measurement. In some patients, WCH may progress to definite sustained hypertension, and all need to be followed-up indefinitely with office and out-of-office measurements of blood pressure. Treatment with antihypertensive drugs may lower the office blood pressure but does not change the ambulatory measurement.[19] This pattern of findings suggests that drug treatment of WCH is less beneficial than treatment of sustained hypertension.

1.1.9 Masked Hypertension or Isolated Ambulatory Hypertension

Somewhat less frequent than WCH but more problematic to detect is the converse condition of normal blood pressure in the office and elevated blood pressures elsewhere, eg, at work or at home. Lifestyle can contribute to this, eg, alcohol, tobacco, caffeine consumption, and physical activity away from the clinic/office. Target organ damage is related to the more prolonged elevations in pressure away from the physician' s office and the presence of such when the blood pressure is normal in the office can be a clue.[20] There is also some evidence that such patients are at increased risk.[21]

1.1.10 Pseudohypertension

When the peripheral muscular arteries become very rigid from advanced (often calcified) arteriosclerosis, the cuff has to be at a higher pressure to compress them. Rarely, usually in elderly patients or those with longstanding diabetes or chronic renal failure, it may be very difficult to do so. The brachial or radial artery may be palpated distal to the fully inflated cuff in these instances (positive Osler sign). The patients may be overdosed with

antihypertensive medications inadvertently, resulting in orthostatic hypotension and other side effects. When suspected, an intra-arterial radial artery blood pressure can be obtained for verification. The Osler maneuver is not a reliable screen for pseudohypertension. It was present in 7.2% of 3387 persons older than 59 years screened for the Systolic Hypertension in the Elderly Program (SHEP) study—more common in men, those found to be hypertensive, and those with a history of stroke.[22] However, the Osler maneuver may be positive in the absence of pseudohypertension in one-third of hospitalized elderly subjects.[23]

1.1.11 Orthostatic or Postural Hypotension

Orthostatic hypotension is defined as a reduction of systolic blood pressure of at least 20 mm Hg or 10 mm Hg in diastolic blood pressure within 3 minutes of quiet standing.[15] An alternative method is to detect a similar fall during head-up tilt at 60 degrees. This may be asymptomatic or accompanied by symptoms of lightheadedness, faintness, dizziness, blurred vision, neck ache, and cognitive impairment. Factors affecting this response to posture include food ingestion, time of day, medications, ambient temperature, hydration, deconditioning, standing after vigorous exercise, and age.[24,25] If chronic, the fall of blood pressure may be part of pure autonomic failure, multiple system atrophy, associated with Parkinsonism or a complication of diabetes, multiple myeloma, and other dysautonomias. Patients with autonomic failure exhibit a disabling failure of control of many autonomic functions. The major life-limiting failure is inability to control the level of blood pressure, especially in those patients with orthostatic hypotension who concomitantly have supine hypertension. In these patients, there are great and swift changes in pressure so that the patients faint because of profound hypotension on standing and have very severe hypertension when supine during the night. Often the heart rate is fixed as well. The supine hypertension subjects them to life-threatening target organ damage such as left ventricular hypertrophy, coronary heart disease, flash pulmonary edema, heart failure, renal failure, stroke, and sudden death (presumably caused by central apnea or cardiac arrhythmias).[26– 28]

Blood Pressure Measurement Methods

The auscultatory method has been the mainstay of clinical blood pressure measurement for as long as blood pressure has been measured but is gradually being supplanted by other techniques that are more suited to automated measurement.

1.1.12 The Auscultatory Method—Mercury, Aneroid, and Hybrid Sphygmomanometers

It is surprising that nearly 100 years after it was first discovered, and the subsequent recognition of its limited accuracy, the Korotkoff technique for measuring blood pressure has continued to be used without any substantial improvement. The brachial artery is occluded by a cuff placed around the upper arm and inflated to above systolic pressure. As it is gradually deflated, pulsatile blood flow is re-established and accompanied by sounds that can be detected by a stethoscope held over the artery just below the cuff. Traditionally, the sounds have been classified as 5 phases: phase I, appearance of clear tapping sounds corresponding to the appearance of a palpable pulse; phase II, sounds become softer and longer; phase III, sounds become crisper and louder; phase IV, sounds become muffled and softer; and phase V, sounds disappear completely. The fifth phase is thus recorded as the last audible sound.

The sounds are thought to originate from a combination of turbulent blood flow and oscillations of the arterial wall. There is agreement that the onset of phase I corresponds to systolic pressure but tends to underestimate the systolic pressure recorded by direct intra-arterial measurement.[29] The disappearance of sounds (phase V)

corresponds to diastolic pressure but tends to occur before diastolic pressure determined by direct intra-arterial measurement.[29] No clinical significance has been attached to phases II and III.

The Korotkoff sound method tends to give values for systolic pressure that are lower than the true intra-arterial pressure, and diastolic values that are higher.[30,31] The range of discrepancies is quite striking: One author commented that the difference between the 2 methods might be as much as 25 mm Hg in some individuals.[32] There has been disagreement in the past as to whether phase IV or V of the Korotkoff sounds should be used for recording diastolic pressure, but phase IV tends to be even higher than phase V when compared against the true intra-arterial diastolic pressure and is more difficult to identify than phase V. There is now general consensus that the fifth phase should be used, except in situations in which the disappearance of sounds cannot reliably be determined because sounds are audible even after complete deflation of the cuff, for example, in pregnant women, patients with arteriovenous fistulas (eg, for hemodialysis), and aortic insufficiency.[33– 35] Most of the large-scale clinical trials that have evaluated the benefits of treating hypertension have used the fifth phase.

In older patients with a wide pulse pressure, the Korotkoff sounds may become inaudible between systolic and diastolic pressure, and reappear as cuff deflation is continued. This phenomenon is known as the auscultatory gap. In some cases, this may occur because of fluctuations of intra-arterial pressure and is most likely to occur in subjects with target organ damage.[36] The auscultatory gap often can be eliminated by elevating the arm overhead for 30 seconds before inflating the cuff and then bringing the arm to the usual position to continue in the measurement. This maneuver reduces vascular volume in the limb and improves inflow to enhance the Korotkoff sounds. The auscultatory gap is not an issue with nonauscultatory methods.

1.1.12.1 *Mercury Sphygmomanometers*

The mercury sphygmomanometer has always been regarded as the gold standard for clinical measurement of blood pressure, but this situation is likely to change in the near future, as discussed. The design of mercury sphygmomanometers has changed little over the past 50 years, except that modern versions are less likely to spill mercury if dropped. In principle, there is less to go wrong with mercury sphygmomanometers than with other devices, and one of the unique features is that the simplicity of the design means that there is negligible difference in the accuracy of different brands, which certainly does not apply to any other type of manometer. However, this should not be any cause for complacency. One hospital survey found that 21% of devices had technical problems that would limit their accuracy,[37] whereas another found >50% to be defective.[38] The random zero sphygmomanometer was designed to eliminate observer bias but is no longer available.

1.1.12.2 *Aneroid Sphygmomanometers*

In these devices, the pressure is registered by a mechanical system of metal bellows that expands as the cuff pressure increases and a series of levers that register the pressure on a circular scale. This type of system does not necessarily maintain its stability over time, particularly if handled roughly. They therefore are inherently less accurate than mercury sphygmomanometers and require calibrating at regular intervals. Recent developments in the design of aneroid devices may make them less susceptible to mechanical damage when dropped. Wall-mounted devices may be less susceptible to trauma and, hence, more accurate than mobile devices.[39]

The accuracy of the manometers varies greatly from one manufacturer to another. Thus, 4 surveys conducted in hospitals in the past 10 years have examined the accuracy of the aneroid devices and have shown significant

inaccuracies ranging from 1%[39,40] to 44%.[37] The few studies that have been conducted with aneroid devices have focused on the accuracy of the pressure registering system as opposed to the degree of observer error, which is likely to be higher with the small dials used in many of the devices.

1.1.12.3 *Hybrid Sphygmomanometers*

Devices have been developed that combine some of the features of both electronic and auscultatory devices, and are referred to as " hybrid" sphygmomanometers. The key feature is that the mercury column is replaced by an electronic pressure gauge, such as are used in oscillometric devices. Blood pressure is taken in the same way as with a mercury or aneroid device, by an observer using a stethoscope and listening for the Korotkoff sounds. The cuff pressure can be displayed as a simulated mercury column, as a digital readout, or as a simulated aneroid display. In one version, the cuff is deflated in the normal way, and when systolic and diastolic pressure are heard a button next to the deflation knob is pressed, which freezes the digital display to show systolic and diastolic pressures. This has the potential of minimizing terminal digit preference, which is a major source of error with mercury and aneroid devices. The hybrid sphygmomanometer has the potential to become a replacement for mercury, because it combines some of the best features of both mercury and electronic devices at any rate until the latter become accurate enough to be used without individual validation.[41]

1.1.13 The Oscillometric Technique

This was first demonstrated by Marey in 1876,[42] and it was subsequently shown that when the oscillations of pressure in a sphygmomanometer cuff are recorded during gradual deflation, the point of maximal oscillation corresponds to the mean intra-arterial pressure.[43,44] The oscillations begin well above systolic pressure and continue below diastolic, so that systolic and diastolic pressures can only be estimated indirectly according to some empirically derived algorithm. One advantage of the method is that no transducer need be placed over the brachial artery, so that placement of the cuff is not critical. Other potential advantages of the oscillometric method for ambulatory monitoring are that it is less susceptible to external noise (but not to low-frequency mechanical vibration), and that the cuff can be removed and replaced by the patient, for example, to take a shower. The main problem with the technique is that the amplitude of the oscillations depends on several factors other than blood pressure, most importantly the stiffness of the arteries. Thus, in older people with stiff arteries and wide pulse pressures the mean arterial pressure may be significantly underestimated.[45] The algorithms used for detecting systolic and diastolic pressures are different from one device to another and are not divulged by the manufacturers. The differences between devices has been dramatically shown by studies using simulated pressure waves, in which a systolic pressure of 120 mm Hg was registered as low as 110 and as high as 125 mm Hg[46] by different devices. Another disadvantage is that such recorders do not work well during physical activity, when there may be considerable movement artifact. Additionally, the bladders deflate at a manufacturer-specific " bleed rate," which assumes a regular pulse between bleed steps as part of the algorithms used to determine systolic and diastolic pressure.

The oscillometric technique has been used successfully in ambulatory blood pressure monitors and home monitors. Comparisons of several different commercial models with intra-arterial and Korotkoff sound measurements have shown generally good agreement,[47– 49] but the results have been better with ambulatory monitors than with the cheaper devices marketed for home use. Oscillometric devices are also now available for taking multiple measurements in a clinic setting.

1.1.14 The Finger Cuff Method of Penaz

This interesting method was first developed by Penaz[50] and works on the principle of the " unloaded arterial wall." Arterial pulsation in a finger is detected by a photoplethysmograph under a pressure cuff. The output of the plethysmograph is used to drive a servo-loop, which rapidly changes the cuff pressure to keep the output constant, so that the artery is held in a partially opened state. The oscillations of pressure in the cuff are measured and have been found to resemble the intra-arterial pressure wave in most subjects. This method gives an accurate estimate of the changes of systolic and diastolic pressure, although both may be underestimated (or overestimated in some subjects) when compared with brachial artery pressures[50]; the cuff can be kept inflated for up to 2 hours. It is now commercially available as the Finometer (formerly Finapres) and Portapres recorders, and has been validated in several studies against intra-arterial pressures.[51,52] The Portapres enables readings to be taken over 24 hours while the subjects are ambulatory, although it is somewhat cumbersome.[53]

This method in its present form is not suited to clinical use because of its cost, inconvenience, and relative inaccuracy for measuring absolute levels of blood pressure. Its greatest value is for research studies assessing short-term changes of blood pressure and its variability. The finger blood pressure monitors that are available in drug stores do not use this method.

1.1.15 Ultrasound Techniques

Devices incorporating this technique use an ultrasound transmitter and receiver placed over the brachial artery under a sphygmomanometer cuff. As the cuff is deflated, the movement of the arterial wall at systolic pressure causes a Doppler phase shift in the reflected ultrasound, and diastolic pressure is recorded as the point at which diminution of arterial motion occurs.[54] Another variation of this method detects the onset of blood flow, which has been found to be of particular value for measuring systolic pressure in infants and children.[55]

In patients with very faint Korotkoff sounds (for example those with muscular atrophy), placing a Doppler probe over the brachial artery may help to detect the systolic pressure, and the same technique can be used for measuring the ankle– arm index, in which the systolic pressures in the brachial artery and the posterior tibial artery are compared to obtain an index of peripheral arterial disease.

1.1.16 Tonometry

The principle of this technique is that when an artery is partially compressed or splinted against a bone, the pulsations are proportional to the intra-arterial pressure. This has been developed for measurement of the blood pressure at the wrist, because the radial artery lies just over the radius bone.[56] However, the transducer needs to be situated directly over the center of the artery; hence, the signal is very position-sensitive. This has been dealt with by using an array of transducers placed across the artery. Although the technique has been developed for beat-to-beat monitoring of the wrist blood pressure, it requires calibration in each patient and is not suitable for routine clinical use.

Another application is applanation tonometry, in which a single transducer is held manually over the radial artery to record the pressure waveform while systolic and diastolic pressures are measured from the brachial artery. This technique has been used to estimate central aortic pressure. The rationale for this is that the arterial pressure at the level of the aortic root is different from the brachial artery pressure, and that this difference varies according to a number of physiological and pathological variables. Thus, it might be expected that the aortic pressure might predict cardiac events more closely than the brachial artery pressure. The shape of the pressure waveform in the arterial

tree is determined by a combination of the incident wave and the wave reflected from the periphery. In hypertensive subjects and subjects with stiff arteries, the systolic pressure wave in the aorta and brachial artery is augmented by a late systolic peak, which can be attributed to wave reflection and which is not seen in more peripheral arteries such as the radial artery. Using Fourier analysis, it is possible to derive the central aortic pressure waveform from the radial artery trace. However, comparisons with directly recorded aortic pressure made during cardiac catheterization have shown considerable scatter between the estimated and true values,[57] so the technique cannot yet be recommended for routine clinical practice.

1.1.17 Location of Measurement—Arm, Wrist, Finger

The standard location for blood pressure measurement is the upper arm, with the stethoscope at the elbow crease over the brachial artery, although there are several other sites where it can be performed. Monitors that measure pressure at the wrist and fingers have become popular, but it is important to realize that the systolic and diastolic pressures vary substantially in different parts of the arterial tree. In general, the systolic pressure increases in more distal arteries, whereas the diastolic pressure decreases. Mean arterial pressure falls by only 1 to 2 mm Hg between the aorta and peripheral arteries.[58]

1.1.17.1 ***Wrist Monitors***

Wrist monitors have the advantages of being smaller than the arm devices and can be used in obese people, because the wrist diameter is little affected by obesity. A potential problem with wrist monitors is the systematic error introduced by the hydrostatic effect of differences in the position of the wrist relative to the heart.[59] This can be avoided if the wrist is always at heart level when the readings are taken, but there is no way of knowing retrospectively whether this was performed when a series of readings are reviewed. Devices are now available that will only record a measurement when the monitor is held at heart level. Wrist monitors have potential but need to be evaluated further.[60]

1.1.17.2 ***Finger Monitors***

Finger monitors have so far been found to be inaccurate and are not recommended.[61]

1.1.18 Validation of Monitors

All monitors in clinical use should be tested for accuracy. This involves 2 stages. First, all oscillometric automated monitors that provide read-outs of systolic and diastolic pressure should be subjected by independent investigators to formal validation protocols. The original 2 protocols that gained the widest acceptance were developed by the Association for the Advancement of Medical Instrumentation (AAMI) in 1987 and the British Hypertension Society (BHS) in 1990, with revisions to both in 1993, and to AAMI in 2002.[62] These required testing of a device against 2 trained human observers in 85 subjects, which made validation studies difficult to perform. One consequence of this has been that there are still many devices on the market that have never been adequately validated. More recently, an international group of experts who are members of the European Society of Hypertension Working Group on Blood Pressure Monitoring has produced an International Protocol that could replace the 2 earlier versions[63] and is easier to perform. Briefly, it requires comparison of the device readings (4 in all) alternating with 5 mercury readings taken by 2 trained observers. Devices are recommended for approval if both systolic and diastolic readings taken are at least within 5 mm Hg of each other for at least 50% of readings.

It is recommended that only those devices that have passed this or similar tests should be used in practice. However, the fact that a device passed a validation test does not mean that it will provide accurate readings in all patients. There can be substantial numbers of individual subjects in whom the error is consistently >5 mm Hg with a device that has achieved a passing grade.[64] This may be more likely to occur in elderly[65] or diabetic patients.[66] For this reason, it is recommended that each oscillometric monitor should be validated on each patient before the readings are accepted. No formal protocol has yet been developed for doing this, but if sequential readings are taken with a mercury sphygmomanometer and the device, then major inaccuracies can be detected.

Another problem is that manufacturers may change the model number after a device has been tested without indicating whether the measurement algorithm has also been changed.

With nonautomatic devices, such as mercury and aneroid monitors, it is recommended that the accuracy of the pressure registration mechanism be checked. In the case of mercury sphygmomanometers, this involves checking that the upper curve of the meniscus of the mercury column is at 0 mm Hg, that the column is free of dirt, and that it rises and falls freely during cuff inflation and deflation.

Aneroid devices or other nonmercury devices should be checked by connecting the manometer to a mercury column or an electronic testing device with a Y-tube. The needle should rest at the zero point before the cuff is inflated and should register a reading that is within 4 mm Hg of the mercury column when the cuff is inflated to pressures of 100 and 200 mm Hg. The needle should return to zero after deflation.

Blood Pressure Measurement in the Clinic or Office

Accurate auscultatory office blood pressure measurement is the bedrock of the diagnosis and treatment of hypertension and has been the standard method used in the major epidemiologic and treatment trials of the past 50 years. However, it is becoming increasingly clear that as it is used in everyday practice, there are major shortcomings. Thus, surveys of mercury devices in clinical practices have shown that there are frequently mechanical defects,[67] and physicians rarely follow official guidelines for their use.[67] Added to these is the phenomenon of the white coat effect, whereby the recorded blood pressure may be unrepresentative of the patient’ s true blood pressure.

1.1.19 Subject Preparation

A number of factors related to the subject can cause significant deviations in measured blood pressure. These include room temperature, exercise, alcohol or nicotine consumption, positioning of the arm, muscle tension, bladder distension, talking, and background noise.[28] The patient should be asked to remove all clothing that covers the location of cuff placement. The individual should be comfortably seated, with the legs uncrossed, and the back and arm supported, such that the middle of the cuff on the upper arm is at the level of the right atrium (the mid-point of the sternum). Measurements made while the patient is on an examining table do not fulfill these criteria and should preferably be made while the patient is seated in a chair. At the initial visit, blood pressure should be measured in both arms. The patient should be instructed to relax as much as possible and to not talk during the measurement procedure; ideally, 5 minutes should elapse before the first reading is taken.

1.1.20 Choice of Blood Pressure Measurement Devices

The " gold standard" device for office blood pressure measurement has been the mercury sphygmomanometer, but these are being removed from clinical practice because of environmental concerns about mercury contamination.[68] Mercury sphygmomanometers are already banned in Veterans Administration hospitals. There is a role for other types of device in office use, both as a substitute for the traditional mercury readings (eg, aneroid and hybrid sphygmomanometers) and as supplements to them (eg, oscillometric automatic devices). However, because there is currently no generally accepted replacement for mercury, it is recommended that, if available, a properly maintained mercury sphygmomanometer be used for routine office measurements. Mercury sphygmomanometers are critical for evaluating the accuracy of any type of nonmercury device. Nonmercury pressurometers that use electronic pressure transducers with a digital read-out are available for calibrating the pressure detection systems of aneroid or oscillometric devices.

1.1.21 Cuff Size

Von Recklinghausen in 1901 recognized that Riva Rocci' s device for determination of accurate systolic blood pressure by palpation had a significant flaw, its 5-cm-width cuff.[69] Multiple authors have shown that the error in blood pressure measurement is larger when the cuff is too small relative to the patient' s arm circumference[70– 76] than when it is too large. Previous epidemiological data from Britain[77] and Ireland[78] had suggested that arm circumferences of >34 cm were uncommon. Data from NHANES III and NHANES 2000 have shown the opposite in the United States. In the United States during the period from 1988 to 2000, there has been a significant increase in mean arm circumference and an increase in the frequency of arm circumferences of >33 cm was found because of increasing weight in the American population.[79] This should not be surprising, because the prevalence of obesity in the United States has increased from 22.9% in NHANES III (1988 to 1994) to >30% in 2000.[80] Similar data regarding the increased frequency of larger arm circumferences were also found in a study of a referral practice of hypertensive subjects, in which a striking 61% of 430 subjects had an arm circumference of ≥ 33 cm.[81] Recognition of the increasing need for the " large adult" cuff, or even the thigh cuff, for accurate blood pressure measurement is critical, because frequently in practice only the standard adult size has been demonstrated to be available.[82] More importantly, it has been demonstrated that the most frequent error in measuring blood pressure in the outpatient clinic is " miscuffing," with undercuffing large arms accounting for 84% of the " miscuffings." [83]

The " ideal" cuff should have a bladder length that is 80% and a width that is at least 40% of arm circumference (a length-to-width ratio of 2:1). A recent study comparing intra-arterial and auscultatory blood pressure concluded that the error is minimized with a cuff width of 46% of the arm circumference.[84] The recommended cuff sizes are:

- For arm circumference of 22 to 26 cm, the cuff should be " small adult" size: 12×22 cm
- For arm circumference of 27 to 34 cm, the cuff should be " adult" size: 16×30 cm
- For arm circumference of 35 to 44 cm, the cuff should be " large adult" size: 16×36 cm
- For arm circumference of 45 to 52 cm, the cuff should be " adult thigh" size: 16×42 cm

The optimum ratios of width and length to arm circumference are shown for the small adult and standard adult cuffs. For the large adult and thigh cuffs, the ideal width ratio of 46% of arm circumference is not practical, because it would result in a width of 20 cm and 24 cm, respectively. These widths would give a cuff that would not be clinically usable for most patients, so for the larger cuffs, a less than ideal ratio of width to arm circumference must be accepted. The ideal ratio of length to arm circumference is maintained in all 4 cuffs.

In practice, bladder width is easily appreciated by the clinician but bladder length often is not, because the bladder is enclosed in the cuff. To further complicate the issue for clinicians, there are no standards for manufacturers of different sizes of blood pressure cuff. This has led to significant differences in which arm circumferences are accurately measured by individual manufacturers' standard adult and large adult cuffs.

Individual cuffs should be labeled with the ranges of arm circumferences, to which they can be correctly applied, preferably by having lines that show whether the cuff size is appropriate when it is wrapped around the arm. In patients with morbid obesity, one will encounter very large arm circumferences with short upper arm length. This geometry often cannot be correctly cuffed, even with the thigh cuff. In this circumstance, the clinician may measure blood pressure from a cuff placed on the forearm and listening for sounds over the radial artery (although this may overestimate systolic blood pressure)[85] or use a validated wrist blood pressure monitor held at the level of the heart.[86,87]

1.1.22 Effects of Body Position

Blood pressure measurement is most commonly made in either the sitting or the supine position, but the 2 positions give different measurements. It is widely accepted that diastolic pressure measured while sitting is higher than when measured supine (by ≈ 5 mm Hg), although there is less agreement about systolic pressure.[88] When the arm position is meticulously adjusted so that the cuff is at the level of the right atrium in both positions, the systolic pressure has been reported to be 8 mm Hg higher in the supine than the upright position.[89]

Other considerations include the position of the back and legs. If the back is not supported (as when the patient is seated on an examination table as opposed to a chair), the diastolic pressure may be increased by 6 mm Hg.[90] Crossing the legs may raise systolic pressure by 2 to 8 mm Hg.[91]

In the supine position, the right atrium is approximately halfway between the bed and the level of the sternum[92]; thus, if the arm is resting on the bed, it will be below heart level. For this reason, when measurements are taken in the supine position the arm should be supported with a pillow. In the sitting position, the right atrium level is the midpoint of the sternum or the fourth intercostal space.

1.1.23 Effects of Arm Position

The position of the arm can have a major influence when the blood pressure is measured; if the upper arm is below the level of the right atrium (when the arm is hanging down while in the sitting position), the readings will be too high. Similarly, if the arm is above the heart level, the readings will be too low. These differences can be attributed to the effects of hydrostatic pressure[59] and may be 10 mm Hg or more,[93] or 2 mm Hg for every inch above or below the heart level.

Other physiological factors that may influence the blood pressure during the measurement process include muscle tension. If the arm is held up by the patient (as opposed to being supported by the observer), the isometric exercise will raise the pressure.

1.1.24 Differences Between the 2 Arms

Several studies have compared the blood pressure measured in both arms, mostly using the auscultatory technique. Almost all have reported finding differences, but there is no clear pattern; thus, the difference does not appear to be determined by whether the subject is right- or left-handed.[94] One of the largest studies was conducted

in 400 subjects using simultaneous measurements with oscillometric devices, which found no systematic differences between the 2 arms, but 20% of subjects had differences of >10 mm Hg.[94] Although these findings are disturbing, it is not clear to what extent the differences were consistent and reproducible, as opposed to being the result of inherent blood pressure variability. Nevertheless, it is recommended that blood pressure should be checked in both arms at the first examination. This may be helpful in detecting coarctation of the aorta and upper extremity arterial obstruction. When there is a consistent interarm difference, the arm with the higher pressure should be used. In women who have had a mastectomy, blood pressure can be measured in both arms unless there is lymphedema.

1.1.25 Cuff Placement and Stethoscope

Cuff placement must be preceded by selection of the appropriate cuff size for the subject' s arm circumference. The observer must first palpate the brachial artery in the antecubital fossa and place the midline of the bladder of the cuff (commonly marked on the cuff by the manufacturer) so that it is over the arterial pulsation over the patient' s bare upper arm. The sleeve should not be rolled up such that it has a tourniquet effect above the blood pressure cuff. The lower end of the cuff should be 2 to 3 cm above the antecubital fossa to allow room for placement of the stethoscope. However, if a cuff that leaves such space has a bladder length that does not sufficiently encircle the arm (at least 80%), a larger cuff should be used, recognizing that if the cuff touches the stethoscope, artifactual noise will be generated. The cuff is then pulled snugly around the bare upper arm. Neither the observer nor the patient should talk during the measurement. Phase 1 (systolic) and phase 5 (diastolic) Korotkoff sounds are best heard using the bell of the stethoscope over the palpated brachial artery in the antecubital fossa, although some studies have shown that there is little difference[90,95] when using the bell or the diaphragm. The key to good measurement is the use of a high-quality stethoscope with short tubing, because inexpensive models may lack good tonal transmission properties required for accurate auscultatory measurement.

1.1.26 Inflation/Deflation System

Indirect blood pressure measurement requires that occlusion of the brachial artery is produced by gradual inflation and deflation of an appropriately sized cuff. The tubing from the device to the cuff must be of sufficient length (70 cm or more) to allow for its function in the office setting. Successful inflation and deflation requires an airtight system; ongoing inspection and maintenance of the tubing for deterioration of the rubber (cracking) and the release valve are required. The cuff should initially be inflated to at least 30 mm Hg above the point at which the radial pulse disappears. The rate of deflation has a significant effect on blood pressure determination. Deflation rates >2 mm per second can lead to a significant underestimation of systolic and overestimation of diastolic blood pressure. Automated devices with a linear deflation rate may have improved accuracy over the more common circumstances in automated devices that have stepwise deflation. It is recommended that a deflation rate of 2 to 3 mm Hg per second (or per pulse when the heart rate is very slow) be used.[96,97]

1.1.26.1 ***Important Points for Clinical Blood Pressure Measurement***

- The patient should be seated comfortably with the back supported and the upper arm bared without constrictive clothing. The legs should not be crossed.
- The arm should be supported at heart level, and the bladder of the cuff should encircle at least 80% of the arm circumference.
- The mercury column should be deflated at 2 to 3 mm/s, and the first and last audible sounds should be taken as systolic and diastolic pressure. The column should be read to the nearest 2 mm Hg.

- Neither the patient nor the observer should talk during the measurement.

1.1.27 Observer

The observer is the most critical component of accurate blood pressure measurement. For accurate blood pressure measurement, the observer must: (1) be properly trained in the techniques of blood pressure measurement; (2) use an accurate and properly maintained device; (3) recognize subject factors, such as anxiety and recent nicotine use, that would adversely affect blood pressure measurements; (4) position the subject appropriately; (5) select the correct cuff and position it correctly; and (6) perform the measurement using the auscultatory or automated oscillometric method and accurately record the values obtained.

Observer error is a major limitation of the auscultatory method.[98] Systematic errors lead to intra-observer and interobserver error. Terminal digit preference is perhaps the most common manifestation of suboptimal blood pressure determination. It is generally recommended that the observer should read the blood pressure to the nearest 2 mm Hg, but an inappropriate excess in the recording of " zero" as the last digit in auscultatory blood pressure determinations has been reported by multiple investigators in clinical and research settings.[99,100] Digit bias or digit prejudice is particularly common when the observer recognizes a specific threshold value for blood pressure and, depending on the circumstances, records a pressure just above or below that number. A good example is the Syst-Eur Trial, which showed both increased zero preference and a significant digit bias for 148 mm Hg systolic, the threshold for successful treatment in that trial.[95]

1.1.28 Number of Measurements

It is well recognized that the predictive power of multiple blood pressure determinations is much greater than a single office reading.[101] One of the potential advantages of supplementing auscultatory readings with readings taken by an automated device is the ability to obtain a larger number of readings. When a series of readings is taken, the first is typically the highest. A minimum of 2 readings should be taken at intervals of at least 1 minute, and the average of those readings should be used to represent the patient' s blood pressure. If there is >5 mm Hg difference between the first and second readings, additional (1 or 2) readings should be obtained, and then the average of these multiple readings is used.

1.1.29 Automated Methods

Automated oscillometric blood pressure devices are increasingly being used in office blood pressure measurement, as well as for home and ambulatory monitoring. When they are used in the office, the readings are typically lower than readings taken by a physician or nurse. The potential advantages of automated measurement in the office are the elimination of observer error, minimizing the white coat effect, and increasing the number of readings. The main disadvantages are the error inherent in the oscillometric method and the fact that epidemiologic data are mostly based on auscultated blood pressure measures.

Automated devices may also offer the opportunity to avoid expensive and repetitive training of health care professionals in auscultation, which is necessary to reduce observer errors. Their use still requires careful patient evaluation for caffeine or nicotine use, selection of the correct cuff size, and proper patient positioning if accurate blood pressures are to be obtained. Devices are now available that can take a series of sequential readings and automatically average them.

1.1.30 The White Coat Effect and the Differences Between Physician and Nurse Blood Pressure Measurements

The initial epidemiological studies of hypertension and the first major hypertension treatment trial (VA Cooperative Study) were performed using physician blood pressure measurements.[102– 104] Since that time, all the major hypertension treatment trials have used a nurse, " a trained observer," or automated blood pressure measurements. In hypertensive patients (but not necessarily in normotensive patients), the blood pressure recorded by a physician or nurse is typically higher than the average daytime level, and this difference is commonly referred to as the white coat effect.

In addition to these effects of the medical environment on blood pressure measurement, there is a recognized difference between blood pressure levels measured by a physician versus a nurse in the same subjects. In the largest study of physician– nurse blood pressure differences, it was found that a nurse recorded significantly lower mean systolic and diastolic pressures than a physician (by 6.3/7.9 mm Hg).[105] This difference is not caused by any difference in technique, because when a dual-headed stethoscope is used and the physician and nurse simultaneously take the blood pressure, the physician– nurse difference is insignificant. In addition, the nurse-recorded blood pressure is usually closer to the patient' s daytime average pressure than the pressure recorded by the physician. Because all of the most recent treatment trials of hypertension are based on blood pressure measurements made by nurses or other professionals, but not by physicians, the difference in office blood pressure measured by physicians and nurses suggests that physician blood pressures should not be used exclusively in the routine management of the hypertensive subject.

Training of Observers

As the number and type of blood pressure measurement devices and direct-to-consumer advertising increase, more people are measuring blood pressure more frequently. In medical settings, physicians, nurses, nurses' aids, students, and pharmacists all measure blood pressure and record the values in a patient' s records. Outside medical settings, patients, family members, or lay persons also measure blood pressure. The training given to lay observers should be as comprehensive and similar to that recommended for health care professionals in ambulatory and community settings.[106] With careful training even unpaid volunteers in large population surveys can measure blood pressure accurately.[107] However, even with the newer automated devices, the accuracy of the readings can be optimal only if all observers are appropriately trained and retrained and conscientious about using appropriate techniques.

1.1.31 Required Competencies

Before training begins, potential observers should be assessed for physical and cognitive competencies required to perform the procedure. The physical requirements include the following:

- Vision. The observer must be able to see the dial of the manometer or the meniscus of the mercury column at eye level without straining or stretching, and must be able to read well enough to see the sphygmomanometer or digital display no further than 3 feet away.
- Hearing. The observer must be able to hear the appearance and disappearance of Korotkoff sounds.
- Eye/hand/ear coordination. This is required for the use of mercury and aneroid sphygmomanometers but not for the newer electronic technologies.

1.1.32 Training

Traditionally, health professionals are trained in blood pressure measurement in introductory courses on physical assessment. They may receive a classroom lecture with a video on how to measure blood pressure, some laboratory skills training with demonstration and practice on fellow trainees, and mentored experience measuring blood pressure of patients, potential research subjects, or community volunteers. In clinical trials, standardized programs with audiovisual tapes that test and retest accuracy in measurement are extremely effective in training and retraining. In contrast, such training and retraining is not routinely required in nonresearch settings.

Some information is available on the Internet,[108] and the British Hypertension Society has a web-based video that can be used for the training and evaluation of observers.[109]

1.1.33 Evaluation of Observers

Pencil-and-paper questionnaires or interviews can be used to assess knowledge of the correct methodology of blood pressure measurement. The evaluation of observers should include an assessment of their knowledge of the different types of observer bias, general technique, and the interpretation of the measurements, including an understanding of the normal variability of blood pressure by time of day, exercise, timing of antihypertensive medications, etc. The observers should also know how and when to communicate blood pressure readings gathered at home or other settings to the health care professional responsible for the care of the patient and management of hypertension.

Observers should be aware of the need to use only well-maintained and calibrated equipment, choosing a quiet location with adequate room temperature, correctly positioning the person having blood pressure measured, and ensuring that the person does not talk or move during the measurement.

The skills of the observer should be demonstrated by assessing items such as positioning the patient, selecting the right size cuff, obtaining a valid and reliable measurement, recording the measurement accurately, and appropriate reporting of abnormal levels.

1.1.34 Retraining

Correct blood pressure measurement technique is difficult to maintain without careful attention to all steps in the protocol and retraining. The gold standard for retraining has been set by federally funded multisite clinical trials of hypertension care and control, in which retraining is required of all blood pressure observers every 6 months. Retraining requires competency in cuff selection, patient positioning, no talking, and accurate observation of the blood pressure level by either auditory or visual assessment. Four methods of assessment are used: audio– video test tapes; Y-tube– connected simultaneous readings by 2 trained observers; a written quiz; and direct observation. In the National Heart, Lung, and Blood Institute (NLHBI)-sponsored multisite clinical trials, a senior experienced person is assigned as the central trial master trainer and a master trainer is designated for each site. The central master trainer trains the site master trainers, and they in turn train the observers at each site. This model could be replicated within hospitals, ambulatory care settings, and community agencies. Retraining of all health care professionals is strongly recommended.

Blood Pressure Measurement in Other Settings

1.1.35 Acute Care

Blood pressure measurements in acute care settings, such as the emergency department, dialysis unit, or operating suite, are usually performed to judge vital signs and volume status of the patient rather than the presence or absence of hypertension. Oscillometric devices are widely used for this purpose and may give accurate assessment of mean arterial pressure, but are often inaccurate for registering systolic and diastolic pressure.[110,111] Blood pressure values obtained in acute care settings are unlikely to be useful for decisions on chronic hypertension management,[112] because of inadequate patient preparation, faulty equipment,[82] and the impact of the acute illness on blood pressure. Still, high readings recorded in the emergency room do predict hypertension on subsequent clinic visits, to some extent,[113] and warrant follow-up.

Blood pressure measurement is also important in the prehospital setting. Multiple techniques of blood pressure determination in the field and ambulance and helicopter transportation environments, including auscultatory, oscillometric, palpation, and use of obliteration of the pulse wave on the pulse oximeter, have been used. All of these suffer from a high degree of error that is worse with systolic blood pressures of <90 mm Hg.[114– 116] In addition, it has been shown that standard equipment used by emergency medical services for blood pressure determination is often highly unreliable.[117] Determining blood pressures in prehospital settings requires a high degree of clinical experience and repetitive measurement. In this setting, establishment of trends in blood pressure before arriving in the more controlled hospital environment is more important than the absolute value of the blood pressure.

An elevated blood pressure in the acute care setting should raise the suspicion that the patient has hypertension, and a referral to the outpatient setting for further evaluation is warranted. Because of the lack of precision of blood pressure measurement (and the impact of bed rest, acute illness, medication administration, and alteration in the patient' s usual diet while in the hospital), blood pressures obtained in the acute care setting should not be used to judge the adequacy of blood pressure control.

1.1.36 Public Places

Automated blood pressure devices are commonly found in public places and represent a potential mechanism for increased screening for hypertension. In 1995, Whitcomb et al[118] reported that because the introduction of the VitaStat device in 1976, >8000 devices were in use in the United States, providing >10 million measurements per year. The initial version was the 8000 model, which was never tested by approved protocols and which was found to give very inconsistent results, particularly for systolic pressure.[119– 121] A later model (the 90550) has been tested in a community setting and has also failed to meet the BHS or AAMI criteria for accuracy.[122] Other potential problems with these devices are that the cuff size (23×33 cm) is inadequate for patients with large arms, and that they are not labeled to show when or if there has been recent maintenance and revalidation of the device' s performance. Clear demonstration to the user of ongoing device servicing and validation would be critical to acceptance of the devices for public blood pressure screening.

Self-Measurement

1.1.37 Types of Monitor

When self-monitoring or home-monitoring was first used, the majority of studies used aneroid sphygmomanometers.[123] In the past few years, automatic electronic devices have become increasingly popular.

The standard type of monitor for home use is now an oscillometric device that records pressure from the brachial artery.[124] Unfortunately, only a few have been subjected to proper validation tests such as the AAMI and BHS protocols, and of 24 devices that have been tested by these, only 5 have passed.[125] An up-to-date list of validated monitors is available.[126] The advantages of electronic monitors have begun to be appreciated by epidemiologists,[127] who have always been greatly concerned about the accuracy of clinical blood pressure measurement and have paid much attention to the problems of observer error, digit preference, and the other causes of inaccuracy described. It has been argued that the ease of use of the electronic devices and the relative insensitivity to who is actually taking the reading can outweigh any inherent inaccuracy compared with the traditional sphygmomanometer method.[127] This issue remains controversial, however.

Electronic devices are now available that will take blood pressure from the upper arm, wrist, or finger. Although the use of the more distal sites may be more convenient, measurement of blood pressure from the arm (brachial artery) has always been the standard method and is likely to remain so for the foreseeable future. The fact that a device has passed the validation criteria does not guarantee accuracy in the individual patient, and it is essential that each device be checked on each patient before the readings are accepted as being valid (see the previous section on Validation of Monitors). Home-monitoring devices should be checked for accuracy every 1 to 2 years.

1.1.38 Clinical Applications

Home- or self-monitoring has numerous advantages over ambulatory monitoring, principal among which are that it is relatively cheap and provides a convenient way for monitoring blood pressure over long periods of time. There is some evidence that it improves both therapeutic compliance and blood pressure control.[128– 130] However, technical, economic, and behavioral barriers have until now inhibited the widespread use of home-monitoring in clinical practice. Two technological developments, low-cost monitors with memory and systems for sending stored readings over the telephone, have the potential of overcoming these barriers.

Unfortunately, accurate readings do not guarantee accurate reporting to the physician. In 2 separate studies, patients were given home monitors, but they were not told that the devices had memory. Patients were urged to carefully record all readings, but in both studies, more than half the subjects omitted or fabricated readings.[131,132] Devices that have memory or printouts of the readings are therefore recommended.

It is recommended that when readings are taken, the patient should not have recently indulged in any activity such as exercise or eating that is likely to affect the blood pressure, and the patient should be resting quietly in a comfortable chair for 3 to 5 minutes with the upper arm at heart level. Three readings should be taken in succession, separated by at least 1 minute. The first is typically the highest, and the average should be used as the blood pressure reading. It is helpful to get readings in the early morning and the evening.

1.1.39 What Is Normal Home Blood Pressure?

Home blood pressures are consistently lower than clinic pressures in most hypertensive patients.[133] Several recent studies have addressed the question of the level of home pressure that best corresponds to a normal clinic pressure of 140/90 mm Hg. The largest, the Ohasama study, proposed a level of 137/84 mm Hg as an acceptable upper limit for home readings[134– 136] on the grounds that cardiovascular risk increases above this level. An ad hoc committee of the American Society of Hypertension, reviewing several studies, recommended 135/85 mm Hg as the upper limit of normal for home and ambulatory blood pressure.[137] As with office blood pressure, a lower home blood

pressure goal is advisable for certain patients, including diabetic patients, pregnant women, and patients with renal failure.

1.1.40 Prognostic Significance

One factor that has held back the wider use of self-monitoring in clinical practice has been the lack of prognostic data. Two prospective studies, 1 from Japan[134– 136] and 1 from France,[21] have found that home blood pressure predicts morbid events better than conventional clinic measurements. There is an increasing body of evidence that home blood pressure may also predict target organ damage better than clinic pressure.[123,138– 140]

1.1.41 Telemonitoring

Devices are now available that have the capacity to store readings in their memory and then transmit them via the telephone to a central server computer, and then to the health care provider. They have the potential to improve patient compliance and, hence, blood pressure control.[140,141] Readings taken with a telemonitoring system may correlate more closely than clinic readings with ambulatory blood pressure.[133]

Features of different methods of BP measurement are provided in Table 2.

TABLE 2. Features of Different Methods of BP Measurement

	Clinic	Home	Ambulatory
Predicts outcome	Yes	Yes	Yes
Initial dagnosis	Yes	Yes	Yes
Upper limit of normal	140/90	135/85	135/85 (day)
Evaluation of Treatment	Yes	Yes	Limited
Assess diurnal rhythm	No	No	Yes
Cost	Inexpensive	Inexpensive	Moderate

Ambulatory Blood Pressure Measurement

1.1.42 Types of Monitor

Ambulatory blood pressure (ABP) monitoring is a noninvasive, fully automated technique in which blood pressure is recorded over an extended period of time, typically 24 hours. It has been used for many years as a research procedure and has recently been approved by Medicare for reimbursement of a single recording in patients with suspected WCH. The standard equipment includes a cuff, a small monitor attached to a belt, and a tube connecting the monitor to the cuff. Most, but not all, ABP devices use an oscillometric technique. Of the available ABP devices, most have undergone validation testing as recommended by the AAMI or the BHS. An up-to-date list of validated monitors is available.[126]

During a typical ABP monitoring session, blood pressure is measured every 15 to 30 minutes over a 24-hour period including both awake and asleep hours, preferably on a workday. The total number of readings usually varies between 50 and 100. Blood pressure data are stored in the monitor and then downloaded into device-specific computer software. The raw data can then be synthesized into a report that provides mean values by hour and period: daytime (awake), nighttime (asleep), and 24-hour blood pressure, both for systolic and diastolic blood

pressure. The most common output used in decision-making are absolute levels of blood pressure, that is, mean daytime, nighttime, and 24-hour values.

The monitors can be attached by a trained technician, who should be skilled in blood pressure measurement techniques (see the previous section on Blood Pressure Measurement in Other Settings). The cuff is attached to the nondominant upper arm, and a series of calibration readings are taken with a mercury sphygmomanometer to ensure that the device is giving accurate readings (within 5 mm Hg of the mercury readings). It is important to instruct the patient to hold the arm still by the side while the device is taking a reading. It may be helpful to ask the patient to keep a diary of activities, particularly when going to bed and getting up in the morning.

1.1.43 Clinical Applications

Although ABP could be used to monitor therapy, the most common application is diagnostic, that is, to ascertain an individual' s usual level of blood pressure outside the clinic setting and thereby identify individuals with WCH. Other potential applications of ABP include the identification of individuals with a nondipping blood pressure pattern (eg, in diabetes), patients with apparently refractory hypertension but relatively little target organ damage, suspected autonomic neuropathy, and patients in whom there is a large discrepancy between clinic and home measurements of blood pressure. The Centers for Medicare and Medicaid Services has approved the use of ABP measurement for the diagnosis of patients with suspected WCH (documented high clinic pressures and normal pressures in other settings, and no evidence of target organ damage).

A recent overview sponsored by Agency for Healthcare Research and Quality summarized available evidence on cross-sectional associations of ABP with subclinical outcomes and on prospective associations of ABP with clinical outcomes.[142] In cross-sectional studies of blood pressure with left ventricular mass (22 studies) and albuminuria (6 studies), ABP levels were directly associated with both measurements. Left ventricular mass was less in individuals with WCH than in those with sustained hypertension but was greater in WCH than in nonhypertensive subjects. Such evidence suggests that WCH is an intermediate phenotype. In each of 10 prospective studies, at least one dimension of ABP predicted clinical outcomes. In studies that compared the prognostic importance of ABP to clinic measurements, ABP was usually superior to clinic measurements. In some instances, including a recent study unavailable at the time of the overview,[143] mean ABP levels provided additional predictive information beyond that of clinic measurements, confirming the seminal study by Perloff et al.[144] In a few prospective studies, WCH predicted a reduced risk of cardiovascular disease events compared with sustained hypertension. However, data were inadequate to compare the risk associated with WCH to the risk associated with normotension. A nondipping or inverse dipping pattern predicted an increased risk of clinical outcomes. Just 2 ABP trials tested the usefulness of ABP to guide blood pressure management. Overall, available studies indicate that ABP monitoring can provide useful prognostic information.[145]

1.1.44 What Is Normal ABP?

The normal range for ABP has been established in 2 ways: first, by comparison of the ABP level that corresponds to a clinic pressure of 140/90 mm Hg and, second, by relating ABP to risk in prospective studies. The suggested values for daytime, nighttime, and 24-hour average levels are shown in Table 3.

TABLE 3. Suggested Values for the Upper Limit of Normal Ambulatory Pressure

	Optimal	Normal	Abnormal
Daytime	<130/80	<135/85	>140/90
Nighttime	<115/65	<120/70	>125/75
24-Hour	<125/75	<130/80	>135/85

1.1.45 Prognostic Significance

Several prospective studies have documented that the average level of ABP predicts risk of morbid events better than clinic blood pressure.[136,143,144,146– 149] In addition to mean absolute levels of ABP, certain ABP patterns may predict blood pressure-related complications. The patterns of greatest interest are WCH and nondipping blood pressure. WCH is a pattern in which clinic blood pressure is in the hypertensive range but ABP is normal or low. Individuals with WCH are at lower risk for blood pressure-related complications in comparison to individuals with sustained hypertension. An important but unresolved issue is whether the risk of cardiovascular disease in WCH exceeds that of nonhypertensive subjects. Using both daytime and nocturnal ABP, one can identify individuals, termed nondippers, who do not experience the decline in blood pressure that occurs during sleep hours. Usually, nighttime (asleep) blood pressure drops by 10% or more from daytime (awake) blood pressure. Individuals with a nondipping pattern (<10% blood pressure reduction from night to day) appear to be at increased risk for blood pressure-related complications compared with those with a normal dipping pattern.[146,150] Other evidence suggests that the nighttime blood pressure may be the best predictor of risk.[151]

Blood Pressure Recording in Special Situations

1.1.46 Elderly Patients

Elderly patients are more likely to have WCH, isolated systolic hypertension, and pseudohypertension (see the previous section on Pseudohypertension). Blood pressure should be measured while seated, 2 or more times at each visit, and the readings should be averaged. Blood pressure should also be taken in the standing position routinely because the elderly may have postural hypotension. Hypotension is more common in diabetic patients. It is frequently noticed by patients on arising in the morning, after meals, and when standing up quickly. Self-measurements can be quite helpful when considering changes in dosage of antihypertensive medications. Ambulatory blood pressure monitoring, sometimes coupled with Holter recordings of ECGs, can help elucidate some symptoms such as episodic faintness and nocturnal dyspnea.

1.1.47 Pulseless Syndromes

Rarely, patients present with occlusive arterial disease in the major arteries to all 4 limbs (eg, Takayasu arteritis, giant cell arteritis, or atherosclerosis) so that a reliable blood pressure cannot be obtained from any limb. In this situation, if a carotid artery is normal, it is possible to obtain retinal artery systolic pressure and use the nomogram in reverse to estimate the brachial pressure (oculoplethysmography), but this procedure and the measurement of retinal artery pressures are not generally available. If a central intra-arterial blood pressure can be obtained, a differential in pressure from a noninvasive method can be established and used as a correction factor.

1.1.48 Arrhythmias

When the cardiac rhythm is very irregular, the cardiac output and blood pressure varies greatly from beat to beat. There is considerable interobserver and intra-observer error.[152] Estimating blood pressure from Korotkoff sounds is a guess at best; there are no generally accepted guidelines. The blood pressure should be measured several times and the average value used. Automated devices frequently are inaccurate for single observations in the presence of atrial fibrillation, for example, and should be validated in each subject before use.[153] However prolonged (2 to 24 hours) ambulatory observations do provide data similar to that in subjects with normal cardiac rhythm.[154,155] Sometimes, an intra-arterial blood pressure is necessary to get a baseline for comparison. If severe regular bradycardia is present (eg, 40 to 50 bpm), deflation should be slower than usual to prevent underestimation of systolic and overestimation of diastolic blood pressure.

1.1.49 Obese Patients

A longer and wider cuff is needed for adequate compression of the brachial artery in the obese patient with a very large upper arm (see the previous section on Cuff Size). A large cuff may also be required for a big, muscular arm with a prominent biceps over which a regular, nontapered cuff might not fit smoothly. In both situations, it is particularly important to place the center of the bladder over the brachial artery pulse. If the upper arm is relatively short despite the large circumference, it may be difficult to fit a standard large adult cuff over the arm. The BHS' s recommendation to use a very long cuff (12×40 cm; BHS web site August 13, 2003, http://w3.abdn.ac.uk/BHS/booklet/special.htm) could obviate this problem. In the rare patient with an arm circumference >50 cm, when even a thigh cuff cannot be fitted over the arm, it is recommended that the health care practitioner wrap an appropriately sized cuff around the patient' s forearm, support it at heart level, and feel for the appearance of the radial pulse at the wrist. Other potential methods for measuring radial artery pressure include listening for Korotkoff sounds over the radial artery, detecting systolic pressure with a Doppler probe, or using an oscillometric device to determine systolic blood pressure; diastolic blood pressure is largely overestimated by both methods.[156] The accuracy of these methods has not been validated, but they provide at least a general estimate of the systolic blood pressure. The error of overestimating the pressure when measuring with a cuff that is too small for an obese arm can be considerable and can lead to misclassification of an individual as hypertensive and to unnecessary concern and therapy.

1.1.50 Children

Blood pressure is most conveniently measured in children by auscultation with a standard mercury sphygmomanometer. As with adults, the stethoscope is placed over the brachial artery pulse, proximal and medial to the antecubital fossa, and below the bottom edge of the cuff. The right arm is generally the preferred arm for blood pressure measurement for consistency and comparison with the reference tables.

Correct blood pressure measurement in children requires the use of a cuff that is appropriate for the size of the child' s upper arm.[156] A technique that can be used to select a blood pressure cuff size of appropriate size is to select a cuff that has a bladder width that is at least 40% of the arm circumference midway between the olecranon and the acromion. This will usually be a cuff bladder that will cover 80% to 100% of the circumference of the arm. The equipment necessary to measure blood pressure in children 3 years of age through adolescence includes pediatric cuffs of different sizes. For newborn– premature infants, a cuff size of 4×8 cm is recommended; for infants, 6×12 cm; and for older children, 9×18 cm. A standard adult cuff, a large adult cuff, and a thigh cuff for leg blood pressure measurement and for use in children with very large arms should also be available.

Blood pressure measurements in children should be conducted in a quiet and comfortable environment after 3 to 5 minutes of rest. With the exception of acute illness, the blood pressure should be measured with the child in the seated position with the antecubital fossa supported at heart level. It is preferable that the child has feet on the floor while the blood pressure is measured, rather than feet dangling from an examination table. Overinflation of the cuff should be avoided because of discomfort, particularly in younger children. It is useful to initially inflate the cuff while palpating the pulse to estimate the approximate range for the systolic pressure and then inflate the cuff to 30 mm Hg above this estimate when the blood pressure is auscultated. The blood pressure should be measured and recorded at least twice on each measurement occasion, and the average of these 2 measurements is the measurement for systolic and diastolic blood pressure.

Systolic blood pressure is determined by the onset of the auscultated pulsation or first Korotkoff sound. The phase of the Korotkoff sounds that defines diastolic blood pressure has been somewhat controversial. The disappearance of Korotkoff sounds or fifth Korotkoff sound (K5, the last sound heard) is the definition of diastolic pressure in adults. In children, particularly preadolescents, a difference of several millimeters of mercury is frequently present between the fourth and fifth Korotkoff sounds.[157,158] In some children, the Korotkoff sounds can be heard to 0 mm Hg, which has limited physiological meaning.

Elevated blood pressure measurements in a child or adolescent must be confirmed on repeated visits before characterizing a child as having hypertension. Within individual children, blood pressure at high levels tends to fall on subsequent measurement as a result of an accommodation effect (reduction of anxiety as the circumstances become more familiar) and regression to the mean, a nonbiological phenomenon that derives, in part, from mathematical considerations. Therefore, a more precise characterization of an individual' s blood pressure level is an average of multiple blood pressure measurements taken for weeks or months. A notable exception to this general guideline for asymptomatic generally well children would be situations in which the child is symptomatic or has profoundly elevated blood pressure. Children who show elevated blood pressure on repeated measurement should also have the blood pressure measured in the leg as a screen for coarctation of the aorta. To measure the blood pressure in the leg, a thigh cuff or an oversized cuff should be placed on the thigh and the blood pressure measured by auscultation over the popliteal fossa. If the systolic blood pressure measured in the thigh is >10 mm Hg lower than the systolic blood pressure measured in the arm, additional studies for coarctation should be performed.

There continues to be an increase in the use of automated devices to measure blood pressure in children. These devices are easier to use and are becoming alternative instruments for blood pressure measurement when use of mercury sphygmomanometers is not permitted for ecological reasons. The most commonly used devices use oscillometric methods (see the previous section on The Oscillometric Technique). Situations in which the use of the automated devices is acceptable include blood pressure measurement in newborn and young infants in whom auscultation is difficult, as well as in an intensive care setting, where frequent blood pressure measurement is necessary. The reliability of these instruments in an ambulatory clinical setting is less clear, however.[45]

The interpretation of the blood pressure measurement in children requires consideration of the child' s age, sex, and height. Hypertension in children and adolescents is defined as systolic and/or diastolic blood pressure that is consistently equal to or greater than the 95th percentile of the blood pressure distribution. Tables are available that provide the systolic and diastolic blood pressure level at the 95th percentile according to age, sex, and height.[159] These tables should be consulted to determine if the blood pressure measurements are normal or elevated.

Children also demonstrate white coat effects, but the role of ambulatory blood pressure monitoring is less clear in children. Validated devices should be used, preferably in a center with experience using ABPM. Large population-based normative data in children using ABPM are limited.[160,161]

1.1.51 Pregnant Women

Hypertension is the most common medical disorder of pregnancy and occurs in 10% to 12% of all pregnancies. The detection of elevated blood pressure during pregnancy is one of the major aspects of optimal antenatal care; thus, accurate measurement of blood pressure is essential.[161] Mercury sphygmomanometry continues to be the recommended method for blood pressure measurement during pregnancy. Blood pressure should be obtained in the seated position. Measurement of blood pressure in the left lateral recumbency, on the left arm, does not differ substantially from blood pressure that is recorded in the sitting position. Therefore, the left lateral recumbency position is a reasonable alternative, particularly during labor. If the patient' s upper arm circumference is 33 cm or greater, a large blood pressure cuff should be used. In the past, there had been some question as to whether the fourth (K4) or fifth (K5) Korotkoff sound should be used to define the diastolic blood pressure. The International Society for the Study of Hypertension in Pregnancy currently recommends using K5 for the measurement of diastolic blood pressure in pregnancy.[161] When sounds are audible with the cuff deflated, K4 should be used.

It is recognized that alternatives to mercury devices may be necessary in the future, and a small number of automated blood pressure recorders have been validated for use in pregnancy.[162] Self-monitoring may be useful in evaluating blood pressure changes during pregnancy.[163,164]

Summary and Recommendations

Accurate measurement of blood pressure is essential to classify individuals, to ascertain blood pressure-related risk, and to guide management. The objective of this report is to provide clinicians with a standardized set of recommendations that, if followed, should lead to accurate estimation of blood pressure.

We recognize that many committees and organizations have published recommendations and that, in practice, blood pressure measurement remains suboptimal. In view of the consequences of inaccurate measurement, including both the risks of overtreatment and undertreatment, it is the opinion of the committee that regulatory agencies should establish standards to ensure the use of validated devices, routine calibration of equipment, and the training and retraining of manual observers. Because the use of automated devices does not eliminate all major sources of human error, the training of observers should be required even when automated devices are used

Footnotes

- The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.
- This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on October 13, 2004. A single reprint is available by calling 800-242-8721 (US only) or writing the American Heart Association, Public Information, 7272 Greenville Ave, Dallas, TX 75231-4596. Ask for reprint No. 71-0308. To purchase

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*Appendix A8: **Women substudy***

Complementary study of the ANRS163-ETRAL trial: evaluation of the evolution of the cardiovascular disease-related markers in women included in the ETRAL trial according to their ovarian reserve as evaluated by the level of the anti-Müllerian hormone, and their menopausal status.

Investigator Contact Information
Jacqueline Capeau,
Faculty of Medicine Saint-Antoine site, 27 rue chaligny 75012 Paris, FRANCE
+33 668456988
+33 140011432
Jacqueline.capeau@inserm.fr

Objectives & Hypotheses

First objective: to evaluate, at inclusion and after a 48-week follow-up, the ovarian reserve and the menopausal status (by evaluating AMH, anti-Müllerian hormone as a marker of ovarian reserve and from the questionnaire regarding the menopausal status) and to analyze whether the metabolic/inflammatory /immune activation profile is different according to this status in the group of 48 women.

Second objective: to analyze whether switching women towards a dual therapy raltegravir plus etravirine could improve cardiovascular-related markers and inflammatory/immune activation biomarkers to a different extent in women according to their ovarian reserve/menopausal status.

Third objective: to compare in women and men from the ETRAL study (165 patients) whether metabolic, inflammatory, innate immune activation, fat and bone parameters were different at inclusion

Fourth objective: to comparatively evaluate in women and men from the ETRAL study whether metabolic, inflammatory, innate immune activation, fat and bone parameters were modified differently after 1 year, according to sex

Background & Rationale, Significance of Selected Topic & Preliminary Data

HIV-infected women present an altered menopausal status and several studies have reported an early onset of natural menopause, which is a risk factor for bone loss and cardiovascular diseases (GA Calvet Am J Obstet Gynecol 2015;216:765,). In addition, HIV-infected women were found to present a decreased level of ovarian reserve, as evaluated by serum anti-Müllerian hormone (AMH), compared to seronegative women (P Santulli AIDS, 2016;30:1083). Interestingly, in HIV-infected women, AMH can be used to predict the menopausal transition (R Scherzer Am J Obstet Gynecol 2017;216:46).

When aging, HIV-infected patients are at high risk of cardiovascular disease, in relation to personal factors, to the virus but also to ART, in particular to PIs (group D:A:D, NEJM 2007, S Lang Arch Int Med 2010, L Ryom CROI 2017). Inflammation and immune activation probably play a specific role in the increased CVD risk observed in these patients (VA Triant JAIDS 2009, DA Duprez PLOS One 2012, T Kelesidis JID 2012, E Merlini PLOS One 2012).

More specifically, in women, a recent study revealed that biomarkers of innate immune activation were increased in women with reduced ovarian reserve as evaluated by AMH. Moreover, these women have increased subclinical coronary atherosclerotic plaques compared to premenopausal women in whom AMH is measurable (SE Looby AIDS 2016;30:383). In these women, with often perturbed menstrual cycles, measuring AMH is easier than measuring other female hormones since it has not to be timed to menstrual cycle phase.

Thus, in order to assess the cardiovascular risk in these women aging with HIV infection, it would be interesting to evaluate their metabolic status according to their ovarian reserve and their menopausal condition.

Preliminary data: First results of the ETRAL trial have shown that switching middle-aged HIV-infected individuals with suppressed HIV viremia under a PI-containing regimen towards the dual association etravirine/raltegravir resulted in excellent virological efficacy. It also resulted into a marked improvement in lipid parameters, decreased inflammatory profile, moderate weight gain both peripheral and central and associated bone gain.
In the ETRAL study, the median age was 52 years old and 48 out of 165 subjects were female (29%). To study the ovarian reserve/menopausal status of women included in the ETRAL trail could add important results regarding women infected by HIV with regard to their risk of comorbidities when aging. This could also be important regarding their ART strategies.

Study Design
This study is observational and is a sub-study of the ETRAL study, that is a phase II trial, non-comparative, with inclusion of 165 patients from 20 clinical sites. All the samples for the patients have been collected and are stored in the Biomarkers Unit at Tenon hospital (Paris), where a number of immune activation /inflammatory /metabolic parameters have been already analyzed.

We propose to comparatively evaluate in the female and male groups of the ETRAL trial whether metabolic, inflammatory, innate immune activation, fat and bone parameters were different at inclusion and whether they were modified differently after 1 year according to sex.

In the group of 48 women, we propose to evaluate the ovarian reserve and the menopausal status and their evolution after 48 weeks by evaluating AMH (anti-Müllerian hormone as a marker of ovarian reserve) and from the questionnaire (menopausal status) and to separate the women into 3 groups (as in the paper of SE Lobby AIDS 2016).

- Non-menopausal with detectable AMH level (premenopausal with measurable AMH)
- Non-menopausal with undetectable AMH level (premenopausal with reduced ovarian reserve)
- Menopausal with undetectable AMH level (post-menopausal).

The evolution of the metabolic, inflammatory, innate immune activation, fat and bone parameters will be followed according to the initial values. We plan to add the dosage of MCP-1 to the AMH dosage.
To that end, the evaluation of the AMH level will be performed in the team of B Fève (Saint-Antoine Research Center) by Nathalie Di Clemente, an international expert in the domain (A Pierre JCEM 2017, A Pierre JCEM 2016a, A Pierre JCEM 2016b). Most inflammatory and immune activation markers have already been evaluated. We will add the marker MCP-1/CCL2, which was shown to be of interest in this regard (SE Looby AIDS 2016) to be performed in the UF of JP Bastard at Tenon hospital (APHP and UMR_S938)

Expected results
First, we want to analyze whether the metabolic/inflammatory profile is different at inclusion between men and women and whether its evolution differs according to sex.
Second, since the ovarian reserve/menopausal status could affect the cardiovascular risk, we want to analyze whether the metabolic/inflammatory/immune activation profile is different according to this status in HIV-infected women receiving PIs.
Then we want to analyze whether switching women towards a PI-avoiding regimen comprising ART considered as lipid friendly and with few adverse impact of age-related comorbidities, could improve cardiovascular-related markers and inflammatory/immune activation biomarkers to a different extent in women according to their ovarian reserve/menopausal status.

Study Flowchart
April to May 2018: data analyses in the entire group of 165 patients comparing women and men
April to June 2018: dosages of AMH and MCP-1
June to July 2018 : data analyses of the date obtained in the woman group.
September 2018 : redaction of the report

October to November 2018 : redaction of the paper
Duration : 8 months (with the redaction of the paper)

Study Procedures
The data entry and data mining analyses will be performed by the team of L Assoumou, working within the Institute of Epidemiology and public Health IPLESP (UPMC Inserm UMR_S1136) directed by D Costagliola by using the adapted statistical tools (see below).
The dosage of AMH will be performed by the team of N Di Clemente by using an in-house dosage technique
The dosage of MCP-1 will be performed by the team of JP Bastard and S Fellahi in the biomarker unit of Hôpital Tenon using the ELLA system by an ELISA technique (Biotechne).

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