ANRS 12374

Dolutegravir, Darunavir/ritonavir and Optimized NRTI recycling as a third-line antiretroviral regimen in Cambodia

Protocol version 1.0 - October *20, 2017*

Clinicaltrial.gov registration number ___

Ethics committee approvals

Cambodia: Name of the committee: NECHR

Date of approval: 05/12/2017

Sponsor:

Institut national de la santé et de la recherche médicale-ANRS (France REcherche Nord&Sud Sida-hiv Hépatites **(Inserm - ANRS)**
101 rue de Tolbiac
75013 PARIS
FRANCE
Tél. : 01 53 94 60 00 - Fax : 01 53 94 60 01

Investigateur Coordonnateur :

Pr Cécile GOUJARD Service de Médecine Interne, CHU Bicêtre Rue du général Leclerc, 94270 Le Kremlin Bicêtre, France Phone: +33, Fax +33. E-mail: cecile.goujard@aphp.fr	Dr LY Penhsun National Center for HIV/AIDS, Dermatology and STD (NCHADS) #245H, Sreet 6A, Phum Kean Khlang, Sangkat Prekleap Russey Keo, Phnom Penh Cambodia Phone: +855 977575405 1.1.1.1.1.1 E-mail: penhsun@nchads.org

MONITORING AND DATA MANAGEMENT CENTER (MDMC):
Dr PHENG Phearavin
University of Health Sciences
Phnom Penh, Cambodia
Phone: +855 , Fax: +33 557 57 45 28

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Sponsor signature

National Agency for Research on AIDS and Viral Hepatitis (ANRS)
Director: Pr François DABIS
101, rue de Tolbiac
75013 Paris, France
Tel: +33 153 94 60 46 / 60 00
Fax : +33 153 94 60 01

Paris, Date : 22/11/2018
Name : Pr François DABIS
Signature

Coordinating investigators signature

Pr Cécile GOUJARD
Service de Médecine Interne et Immunologie Clinique
CHU Bicêtre
78, Rue du général Leclerc, 94275 Le Kremlin Bicêtre CEDEX, France
Phone: +33 1 45 21 79 32/ 23 25
Fax +33 1 45 21 79 34
E-mail: cecile.goujard@aphp.fr

Date: 21/11/2018
Name : Pr Cécile GOUJARD
Signature

Dr LY Penhsun
National Center for HIV/AIDS, Dermatology and STD (NCHADS)
#245H, Sreet 6A, Phum Kean Khlang,
Sangkat Prekleap Russey Keo,
Phnom Penh Cambodia
Phone: +855 977575405
E-mail: penhsun@nchads.org

Date :
Name : Dr LY Penhsun
Signature

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STUDY PROTOCOL VERSIONS

LIST OF ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
ANRS	Agence Nationale de Recherches sur le Sida et les hépatites virales
ARV	Antiretroviral drugs
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
ATV	Atazanavir
BAC	Boosted Adherence Counseling
BMI	Body mass index
CBC	Complete blood count
CHAI	Clinton Health Access Initiative
CRF	Case report form
DRV	Darunavir
DSC	Decision Support Committee
DSMB	Data safety & monitoring board
DTG	Dolutegravir
ELISA	Enzyme-linked immunosorbent assay
ERHZ	Ethambutol rifampicin isoniazid pyrazinamide
GCLP	Good clinical laboratory practice
GCP	Good clinical practice
GRT	Genotyping Resistance Test
HCV Ab	Hepatitis C virus antibody
HBs Ag	Hepatitis B virus surface antigen
HIV	Human immunodeficiency virus
IMP	Investigational medicinal product
INH	Isoniazid
IPC	Institut Pasteur du Cambodge
LAM	Lipoarabinomannan
MIC	Minimum inhibitory concentration
MDR	Multi drug resistant
NCHADS	National Center for HIV/AIDS, Dermatology and STD
NRTI	Nucleoside reverse transcriptase inhibitor
PCR	Polymerase chain reaction
PI	Protease Inhibitor
PK	Pharmacokinetic
PMTCT	Prevention of mother-to-child transmission
RH	Rifampicin isoniazid
RNA	Ribonucleic acid
(S)AE	(Serious) Adverse event
(S)AR	(Serious) Adverse reaction
SmPC	Summary of the product characteristics

SOC	System organ class
SOPs	Standardized operating procedures
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TDF	Tenofovir
TMF	Study master file
TWG	Technical Working Group
USAID	United States agency for international development
XTC	Lamivudine (3TC) or emtricitabine (FTC)
WHO	World health organization
ZDV	Zidovudine

1. STUDY TEAM MEMBERS

SPONSOR	
Inserm / ANRS 101 rue de Tolbiac 75013 Paris, France. Phone: +33 1 53 94 60 00	
Dr Nicolas ROUVEAU Research in Resource-limited settings Office Phone: +33 1 53 94 80 90 E-mail: nicolas.rouveau@anrs.fr	Dr Alpha DIALLO, Dr Stephany PONG Pharmacovigilance Department Phone: +33 153 94 60 40 E-mail: alpha.diallo@anrs.fr; stephany.pong@anrs.fr

COORDINATING INVESTIGATORS	
Pr Cécile GOUJARD Service de Médecine Interne et Immunologie Clinique - CHU Bicêtre Phone: +33 1 45 21 79 32/ 23 25 Fax +33 1 45 21 79 34 E-mail: cecile.goujard@aphp.fr	Dr LY Penhsun National Center for HIV/AIDS, Dermatology and STD (NCHADS) Phnom Penh Cambodia Phone: +855 977575405 E-mail : penhsun@nchads.org

VICE COORDINATING INVESTIGATORS	
Pr SAPHONN Vonthanak / Dr Olivier SEGERAL ANRS University of Health Sciences Phnom Penh, Cambodia Phone: +855 12 479 313 E-mail: vonthanak@uhs.edu.kh / oliseg@hotmail.com	Dr SAMRET Sovannarith National Center for HIV/AIDS, Dermatology and STD (NCHADS) Phnom Penh Cambodia Phone: +855 977575405 E-mail: sovannarith@nchads.org

CO-INVESTIGATORS	
Dr NGAUV Bora NCHADS Phnom Penh, Cambodia Phone: E-mail:	Dr KHOL Vohith NCHADS Phnom Penh, Cambodia Phone: E-mail :

INTERNATIONAL PARTNERS	
Dr Joseph HARWELL CHAI NCHADS Phnom Penh, Cambodia Phone: +33, Fax +33 E-mail:	Dr Laurent FERRADINI HIV unit, WHO Phnom Penh, Cambodia Phone: E-mail : ferradinil@who.int

MONITORING AND DATA MANAGEMENT CENTER (MDMC)
Monitoring and biostatistics Dr PHENG Phearavin University of Health Sciences Phnom Penh, Cambodia Phone: +855 , Fax: +33 557 57 45 28 **System development and data managing:** Dr MAM Sovatha, NCHADS Dr UN Virak, UHS **Biostatistics** Dr Remonie SENG INSERM CHU Kremlin Bicêtre Paris, France Email : remonie.seng@inserm.fr

PHARMACOLOGY	
Dr Anne-Marie TABURET UMR1184 INSERM/Univ Paris Sud/CEA Le Kremlin Bicêtre, France E-mail: anne-marie.taburet@aphp.fr	Pr CHOU Monidarin University of Health Sciences Phnom Penh Cambodia E-mail : cmonidarin@uhs.edu.kh

VIROLOGY	
Dr François ROUET HIV/hepatitis unit Institut Pasteur du Cambodge Phnom Penh, Cambodia Phone: +855 E-mail: frouet@pasteur-kh.org	Dr MOM Chandara National Center for HIV/AIDS, Dermatology and STD (NCHADS) Phnom Penh Cambodia Phone: E-mail: chandara@nchads.org

2 STUDY SUMMARY

Clinicaltrial Id:

Title of Study: Dolutegravir, darunavir/ritonavir and optimized NRTI recycling as a third-line antiretroviral regimen in Cambodia

Short title – Sponsor N°: -ANRS 12374

Sponsor	French National Institute for Health and Medical Research-French National agency for Research on AIDS and viral hepatitis **(Inserm-ANRS)**

Coordinating Investigator(s): Pr Cécile GOUJARD / Dr LY Penhsun

Participating countries: CAMBODIA AND FRANCE

Objectives

Principal objective: To assess the virological effectiveness of a third-line regimen combining dolutegravir (DTG), ritonavir-boosted darunavir (DRV/r) and optimized NRTI recycling after 6 months of treatment, in Cambodian HIV-infected adults, who failed a protease inhibitors (PI)-based second-line regimen despite 3 months of boosted adherence counseling (BAC), with evidence of intermediate or fully resistance to atazanavir (ATV) OR sensitivity to ATV but resistance to all NRTI.

Secondary objectives

- Evaluate the safety of third-line regimen combination
- Evaluate the adherence of third-line regimen combination
- Evaluate the immune restoration (increase in CD4 cell-count) and the frequency of IRIS
- Estimate plasma exposure and pharmacokinetic parameters of DRV/r 600/100 twice daily and DTG 50 mg once daily
- Assess the effectiveness of switching DRV/r from 600/100 twice daily to 800/100 once daily for patients with plasma HIV1 RNA < 40 copies/mL at 6 months
- Estimate the pharmacokinetic parameters of DRV/r 800/100 once daily vs DRV/r 600/100 bid in the patients who switched

Methodology: Phase II non-comparative multicenter pilot prospective study

Expected enrolment	54 patients

Outcomes **Primary outcome:** Proportion of patients with plasma HIV-1 RNA < 40 copies/mL by FDA Snapshot analysis at 6 months

Secondary outcomes :

- Proportion of patients with plasma HIV-1 RNA < 40 copies/mL by FDA Snapshot analysis at 12 months
- CD4 cell count at 6 and 12 months
- Proportion of patients with IRIS
- Proportion of patients stopping treatment during the first year
- Incidence of grade 3-4 adverse events (ANRS grading table)
- Proportion of patients with adherence > 90% during one year

- Proportion of patients switched from 600/100 twice daily to 800/100 once daily at 6 months
- Plasma darunavir concentration with 600/100 twice daily and 800/100 once daily
- Plasma dolutegravir concentration
- Proportion of patients with plasma HIV-1 RNA < 40 copies/mL by FDA Snapshot analysis at 12 months among those switched from 600/100 twice daily to 800/100 once daily

Eligibility	**Inclusion criteria**

- >= 15 years old the day of inclusion
- Documented HIV-1 infection
- Failing a NNRTI-based first-line regimen
- Failing a PI-based second-line regimen after 3 months of adherence boosting (VL > 1000 copies/mL)
- HIV strain intermediate or fully resistant to ATV/r OR sensitive to ATV but both resistant to AZT, ABC and TDF
- Informed consent obtained with information sheet given and explained before the inclusion visit and the consent form signed by the participant and the project investigator at the latest the day of the inclusion

Non-inclusion criteria

- History of antiretroviral treatment including darunavir and integrase inhibitor
- Active pregnancy (and desire of pregnancy)
- Opportunistic infection in acute phase at inclusion including tuberculosis
- Advanced cirrhosis (Child-Pugh score B or C)
- Creatinine clearance < 50 ml/mn
- Any concomitant medical condition that, according to the clinical site investigator would contraindicate participation in the study
- Concurrent participation in any other clinical study without written agreement of the two study teams

Intervention

Each patient will be informed of the objectives and the total duration of the study as well as the benefits and risks to participate. An information sheet in Khmer will be given to each patient. After signature of consent form, Genotyping Resistance Test (GRT) and pre-inclusion samples will be done for all patients with HIV RNA > 1000 copies/mL after 3 months of boosted adherence counselling (BAC). After receiving results of the GRT and the pre-inclusion sample, the technical working group (TWG) of NCHADS will decide to switch the patient to third-line regimen or to continue second-line regimen with new BAC. PI-based second-line regimen will be continue if 1/ GRT shows sensitivity to ATV 2/ GRT shows sensitivity to at least one of the 3 NRTI recommended in Cambodia (AZT, ABC and TDF). In that case, adherence counselling will be boosted according to the new national guidance and the patient will not be enrolled in the study.

In case of intermediate or fully resistance to ATV/r OR sensitivity to ATV but both resistances to AZT, ABC and TDF and after confirmation of eligibility criteria, patient could be enrolled in the study. A third-line regimen will be started including DRV/r 600/100 twice daily + DTG 50 mg once daily + 3TC 300 mg once daily +/- one fully or intermediate sensitive NRTI among TDF, ABC and AZT. The choice of the last NRTI will be discussed and decided by the TWG according to the HBsAg status, to the result of the GRT and to the medical history of the patient.

At 6 months, plasma HIV-1 RNA will be measured:

• HIV1-RNA < 40 copies/mL: a switch to DRV/r 800/100mg once daily will be done and adherence counseling provided to confirm the new dosing with the patient

• HIV1-RNA > 40 copies/mL: the same regimen will be continued and adherence counseling provided

For all patients, a new virological assessment will be done at 9 and 12 months.

DRV and DTG exposure and pharmacokinetic parameters (Cmax, Cmin and AUC) will be estimated for the 20 first enrolled patients, allowing an intra-patient comparison of the 2 dosing regimens of DRV/r for at least 15 patients.

Statistical methods

According to data available with the ANRS 139 TRIO and ANRS 143 NEAT studies, we could expect that at least 80% of patients will be in virological success after 6 months and we wish to conclude that treatment will be effective for more than 60% of patients

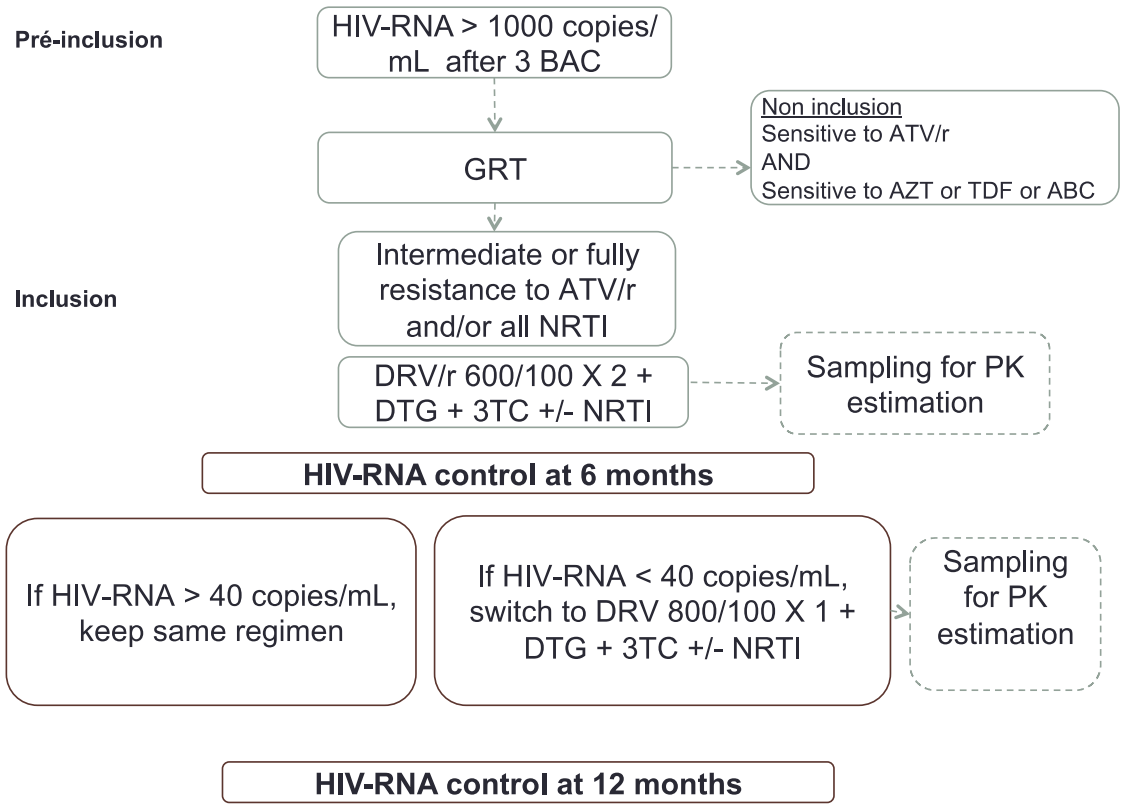
With a sample size of 45 patients, we could conclude that success rate is at least 60% if the total number of failure does not exceed 12 (alpha 0.05, power 90%, Fleming method with one stage).

Among the 3500 patients on PI-based regimen, and according to the results of the 2PICAM study, we could expect than 5% of patients followed in Cambodian sites could be enrolled in the study (175 patients) and one third of them (60 patients) will need third-line regimen at inclusion. With a 10% refusal ratio, we anticipate to enroll 54 patients for third-line regimen while 100 patients will continue second-line regimen.

Estimated planning or study timetable

FPFV : first patient first visit : December 2017
LPFV : last patient first visit : December 2018
FPLV : first patient last visit : December 2018
LPLV : last patient last visit : December 2019

3 STUDY SYNOPSIS



4 SCIENTIFIC RATIONALE

4.1.1 HIV situation in Cambodia

The HIV prevalence was further decreased from 0.9% in 2006 to 0.7% in 2012 (HIV projection). At the end of 2015, among the 72,607-estimated number of people living with HIV (PLHIV), 57,651 (79.4%) were diagnosed and know their status, 54,870 (75.6%) were on ART followed in 63 health care sites (36 pediatric), 37,568 were on ART and virologically tested (51.7%) and 35,056 (48.2%) were virologically suppressed.

The national guidelines were revised in October 2015 and treatment was recommended for all patients whatever the CD4 cell-count. The recommended first line is now TDF/3TC/EFV and the second line AZT/3TC/ATVr. A first viral load is performed at 6 months, 12 months and then yearly. If CD4 > 350/mm3, national guidelines recommend to use only viral load monitoring with no need for ongoing routine CD4 assay. In patients with virological failure, an adherence boosting for 3 months and viral load control at 3 months must be done before switching to a second-line regimen

A viral load scale-up strategy has also been defined in 2015 including dissemination of the new guidelines, strengthening the capacities of the laboratories and implementation of a standard operating procedure. For patients with virological failure, genotyping resistance tests (GRT) are made in Institute Pasteur of Cambodia in partnership with the NCHADS laboratory.

4.1.2 Evaluation of first and second-line regimen in Cambodia

The effectiveness of WHO-recommended first line regimen was assessed in several studies with good outcomes in adults (1)(2)(3) and children (4) related to a high level of adherence (5)(6). In 2011, good outcomes were also reported with lopinavir (LPV/r)-based regimen in a small study of 70 patients after 24 months of follow-up (7). More recently, the TREAT Asia HIV Observational Database reports outcomes of 302 patients under PI-based regimen followed for more than 6 months (8) from different Asian sites, including Cambodia, with a rate of mortality of 1.1 deaths per 100 patients/year and an overall rate of second-line treatment failure of 8.8 failures per 100 patients/year.

The results of the ANRS 12276 2PICAM study were presented at UHS in October 2015 and the article is under process of submission. This study was a nation-wide cross-sectional study aimed to assess the virological effectiveness of PI-based second line regimen in Cambodia as well as the impact of adherence boosting in patients experiencing virological escape. HIV drug resistance mutations were described and an external committee discussed options for alternative second line or third line regimen. Among the 1348 patients receiving PI-based regimen and recruited for the study, 31 were excluded because of non-eligibility criteria and 1317 patients were enrolled for evaluation. The study reports a high rate of virological suppression with 90% of patients exhibiting virological success (< 250 copies/mL) at inclusion. In addition, almost half of those with a detectable VL could be rescued following 3-months of boosted adherence counseling giving a final 94.5% success rate. Higher success rates at baseline were observed in patients with high CD4 cell count, longer duration of PI-based regimen and with ritonavir boosted ATV-containing regimen. Overall, 5.5% of patients on PI-based regimen had confirmed virological failure and 2% were in urgent need of third-line regimen. Such information was of great importance for NCHADS to adapt HIV management guidelines and forecast the needs for alternative second and third line regimen. Following these results, NCHADS has implemented a technical working group (TWG) since September 2016 to help clinicians taking care of patients on 2nd line regimen who had a viral load >1000 copies/mL and to improve quality of adherence support. This TWG is composed of NCHADS staff and different international organizations (CHAI, WHO, FHI, USCDC, ANRS). The first action was to implement a standard adherence tracking form, to be included in all patient charts and to improve adherence support and training of counselors.

4.1.3 Adherence counseling and resistance-associated mutations (RAM) to second-line regimen

The control of adherence is a critical factor of ART success and WHO recommends adherence support intervention prior to deciding any change of ART regimen. Indeed, it was found that a significant number of patients could be rescued after initial identification of treatment failure. In addition to 2PICAM study, similar results of adherence boosting strategy were reported in India where 34% of PI-based regimen patients with virological failure had a suppressed VL after 6 months (9) and more recently in South Africa where 64% of PI-based regimen patients were rescued (10). However in the 2PICAM study, among the 72 patients who could not be rescued by BAC and had confirmed VL failure, 21 patients presented no resistance to PI or NRTI drugs and should have been rescued if adherence counseling was fully effective. This suggests that adherence-counseling interventions still have room for improvement to be fully effective and that GRT seems necessary to detect these patients.

The main observed RAMs in the 2PICAM study were M184I/V, T215F/Y, M41L and D67N for RT and M46I/L and V82A for protease. These protease mutations were similar to those reported in Nigeria (11) and Vietnam (12) which confer high level of resistance to LPV and ATV with a risk of resistance increase overtime and worsening outcomes. Cross-resistance between ATV/r and LPV/r were reported in Cambodia (13), Vietnam (12) and India (14). LPV/r is currently recommended as an alternative option in the national guidelines and prevalence of dyslipidemia

was reported to be high in LPV-treated Cambodian patients with a 10-year risk of coronary heart disease ranging from 8% to 24% according to the score used (15). For these reasons, DRV/r, which presents a favorable lipid profile in clinical studies, seems to be the best option for patients with HIV-1 resistant to ATV/r whatever the sensitivity of LPV/r.

Among the 72 patients with virological failure in the 2PICAM study, 12 were sensitive to ATV/r but resistant to all NRTI. For these patients, a PI/r monotherapy could not be recommended as the viral load may not be fully suppressed; furthermore, this strategy showed a high risk of viral load elevation even for patients suppressed at baseline (16). Association of PI/r and integrase inhibitor seems, in that case, an interesting option (17) as reported by WHO even if data still missing to conclude to a recommendation.

4.1.4 Third-line regimen in LMIC

Third-line treatment in LMIC is still in its infancy as it is estimated that its uptake is limited to 26,000 adult patients. Nevertheless, a recent projected uptake estimates that the total number of people on third-line treatment will increase to half a million by 2025 (26). Current WHO recommendations are:

- National programs should develop policies for third-line ART
- Third-line regimens should include new drugs with minimal risk of cross-resistance to previously used regimens
- WHO recommendations for patients failing first-line with EFV and second-line with PI: DRV/r + DTG (or RAL) ± 1-2 NRTIs
- NRTI-sparing and NRTI-containing regimen seems to be comparable in term of virologic suppression but data are still limited

To our knowledge, only two research studies currently evaluate the effectiveness of third-line regimen in LMIC.
The first one is the ANRS 12269 THILAO study, a multi-country, phase 2b, non-randomized study, in Burkina Faso, Cote d'Ivoire, Mali and Senegal, aiming to assess:

- The efficacy (and associated factors) at 12 weeks of an intensive 3-months adherence reinforcement phase;
- In patients who successfully resuppress at 12 weeks: the percentage of patients with continuing virological supression on 2nd-line ART at 64 weeks (and factors associated to success);
- In patients with persistent virological failure at 12 weeks: the efficacy (and associated factors) at 64 weeks of a darunavir/r + raltegravir-based 3rd-line regimen.

Data were presented in the IAS congress in Paris in July 2017. Among the 198 patients treated with PI-based regimen and with confirmed plasma HIV-RNA > 1000 copies/mL, 5 die (2%), 130 (66%) resuppress at 12 weeks after adherence reinforcement and 63 (32%) were switched to third-line regimen. At month-16, HIV-RNA was > 400 copies/mL for 17 (13%) patients who continued second-line regimen and for 14 (22%) patients on third-line regimen. Accumulation of resistance mutations between inclusion and Month-16 was 5% on second-line regimen and 3% on third-line regimen.

The second one is an observational cohort of 150 HIV-infected Thai children, conducted by HIVNAT, aiming to assess the virologic and immunologic outcomes after at least 48 weeks of third line antiretroviral therapy combining new drugs such as darunavir, tipranavir, etravirine and raltegravir

4.1.5 DRV/r and integrase inhibitor combination

DRV/r was mainly evaluated combined with raltegravir (RAL). This combination, used as a first-line regimen in the NEAT 001/ANRS 143 trial, was reported as non-inferior to a standard tenofovir/emtricitabine plus DRV/r regimen (18) but the cumulative risk of selection of integrase mutations was higher after 96 weeks in the DRV/r + RAL arm compared to the standard arm (19). The same combination, used as a simplification among patients on suppressive ART, was proved to be effective to maintain virological suppression (20). For patients infected with multidrug-resistant virus with few remaining treatment options, the TRIO study showed high rates of virological suppression (90%) and favorable immunological outcomes at 48 weeks with a regimen containing RAL, etravirine, and DRV/r (21). The resistance-associated mutations were low for the 14 patients experiencing virological failure (22).

In India, MSF reported favorable outcomes with the combination DRV/r + RAL in a small group of patients failing a second-line regimen after boosted-adherence counseling (23).

The DRV/r + DTG combination has been less studied. Effectiveness of a salvage therapy with DRV/r and DTG in highly ART-experienced subjects was reported in Italy (24) with a proportion of viremic patients declining from baseline to week 24 from 43.4% to 6.2% and in France in a retrospective study (25). Evaluation of this combination for a second-line regimen compared to current recommendation is ongoing within an international randomized-controlled study conducted by the Kirby Institute in Australia (NCT03017872) but, to our knowledge, no study evaluates this combination for a third-line regimen.

In the SPRING-2 study, once-daily dolutegravir was non-inferior to twice-daily raltegravir in treatment-naive, HIV-infected patients after 96 weeks (27). Effectiveness and safety seem similar but DTG has a higher genetic barrier to resistance compared to the others INSTIs (28). Its pharmacokinetic characteristics allow once-daily administration, without boosting and with a low grade of drug–drug interactions. For all these reasons, DTG is now recommended by WHO as an alternative for first-line regimen.

The place of NRTI in third-line regimen continued to be discussed. NRTI-sparing and NRTI-containing regimens seem to be comparable in terms of virological suppression. Adverse events and treatment discontinuation seem to be lower with NRTI-sparing regimen but the difference is not statistically significant and WHO conclude to « prefer NRTI-containing regimen for HBsAg positive patients and discuss case by case for other patients according to GRT and comorbidities ». Recently, the MOBIDIP study conducted in sub-Saharan Africa reports that maintenance therapy with boosted protease inhibitor plus lamivudine was associated with a high rate of success than boosted protease inhibitor monotherapy, despite the presence of M184V mutations at first-line treatment failure (1).

4.1.6 Pharmacokinetic (PK) characteristics of DRV/r and DTG

PK characteristics of both drugs administered with 2 nucleos(t)ide analogs are well established either in healthy volunteers or HIV-infected patients. Main PK parameters assessed in HIV infected patients are summarized in the table below (29)(30)(31).

	Ritonavir boosted darunavir (DRV/r)		Dolutegravir (DTG)
	600/100 mg BID	800/100 mg QD	50 mg QD
Cmax – µg/mL	8.14	5.47	3.34
Tmax - h	2.5 - 4		2
Food effect	Yes ↗absorption by 40%		Yes ↗absorption by 50%
Cmin or Ctrough – µg/mL	3.20	2.04	0.83
AUC – µg.h/mL	54	88	43
T1/2 - h	15-17		11-12
Protein binding-%	92% (albumin and 1glycoprotein)		>99% (albumin and 1glycoprotein)
Elimination	Mainly biotransformation		
Metabolic pathways	CYP3A		UGT1A1 (main) CYP3A
Transporters	DRV substrate of Pgp;		Substrate of Pgp, BCRP

In brief, darunavir trough concentration when administered on a BID dosing is several folds higher than the protein binding-corrected EC50 value for wild-type virus (0.055µg/mL). As expected Ctrough will be lower on QD dosing than on BID dosing but the average concentration, will be high enough for wild-type virus suppression and for sustained efficacy for patients with undetectable viral load. Interestingly, some PK parameters of DRV/r and DTG in HIV-infected patients are close supporting coadministration of both drugs: rate of absorption is quite rapid with a time to Cmax (Tmax) around 2h and half-lives in the same range.
Although based on different metabolic pathways potent drug-drug interaction is not expected, ritonavir is known to induce UGT1A1 and could lower DTG concentrations. There is only one study conducted in healthy volunteers which assessed the effect of DRV/RTV 600/100 mg BID on DTG concentrations when administered at a 30 mg QD dosing for 5 days (32). A decrease in DTG concentrations was observed as indicated by the geometric mean ratio of AUCt, Cmax and Ctrough of DTG administered with DRV/r versus alone and (90% confidence interval) which are 0.78 (0.72, 0.85), 0.89 (0.83, 0.97), 0.62 (0.56,0.69) respectively. Although there is a 40% decrease in DTG trough concentrations, the geometric mean concentration of DTG when coadministered with DRV/r was 0.45 µg/mL, which are several folds higher than the protein adjusted 90% inhibitory concentration (0.064 µg/mL). Indeed this study was conducted with a 30 mg DTG dosing, lower than the 50 mg recommended dosing which will be used in the proposed study. Although these data are reassuring, there is no data in "real life" situation neither in Caucasian nor Asian HIV-infected patients where the potency of the drug-drug interaction could be altered.

4.1.7 Study main hypothesis

Genotypic resistance test (GRT) is warranted for all patients not rescued after BAC

In case of intermediate or fully resistance to ATV/r, DRV/r is the best option but pharmacokinetic data are missing for Asian population

For patients without HIV-1 resistance to ATV/r but with extensive resistance to all NRTI, a third-line regimen must be considered

DTG is the best option within the integrase inhibitors

Optimized NRTI recycling must be done with at least lamivudine and one other NRTI if sensitive

Switch from DRV 600/100 twice daily to DRV/r 800/100 QD when VL is controlled needs to be evaluated in order to simplify treatment and improve adherence

5 OBJECTIVES OF THE STUDY

5.1.1 Primary objective

The primary objective of the study is to assess the virological effectiveness of a third-line regimen combining dolutegravir (DTG), ritonavir-boosted darunavir (DRV/r) and optimized NRTI recycling after 6 months of treatment, in Cambodian HIV-infected adults, who failed a protease inhibitors (PI)-based second-line regimen despite 3 months of boosted adherence counseling (BAC), with evidence of intermediate or fully resistance to atazanavir (ATV) OR sensitivity to ATV but resistance to all NRTI.

5.1.2 Secondary objectives

The secondary objectives are to:

- Evaluate the safety of third-line regimen combination
- Evaluate the adherence of third-line regimen combination
- Evaluate the immune restoration (increase in CD4 cell-count) and the frequency of IRIS
- Estimate plasma exposure and pharmacokinetic parameters of DRV/r 600/100 twice daily and DTG 50 mg once daily
- Assess the effectiveness of switching DRV/r from 600/100 twice daily to 800/100 once daily for patients with plasma HIV1 RNA < 40 copies/mL at 6 months
- Estimate the pharmacokinetic parameters of DRV/r 800/100 once daily vs DRV/r 600/100 bid in the patients who switched

6 METHODOLOGY

6.1.1 Study design

This is a phase II non-comparative multicenter pilot prospective study to conduct a programmatic evaluation of third line antiretroviral therapy implementation in Cambodia.

6.1.2 Study overview

Patients infected with a viral strain intermediate or fully resistant to ATV/r AND/OR resistant to both zidovudine (AZT), abacavir (ABC) and tenofovir (TDF) will be treated by a combination of DRV/r 600/100 twice daily + DTG 50 mg once daily + 3TC 300 mg once daily +/- one fully or intermediate sensitive NRTI among TDF, ABC and AZT. The choice of the last NRTI will be discussed and decided by the TWG according to the HBsAg status, to the result of the GRT and to the medical history of the patient.

At 6 months, plasma HIV-1 RNA will be measured: the antiretroviral treatment will be switched from DRV/r 600/100 twice daily to DRV/r 800/100 once daily if plasma HIV-RNA is < 40 copies/mL.

For all patients, adverse events occurrence will be recorded very closely.

DRV and DTG exposure and pharmacokinetic parameters (Cmax, Cmin and AUC) will be estimated for the 20 first included patients, allowing an intra-patient comparison of the 2 dosing regimens of DRV/r for at least 15 of them.

According to the NCHADS database, the total number of ART sites with at least one patient with possible inclusion criteria is 25. For pragmatic reason, enrollment will be done in the largest ART sites in a first instance and then progressively expanded to smallest ART sites.

6.1.3 Tentative study agenda

First inclusion: December 2017
Inclusion time: 12 months.
Time of follow-up for each participant: 12 months
Last visit for the last patient: December 2019

7 STUDY POPULATION

7.1.1 Inclusion criteria

- Age >= 15 years old the day of inclusion
- Documented HIV-1 infection
- Failing a NNRTI-based first-line regimen
- Failing a PI-based second-line regimen after 3 months of adherence boosting (HIV RNA > 1000 copies/mL)
- HIV strain intermediate or fully resistant to ATV/r OR sensitive to ATV but both resistant to AZT, ABC and TDF
- Informed consent obtained with information sheet given and explained before the inclusion visit and the consent form signed by the participant and the parents or legal guardians for adolescents at the latest the day of the inclusion

7.1.2 Non-inclusion criteria

- History of antiretroviral treatment including darunavir and integrase inhibitor
- Active pregnancy (and desire of pregnancy)
- Opportunistic infection in acute phase at inclusion including tuberculosis
- Advanced cirrhosis (Child-Pugh score B or C)
- Creatinine clearance < 50 ml/mn
- Any concomitant medical condition that, according to the clinical site investigator would contraindicate participation in the study
- Concurrent participation in any other clinical study without written agreement of the two study teams

8 STUDY ENDPOINTS

8.1.1 Primary endpoint

The primary endpoint is the proportion of patients with plasma HIV-1 RNA < 40 copies/mL by FDA Snapshot analysis at 6 months

8.1.2 Secondary endpoints

The following secondary endpoints will be measured :
- Proportion of patients with plasma HIV-1 RNA < 40 copies/mL by FDA Snapshot analysis at 12 months
- CD4 cell count at 6 and 12 months
- Proportion of patients with IRIS
- Proportion of patients stopping treatment during the first year
- Incidence of grade 3-4 adverse events (ANRS grading table)
- Proportion of patients with adherence > 90% during one year
- Proportion of patients switched from 600/100 twice daily to 800/100 once daily at 6 months
- Plasma darunavir concentration with 600/100 twice daily and 800/100 once daily
- Plasma dolutegravir concentration
- Proportion of patients with plasma HIV-1 RNA < 40 copies/mL by FDA Snapshot analysis at 12 months among those switched from 600/100 twice daily to 800/100 once daily

9 STRATEGIES AND TREATMENTS

9.1.1 Strategies

After signature of consent form, Genotyping Resistance Test (GRT) and pre-inclusion samples will be done for all patients with HIV RNA > 1000 copies/mL after 3 months of boosted adherence counselling (BAC), as proposed to patients in Cambodia with HIV RNA > 1000 copies/mL and after discussion in the TWG. Resistance associated viral mutations (RAMs) and drug resistance interpretations are done using GREG2010 software. Drug resistance mutations are defined according to ANRS algorithms (http://www.hivfrenchresistance.org). Results are sent to the TWG.

After receiving results of the GRT and of the pre-inclusion samples, the TWG will decide to switch the patient to third-line regimen or to continue second-line regimen with new boosted adherence counseling.

Continuation of second-line regimen

PI-based second-line regimen will be continue if 1/ GRT shows sensitivity to ATV; 2/ GRT shows sensitivity to at least one of the 3 NRTI recommended in Cambodia (AZT, ABC and TDF). In that case, the patient will not be enrolled in the study and adherence counseling will be boosted according to the new national guidance. A new virological assessment will be done after 3 months. Clinical, immunological and virological outcomes of these patients will be evaluated by the TWG.

Initiation of third-line regimen

In case of intermediate or fully resistance to ATV/r OR sensitivity to ATV but both resistances to AZT, ABC and TDF and after confirmation of eligibility criteria, patient will be switched to third-line regimen. **The third line regimen will include DRV/r 600/100 twice daily, DTG 50 mg once daily, 3TC 300 mg once daily and one fully or intermediate sensitive NRTI among TDF,**

ABC and AZT. The choice of the last NRTI will be discussed and decided by the TWG according to the HBsAg status, the result of the GRT and the medical history of the patient.

At 6 months, plasma HIV-1 RNA will be measured:

- If HIV1-RNA is < 40 copies/mL: a switch from DRV/r 600/100 twice daily to DRV/r 800/100mg once daily will be done. A specific adherence counseling will be provided to confirm the new dosing with the patient.
- If HIV1-RNA > 40 copies/mL: DRV/r 600/100mg twice daily will be continued and adherence counseling will be reinforced.

For all patients, a new virological assessment will be done at 9 and 12 months.

For patients switched to DRV once daily, HIV RNA will be controlled one month after the switch in addition to 9 and 12 months.

Pharmacokinetic analyses

In the first 20 included patients who agreed and signed the consent form, blood samples will be drawn at steady state one month after treatment initiation (W4). DRV, RTV, DTG and NRTI will be administered in the morning under health care provider supervision and blood samples will be drawn before drug administration and +2h, +4h, +6h and +10h after drugs intake. Samples will be sent twice daily to the pharmacology unit of UHS, centrifuged and the plasma kept frozen until analysis at the end of the study. Participating patients will be hospitalized one day at Social Health Clinic of NCHADS in Phnom Penh. Transportation, food and perdiem for participants will be funded by the study.

In some specific cases, as pregnancy or TB co-infection, supplementary PK analyses could be done.

Tuberculosis occurrence before and during the study

Screening of tuberculosis will be made at pre-inclusion visit using the WHO 4 questions about TB symptoms and a systematic chest X-ray. In case of suspicion of tuberculosis, Xpert MTB/RIF will be made on sputum. Depending on clinical presentation, Xpert MTB/RIF could also be performed on any relevant extra-pulmonary specimen. In addition, TB-LAM Ag test will be performed on a single urine specimen for patients with CD4 cell-count < 100/mm3. If criteria are in favor of a probable or confirmed TB, patients will be addressed to ART sites to receive TB treatment immediately and will not be enrolled in the study.

Screening of tuberculosis will also be made at each follow-up's consultation using the WHO 4 questions about TB symptoms. In case of suspicion of TB, Xpert MTB/RIF will be made on sputum as well as chest X-ray. Depending on clinical presentation, Xpert MTB/RIF could also be performed on any relevant extra-pulmonary specimen. In addition, TB-LAM Ag test will be performed on a single urine specimen for patients with CD4 cell-count < 100/mm3. If criteria are in favor for probable or confirmed TB:

- Tuberculosis treatment will be provided using the standard WHO-recommended regimen (2RHZE/4RH), consisting of a combination of rifampicin (8-12 mg/kg), isoniazid (4-6 mg/kg), ethambutol (15-20 mg/kg) and pyrazinamide (20-30 mg/kg) administered once a day for 2 months, followed by a combination of rifampicin (8-12 mg/kg) and isoniazid (4-6 mg/kg)

administered once a day for the next 4 months. All drugs will be preferentially taken in the early morning before any meal.

- Dolutegravir will be switched to 50 mg once daily to 50 mg twice daily and PK analyses of DTG will be performed two weeks after rifampicin initiation.

- Pharmacokinetic analyses of DRV will be performed two weeks after rifampicin initiation. DRV dosing could be doubled to overcome the inducing effect of rifampicin, although there is few data to support this (33)

Pregnancy occurrence during the study

Women of childbearing age will receive intensive counselling on pregnancy and contraception. They will, in particular, be advised that third-line regimen initiation is not a good time to become pregnant, because: the risk of IRIS is high; viral suppression may not be reached immediately, with subsequent risks of HIV transmission to the baby; tolerance of DRV and DTG during pregnancy is uncertain.

In case of pregnancy occurrence during the study, the United States Food and Drug Administration and European Medicines Agency both recommend that DTG be used in pregnancy only if the potential benefits justify the potential risk. The DSC will have to take a decision for DTG continuation according to the presence of protease mutations at initial GRT and the virological outcomes at the time of pregnancy. Preliminary reports from HIV services in Botswana, which has been using DTG for pregnant women with HIV for over one year, suggest that birth outcomes (stillbirth, neonatal death, preterm birth and small for gestational age) do not differ between women receiving EFV-based therapy and those receiving DTG-based therapy. This observation is based on retrospectively collected data for over 5000 women, 16% of whom were receiving DTG regimens. There was also no excess of congenital anomalies among infants born to women taking DTG, but relatively few of these women started DTG in the first trimester (International AIDS Society Conference on HIV Science, Paris, France, 23–26 July 2017).

9.1.2 Treatments used in the study

None of the drugs used in the study is experimental.

Antiretroviral drugs will be delivered free of charge by NCHADS.

The study will cover the costs of common non-antiretroviral drugs including TB treatment, complementary exams and hospitalizations occurring from inclusion to month 12, if these tests, care and treatment have been judged justified by the study investigators.

ART regimen

Darunavir 600 mg tablet: one tablet twice daily

Darunavir 800 mg tablet: one tablet once daily

Ritonavir 100 mg tablet: one tablet twice or twice daily

Darunavir/ritonavir 400 mg/50 mg : two tablets once daily (available Q3 2018)

Dolutegravir 50 mg: one tablet once daily

Optimized NRTI treatment: could include tenofovir, zidovudine, abacavir and lamivudine

A fixed-dose combination of DRV 400 mg / RTV 50 mg is expected to come to market in 2018. Patients taking DRV 800 mg and RTV 100 mg singles will be switched onto this FDC (two tablets once daily) when it will become available.

The summary of product characteristic of all drugs used in this study is available at the EMA website

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124

TB treatment

TB treatment will be the standard WHO-recommended regimen (2RHZE/4RH), consisting of a combination of rifampicin (8-12 mg/kg), isoniazid (4-6 mg/kg), ethambutol (15-20 mg/kg) and pyrazinamide (20-30 mg/kg) administered once a day for 2 months, followed by a combination of rifampicin (8-12 mg/kg) and isoniazid (4-6 mg/kg) administered once a day for the next 4 months. All drugs will be preferentially taken in the early morning before any meal.

In case of documented resistant TB strain, the 2RHZE/4RH regimen will be modified according to each national guidelines/procedures. In case of multidrug resistant (MDR) TB, second-line TB regimen will be discussed between the country principal investigator and representatives of the National TB program.

Other drugs

All patients with CD4 cell-count < 200/mm3 and no formal contra-indication will be systematically prescribed cotrimoxazole prophylaxis (800/160 mg OD) for the entire study duration. Other chemoprophylaxis (e.g. fluconazole prophylaxis) will be prescribed as per national guidelines.

Patients receiving TB treatment will be systematically prescribed pyridoxine (vitamin B6) for the entire TB treatment duration, unless otherwise recommended by national authorities.

Treatments that could not be used because of potential drug-drug interactions are listed in Annex 2

10 STUDY IMPLEMENTATION

10.1.1 Study schedule

Study visit number	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**
Timing	W - 8	**W0**	W2	W4	W8	W12	W16	W20	**W24**	W26	W30(2)	W36	W48
Checking of eligibility criteria	X	X											
Information about the study	X									X			
Signature of consent form	X												
ART-related and adherence counseling		X	X	X	X	X	X	X	X		X	X	X
4 questions about TB symptoms	X	X	X	X	X	X	X	X	X		X	X	X
Physical examination	X	X	X	X	X	X	X	X	X		X	X	X
Pregnancy test (women of childbearing age)		X[4]											
Complete blood count	X	X	X	X	X	X			X			X	X
Genotyping resistance test	X												
CD4 T-cell count		X							X				X
Serum transaminases	X	X	X	X	X	X			X			X	X
GGT, Bilirubine	X												
Coagulation profile	X												
Albumin	X												
Serum creatinine	X	X	X	X	X	X			X			X	X
Glycemia and lipids evaluation		X											X
RDT HBs antigen		X											
RDT HVC antibodies		X											
Plasma HIV-1 RNA	X			X		X			X		X	X	X
Chest X-ray	X												
Xpert MTB/RIF, sputum (1)	X	X	X	X	X	X	X	X	X		X	X	X
Urine LAM (3)	X	X	X	X	X	X	X	X	X		X	X	X
Sampling for PK				X							X		
Storage of frozen Plasma		X				X			X			X	X

(1) For patients with at least one positive question among the 4 questions about TB symptoms
(2) For patients switched to DRV/r 800/100 once daily
(3) For patients with at least one positive question among the 4 questions about TB symptoms and CD4 < 100/mm3
(4) Pregnancy test will be performed at inclusion for all women of childbearing age but could be repeated during the follow-up in case of period retardations

10.1.2 Patients participation in the study

Information

Patient participation in this clinical study is voluntary. Each potential participant will be informed individually by the investigator of the purpose, scope of the study, procedures involved, duration of follow-up, potential risks and benefits and any discomfort it may entail. In addition to oral explanations, a written information sheet will be systematically provided in Cambodian language (see Appendix A).

Consent

If the patient accepts to be enrolled in the study, he will write his/her full names clearly, and date and sign the consent form, as will do the investigator. Written informed consent must be obtained before any exam related to the study. Before a patient agrees to participate in the pre-inclusion phase and sign the consent form he should be fully aware that the final conclusion regarding eligibility for the study will be taken within one month, according to the results of the tests done at pre-inclusion (see paragraph 9.3).

The original copy of the form will be stored in a location that is secure and inaccessible to other clinic employees. Participants may be given, if they wish, a copy of the consent form after they sign.

In the case of adolescents (between 15 and 18 years old), the authorization of the person(s) legally responsible is a requirement. All measures must be taken to obtain the accord of both parents when possible, or of the adolescent's legal guardian. For orphans, local regulation must be considered to design the person legally responsible. Researchers must also verify that the adolescent is not opposed and signs the assent.

10.1.3 Pre inclusion visit (V0)

During the pre-inclusion visit, the medical investigator will:

- Provide oral information, information sheet
- Check eligibility criteria
- Collect consent form signed
- Collect socio-demographic data, medical history including past OI and treatment received
- Perform a clinical exam including BMI and Karnofsky score
- Ask the 4 questions about TB symptoms and perform specific exam (Xpert MTB/RIF, urine LAM) if one question at least is positive
- Perform biological sample including: complete blood count, serum transaminases, serum creatinine, GGT, bilirubine, coagulation profile, albumin, plasma HIV1-RNA viral load and GRT
- Perform chest X-ray
- Plan the inclusion visit (W0)

Between pre-inclusion visit and inclusion visit, biological samples including GRT and request form will be sent to NCHADS laboratory and UHS for biochemistry and GRT. The TWG will be in charge to collect the results and to take a therapeutic decision. This decision will be communicate to the investigators on ART site in a maximum delay of 8 weeks.

10.1.4 Inclusion visit (V1)

The inclusion visit will occur within 8 weeks after the pre-inclusion visit.

During the inclusion visit, the medical investigator will check the results of the pre-inclusion visit tests and verify that the patient meets all inclusion criteria and exhibits none of the non-inclusion criteria.

Patients who do not meet all inclusion criteria, or meet at least one non-inclusion criterion, will not be enrolled in the study. They will benefit from the routine care provided in the country, according to the NCHADS. The TWG will be in charge to follow the outcomes of these patients, as some of them could be enrolled later in the study (active opportunistic infection cured, pregnant women after delivery, accumulation of resistance mutations). A specific table sheet will be created for these patients.

Patients who meet all inclusion criteria and do not meet any non-inclusion criterion will be enrolled on the same day.

For these patients, the medical investigator will:

- Collect the decision of the TWG for ART regimen
- Inform the patient of the therapeutic decision
- Check eligibility criteria
- Perform a clinical exam including BMI, Karnofsky score and hip and waist size and collect possible events occurred during the last month including concurrent medications
- Ask the 4 questions about TB symptoms and perform specific exam (Xpert MTB/RIF, urine LAM) if one question at least is positive
- Perform biological sample including: complete blood count, serum transaminases, serum creatinine, glycemia and lipids evaluation, CD4 T-cell count, HBsAg, HCV Ab, pregnancy test (women of childbearing age)
- Give prescription of drugs to the patient with the list of contraindicated drugs
- Address the patient to the counselor for ART-related adherence counseling
- Plan the visit W2

10.1.5 Follow-up visits

Visit week 2 (V2) to week 20 (V7)

During these visits, all patients will be systematically asked about their symptoms and drugs intakes, receive a clinical exam, an ART-related adherence counseling and a complete evaluation of adverse events (graded according to ANRS score).

A special attention to IRIS occurrence will be paid. The 4 questions about TB symptoms will be asked at each consultation and Xpert MTB/RIF on single sputum will be performed for patients with at least one positive question. In addition, TB-LAM Ag test will be performed on a single urine specimen for patients with CD4 cell-count < 100/mm3. Xpert MTB/RIF test could be performed on extra-pulmonary specimen in case of clinical suspicion. In case of RIF+ Xpert MTB/RIF tests, documentation of a possible multidrug-resistant strain will be made using TB culture and/or MTBDR test (Hain test). TB treatment will be adapted accordingly.

Adherence assessment will be done at each consultation using the national standard adherence tracking form available in all ART sites in the country. This assessment will comprise self-reporting questionnaire, pill count and visual analog scale. If adherence level is < 90%, supplementary sessions of adherence counseling could be performed.

Adverse events assessment is described in chapter 11.

A biochemical analysis will be realized at V2, V3, V4, and V5 including complete blood count, serum transaminases and serum creatinine.

Plasma HIV-RNA will be performed at week 4 (V3) and week 12 (V5).

Visit week 24 (V8)

This visit is of great importance as the primary endpoint is evaluated during this visit. The investigator:

- Perform a clinical exam including BMI, Karnofsky score and hip and waist size and collect all events occurred during the last 6 months
- Ask the 4 questions about TB symptoms and perform specific exam (Xpert MTB/RIF, urine LAM) if one question at least is positive

- Perform biological sample including: complete blood count, serum transaminases, serum creatinine, CD4 T-cell count and plasma HIV1-RNA viral load
- Collect all adherence and adverse events assessment
- Plan the visit V9 two weeks later to report the results and inform the patient

Visit week 26 (V9) and Visit week 30 (V10)

During the visit week 26, the investigator informs the patient of the results of the week 24 visit.

No serious adverse event were recorded, ART regimen was not stopped and plasma HIV-RNA is < 40 copies/mL

The investigator proposes to the patient to switch from DRV/r 600/100 twice daily to DRV/r 800/100 once daily and to continue other drugs as usual. A new ART-related adherence counseling is performed to explain the new dose.

For these patients, a consultation will be planned at week 30 (V10). During this visit, patients will be asked about their symptoms and drugs intakes, receive a clinical exam and an ART-related adherence counseling. Plasma HIV-RNA will be performed to confirm the maintenance of undetectable viral load. If HIV-RNA is > 40 copies/mL on two consecutives samples, DRV will be switched to 600/100 twice daily.

No serious adverse event were recorded, ART regimen was not stopped but plasma HIV-RNA is > 40 copies/mL

The investigator does not change the ART regimen and address the patient for systematic monthly adherence counseling during 3 months.

The next consultation will be planned at week 36 (V11) with a control of plasma HIV RNA.

Serious adverse event were reported and/or ART regimen was stopped

A decision support committee will help investigators to take a decision on ART: discontinuation of some drugs, change in dose, and improvement of side effects…

The management of adverse events is detailed in chapter 11.

Visit week 36 (V11) and week 48 (V12)

All the patients will be systematically asked about their symptoms and drugs intakes, receive a clinical exam, an ART-related adherence counseling and a complete evaluation of adverse events. A biological sample will be collected including complete blood count, biochemical analysis and plasma HIV RNA for V11 and V12 + glycaemia, lipids profile and CD4 cell-count for V12.

Plasma HIV RNA will be performed:

- For patients switched to DRV once daily, a reversal switch to DRV twice daily will be done if HIV RNA is > 40 copies/mL on two consecutive analyses

- For patients not switched to DRV once daily because of uncontrolled HIV RNA at week 24, a GRT will be performed if HIV RNA is > 1000 copies/mL. If HIV RNA ranges from 40 to 1000 copies/mL, adherence counseling will be done.

10.1.6 End of the study

Study exit preparation

Three months before the end of the study (visit V11, week-36), the medical investigator will explain to the patient, both in verbal and written form, the study exit conditions, the post-study care conditions, and the conditions under which they will be informed about the study results after study completion.

Last study visit

The last visit (V12) will occur 48 weeks after inclusion. Once patients complete 48 weeks of follow-up, they will end their follow-up within the study and will benefit from the regular care provided by the NCHADS.

Post-study care conditions

Once they leave the study, patients will continue to receive care and treatment according to the conditions defined by their country authorities. The country authorities will commit to providing these patients with their ongoing ART regimen at study end.

Communication of study results to the participants

As soon as final results of the study are available, they will be presented, both orally and in writing, to:

- The investigators;
- The national authorities;
- The participants.

A series of documents (written detailed report, and short summary) will be released to help investigators, national authorities and participants to understand the results of the study. Participants may be invited to attend a meeting during which the results will be presented and explained orally.

10.1.7 Withdrawal of consent and loss to follow-up

Consent withdrawal

A patient will be considered to have *withdrawn consent* if s/he no longer wishes to remain in the study. In this case, a "*withdrawal of consent form*" must be filled out.

When a patient who withdraws consent explicitly expresses the will that his/her data be removed from the database and his/her laboratory samples be destroyed, the study team will carry out such will. When a patient who withdraws consent do not express such will, data and samples collected prior to the date of his/her consent withdrawal will be used for the analysis.

Loss to follow-up

When a patient who has not explicitly withdrawn consent does not show up for routine visits, the study team (nurses, counsellors…) will search for him/her by all the way available (phone call, mailing, home-based care team). The study team will contact the patient via phone call or home visit, as long as s/he consented to phone calls and/or home visits in the consent form and provided a phone number and/or home address during the study.

A patient who does not show up for a given scheduled visit will be considered lost-to-follow-up when his/her last contact with the study team (either at the clinic, via telephone, or at home) was recorded prior to the date of his/her last scheduled visit to the clinic as per the study protocol.

11LABORATORY EVALUATIONS

11.1.1 Blood samples collection and tests

Blood samples will be taken:

(i) at pre-inclusion, to measure complete blood count, serum transaminases, serum creatinine, GGT, bilirubine, coagulation profile, albumin, pregnancy test (women of childbearing age), plasma HIV1-RNA viral load and GRT

(ii) at inclusion, to measure complete blood count, serum transaminases, serum creatinine, glycemia and lipids evaluation, CD4 T-cell count, HBsAg, HCV Ab

(iii) at week 2 and week 8, to measure complete blood count, serum transaminases and serum creatinine,

(iv) at week 4 and week 12, to measure complete blood count, serum transaminases, serum creatinine and plasma HIV1-RNA viral load,

(v) at week 24, to measure complete blood count, serum transaminases, serum creatinine, CD4 T-cell count, plasma HIV1-RNA viral load;

(vi) at week 36, to measure complete blood count, serum transaminases, serum creatinine and plasma HIV1-RNA viral load,

(vii) at week 48, to measure complete blood count, serum transaminases, serum creatinine, CD4 T-cell count, plasma HIV1-RNA viral load, glycemia and lipids profile

	V0	V1	V2	V3	V4	V5	V8	V11	V12
Complete blood count: EDTA (mL)	5	5	5	5	5	5	5	5	5
Biochemical analysis: Plasma, heparin lithium (mL)	5	5	5	5	5	5	5	5	5
Coagulation profile: Plasma citrate (mL)	5								
Plasma HIV RNA and GRT: EDTA tube (mL)	5			5		5	5	5	5
CD4 cell-count: EDTA tube (mL)	5								5
Glycemia and lipids profile: Plasma, heparin lithium (mL)		5							5
Albumin: Plasma, heparin lithium (mL)									
Biothèque : EDTA (mL)		5				5	5	5	5
Total number of tubes at each visit	**5**	**4**	**2**	**3**	**2**	**4**	**4**	**4**	**6**
Quantity of blood at each visit (mL)	**25**	**20**	**10**	**15**	**10**	**20**	**20**	**20**	**30**

11.1.2 Tuberculosis tests

The two TB tests to be employed during the study are the Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) and the Determine® TB-LAM Ag test (Alere, Waltham, MA, USA).

Xpert MTB/RIF test will be performed on single sputum or extra-pulmonary specimen. In case of RIF+ Xpert MTB/RIF tests, documentation of a possible multidrug-resistant strain will be made using TB culture and/or MTBDR test (Hain test). TB treatment will be adapted accordingly.

TB-LAM Ag test will be performed on a single urine specimen in accordance with the manufacturer's instruction. For this study, the cut-off point to consider a urine LAM test as positive is grade 2 (visual grade 2 on the Reference Scale Card of the manufacturer).

11.1.3 Pharmacokinetic analyses

For the 20 patients participating in PK analyses, 2 tubes of 5 mL will be collected before the drug intake, then +2h, +4h, +6h and +10h after drugs intake. Samples will be sent twice daily to the pharmacology unit of UHS, centrifuged and the plasma kept frozen until analysis at the end of the study. One tube of 2 mL of plasma will also be kept frozen for further analysis.

11.1.4 Biobank

During the follow-up, blood samples will be collected for all patients and frozen at week 0, 12, 24, 36 and 48. A specific consent form for possible further genetic analyses, including pharmacogenetics, will be provided.
Biobank will be centralized at UHS, in Rodolphe Merieux laboratory and preparation of the aliquots will be done at this location.

12 ADVERSE EVENTS AND *IN UTERO* EXPOSURE

12.1.1 Definitions

12.1.1.1 Adverse Event (AE)

An adverse event is any untoward medical occurrence in a clinical trial participant, which does not necessarily have a causal relationship with the research or the investigational medicinal product.

12.1.1.2 Adverse Reaction (AR)

An adverse reaction is any untoward and unintended response to an investigational medicinal product related to any dose administered.

12.1.1.3 Severity

The severity of an AE/AR refers to its intensity, or grade. All AEs/ARs should be graded for severity, using the ANRS scale for adverse events (www.**anrs**.fr/content/download/2242/12805/file/**ANRS**-GradeEI-V1-En-2008.pdf)

12.1.1.4 Seriousness

The seriousness of an AE/AR refers to whether or not it should be reported immediately to the sponsor and regulatory authorities.

The judgment as to whether an AE/AR is serious or not is made by the investigator, based on the criteria listed in section 11.1.1.5.

12.1.1.5 Serious Adverse Event (SAE)

"Serious adverse event" (SAE) refers to any untoward medical occurrence or reaction 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 4 clinical or biological event;
- Is a grade 3 "special interest" event. For this study, the special interest events are: psychiatric disorders, central neurological disorders, hepatic disorders, renal disorders, mucocutaneous disorders, and all invasive infections;

- Is an "important medical event" (medical events, based upon appropriate medical judgment, which may jeopardize the subject's health or may require medical or surgical intervention to prevent one of the above characteristics/consequences; *e.g.: allergic bronchospasm requiring intensive treatment at an emergency unit or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization,* etc.).

The following events are not SAEs:

- Hospitalizations with no untoward medical occurrence, such as hospitalization for elective surgery if known prior to start study, social and/or convenience admissions, pre-specified study hospitalizations for observation.
- Medical or surgical procedures (e*.g.: surgery, endoscopy, tooth extraction, transfusion*); only the condition that leads to the procedure should be notified if the condition is referring to a seriousness criteria described above.

The following events are SAE, but do not require reporting to the sponsor:

- SAEs related to pre-existing diseases or prevalent conditions that do not worsen (this includes pre-existing grade 3 and 4 biological events);
- Grade 4 biological adverse events detected between the screening visit and the start of study drug administration.

Deaths must be reported as the outcome of a SAE, not as a SAE itself if the cause is known. If the cause of death is unknown, the death should be reported as "unknown cause of death".

12.1.1.6 Causality

"Causality" refers to causal relationship between a given AE/AR, the study intervention/medication, and any other concomitant intervention/medication (e.g. in case of drug-drug interaction). A drug can be associated to a given SAE even if the subject is not receiving the drug at the time of the event.

All SAE for which the investigator or the sponsor considers that a causal relationship is a reasonable possibility are considered as suspected *serious adverse reaction* (SAR).

12.1.1.7 Expectedness

An unexpected adverse reaction is an adverse reaction, the nature, the outcome or severity of which is not consistent with the applicable *Reference Safety Information* (RSI). The RSI is the *Summary of the Product Characteristics* (SmPC) for authorized products, and the Investigator's Brochure for unauthorized investigational products or authorized products used in unapproved indication.

All unexpected SAE for which the investigator or the sponsor considers that a causal relationship is a reasonable possibility are considered as *Unexpected Serious Adverse Reaction* (SUSAR).

12.1.1.8 New fact

A new fact is any safety data that could modify significantly the evaluation of the benefit/risk ratio of the investigational medicinal product or the clinical study, likely to affect the safety of participants or that could modify the investigational medicinal product administration, the trial documentation or the conduct of the trial, or to suspend or interrupt or modify the protocol or similar trials (e*.g.: serious adverse event which could be associated with the study procedures and which could modify the conduct of the study; lack of efficacy of an investigational medicinal product used for the treatment of a life-threatening disease, etc.*).

12.1.2 Responsibilities of the investigators

12.1.2.1 Assessment of severity, seriousness, causality

The investigators are responsible for:

- Grading the severity of all AEs (serious and non-serious)
- Reporting all SAEs to the sponsor and to the NECHR, according to the procedures described in section 11.1.2.2.
- Assessing the causality of all SAEs in relation to the study intervention/medication. In the absence of information on causality from the investigator, the sponsor should encourage him to express an opinion. The sponsor should not downgrade the causality assessment given by the investigator. If the sponsor disagrees with the investigator's causality assessment, the opinion of both the investigator and the sponsor should be provided with the report.

The sponsor, in the light of the reference document (SmPC), will do the assessment on expectedness. However, if information on expectedness has been made available by the investigator, the sponsor should take this into consideration.

12.1.2.2 SAE notification by the investigators

Timeline and contacts

The investigators have to notify:

- All new SAE, immediately and no later than 24 hours of being aware of it (using the *SAE initial notification form*),

- Any SAE worsening, immediately and no later than 24 hours of being aware of it (using the *SAE complementary notification form*),

- All SAE resolutions (upon initial reporting, using the *SAE initial notification form,* if the SAE resolution dates the same day as the SAE initial report; upon SAE resolution, using *SAE complementary notification form*, if SAE resolution dates from after the initial declaration).

- Any relevant change in the data previously reported (*eg.*: change in diagnosis or in causality assessment, new information on drugs taken, etc.) (using *SAE complementary notification form*).

Initial and complementary reports forms should be sent to: (i) the pharmacovigilance unit of the Inserm-ANRS (email: pharmacovigilance@anrs.fr); (ii) the NECHR.

Notification period: SAEs must be reported if they occur between the time when the subject signed the informed consent form and:

- His/her 48-week visit (V12), or:
- 4 weeks after the last study visit if the event is suspected to be related to the study strategies, or:
- Any time after the completion of the study if the event is suspected related to the medicinal product taken during the study follow-up.

The investigators do not need to actively monitor subjects for adverse events once the study has ended. However, serious adverse events occurring to a subject after his/her study follow-up has ended should be reported to the sponsor if the investigators become aware of them.

Initial report: The immediate report must include at least the following information: the subject ID, the name of the person who reports the SAE, one medicinal product, one SAE, the date, and the signature of the reporter. Whenever incomplete, the immediate report must be followed by a detailed report, which should be sent no later than 8 days after the initial report.

Complete initial reports include the grade, causality and outcome of the event.

SAE follow up: The investigator must follow the SAE until its resolution, or until the patient's death, even if resolution or the patient's death occurs after study termination.

Worsening is defined as the SAE grade becoming higher than the grade initially declared. Any SAE worsening must be reported using the SAE complementary notification form.

Resolution is defined as clinical and/or biological conditions getting back to normal or to the conditions that pre-existed the SAE occurrence. SAE resolution must be reported using the SAE complementary notification form, except when the SAE outcome was already reported as "resolved" on the SAE initial form.

A new episode occurring after complete resolution should be declared as a new SAE.

SAE notification forms filling

The investigator should indicate a specific diagnosis whenever possible, and a syndromic diagnosis otherwise. Symptoms occurring within the framework of a given specific diagnosis or syndrome should not be reported separately (e.g. abdominal pain in a patient with pancreatitis).

The "SAE start" cannot be dated from after the "SAE seriousness".

The outcome indicated on the SAE initial report is the outcome at the time of the report. For all SAEs that are not reported as "resolved" at initial report, any change in the initially reported outcome (resolved, back to previous status, worsening) should be reported using complementary notification form(s). Complementary notification form should also be used for all changes in the investigator judgment regarding causality or expectedness.

The end of seriousness is the date when the adverse event is no longer considered as "serious". For all resolved SAE, the date of resolution corresponds to the date of the event resolution, not necessarily to of the end of seriousness. For all SAE which outcome is "back to previous status" or "improvement", the outcome date is the end of seriousness.

Additional documentation

All relevant documents related to the SAE (e.g. hospitalization report, laboratory results) must be attached to the reports, when existing. Documents must be anonymized before being sent, with patients names being erased and replaced with participant identification number.

Fatal or life-threatening SAE:

In case of fatal or life-threatening SAE, special attention should be paid to reporting timelines. Reports should be made as soon as possible and no later than 24 hours after the investigator has been made aware of the case, and all relevant complementary information should be sent within 8 extra-days.

12.1.2.3 Potential risks of the research and management of selected SAEs

The following risks associated with the use of dolutegravir should be considered: hypersensitivity reactions, immune reactivation syndrome, opportunistic infections, osteonecrosis, hepatotoxicity. More details can be found in the SmPC of dolutegravir on the EMA website.

The following risks associated with the use of darunavir should be considered: severe skin reactions, hepatotoxicity, osteonecrosis, immune reconstitution inflammatory syndrome. More details can be found in the SmPC of darunavir on the EMA website.

If there is any suspicion of drug-induced hepatitis, physicians will measure serum transaminases, alkaline phosphatases and bilirubin levels.

Grade 3 or 4 hepatitis or renal insufficiency or severe mucocutaneous events (such as rash associated with blistering, desquamation, mucosal involvement or fever) will lead to the immediate decision to discontinue all drugs possibly implicated. In case of severe neuropsychiatric disorders, the role of DTG will be systematically brought up, and investigators will also consider discontinuation of these drugs.

Once a drug has been discontinued for any reason, reintroduction will be carefully discussed between the DSC and the country investigators, on a case-by-case basis, taking into account the

severity of the event, rapidity of resolution, potential drug causality, and expected benefit of the drug.

12.1.3 Responsibilities of the sponsor

12.1.3.1 SAE Recording and assessment

The sponsor is responsible for:

- Ensuring that all SAE are reported.
- Keeping detailed records of all SAE, which are reported to him by investigators.
- Assessing the causality of the SAE in relation to the study therapy, concomitant medication (e.g. drug-drug interaction) and the research. The sponsor should not downgrade the causality assessment given by the investigator. If the sponsor disagrees with the investigator's causality assessment, the opinion of both the investigator and the sponsor should be provided with the report.
- Assessing the expectedness of the SAR, by using the applicable RSI. If information on expectedness has been made available by the reporting investigator, the sponsor should take this into consideration.

12.1.3.2 Safety reports

Annual safety report

Once a year the ANRS pharmacovigilance unit will release an annual safety report, the Development Safety Update Report (DSUR). The DSUR will be written in coordination with the monitoring and data management centre, and may be submitted to the coordinating investigators for approval.

The DSUR includes:

- a line-listing of all suspected serious adverse reactions that have occurred over this period (expected and unexpected SAR);
- a cumulative summary tabulation of the SAE, expected SAR, and SUSAR, by System Organ Class (SOC);
- a line-listing of deaths;
- any relevant Independent Data Safety Monitoring Board and study Scientific Committee opinion regarding safety;
- a concise, critical analysis of the subjects' safety.

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

Timeline and contacts

The annual DSUR will be sent to: (i) the study coordinating investigators; (ii) the NECHR. The "Development International Birth Date" (DIBD) is the date of the first inclusion of the study. The DSUR is expected to be submitted each year no later than 60 calendar days from the DIBD.

12.1.3.3 SUSAR report

All SUSARs will be reported by the Inserm-ANRS Pharmacovigilance unit to the appropriate country competent authorities, in line with each country's laws and regulations.

In France, this report will be made throught the EudraVigilance Clinical Study Module (EVCTM).

For fatal and life-threatening SUSAR, the initial report should be made as soon as possible and in any case no later than 7 calendar days after the sponsor has been 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. Relevant complementary information should be collected and notified within 8 extra-days.

12.1.3.4 New fact reporting

When a new event is likely to affect the safety of participants, the sponsor and the investigator take appropriate urgent safety measures to protect participants against any immediate hazard.

The sponsor inform without delay the NECHR 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.

The safety office shall transmit a written report, within 15 days to the NECHR

If the new fact requires substantial amendments, the sponsor should notify any substantial protocol modification, to the NECHR, within 15 days of the safety measures implementation.

12.1.4 *In utero* exposure

12.1.4.1 Pregnancy notification

The investigator has to notify all pregnancy, within 24 hours of being aware of it, to the pharmacovigilance unit of the Inserm-ANRS (email: pharmacovigilance@anrs.fr), using the *pregnancy initial report form*.

The "pregnancy report form" must include the following information: estimated date of delivery, obstetrician contact and name of maternity hospital

The investigator has to follow the woman until the end of the pregnancy and notify the outcome to the sponsor using the “pregnancy outcome report form”.

Follow-up of pregnant participant continues until the end of the study. 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 (see section 11.2.2 and 11.2.3).
- Therapeutic interruption of pregnancy, congenital anomalies, birth defects, and miscarriage needing hospitalization are considered and should be notified as SAEs.

12.1.4.2 Pregnancy management

If a participant becomes pregnant, all treatments contraindicated during pregnancy must be discontinued.

Regarding ART, investigators will carefully weight the benefits/risks balance for the mother and for the baby before taking therapeutic decision. The decision should be compatible with the national guidelines on ART and pregnancy.

- ART regimen will not systematically be modified because of the pregnancy. If a modification is deemed necessary (e.g.: virologic failure, drug intolerance, or ART regimen including a drug contraindicated during pregnancy), the ultimate goal will be to reach viral load undetectability as soon as possible, using drugs that have been proved to be acceptable during pregnancy.

- Cotrimoxazole will not be stopped solely because of the pregnancy.

Clinicians could request rapid advice of the DSC any day of the week when urgent decision is needed (see section 12.2.2).

See also paragraph "Pregnancy occurrence during the study" in chapter "8. Strategies and treatments".

12.1.4.3 Children born to mothers participating in the study

Children born while their mothers are participating in the study will be followed according to the national guidelines.

Newborns who do not have a definitive diagnosis or who have been definitively diagnosed with HIV will be referred to a Paediatrics Department to initiate appropriate care.

13TRIAL BOARDS AND COMMITTEES

13.1.1 Trial scientific committee

Composition

The trial scientific committee will consist of: (i) the investigators and statistician of the trial; (ii) external HIV and TB experts including PK of the drugs; (iii) an HIV advocacy organization representative; and (iv) sponsor representatives. Members of the scientific committee are listed in annex 1.

Meeting agenda

The trial scientific committee will meet before the beginning of the inclusion phase, as well as once or twice per year until the end of the trial. The trial sponsor or one or several board members may also request a special meeting at any time.

Role

The role of the trial scientific committee is to ensure that the trial is carried out appropriately, not only scientifically but also clinically and ethically. The members of the scientific committee report directly to the sponsor.

- They will ensure that the trial personnel carry out the trial properly, adhere to the trial protocol and maintain patient safety;
- They will guarantee that the trial remains scientifically relevant by ensuring the relevancy of the trial questions and that the methods used are valid and appropriate;
- They will make all decisions regarding necessary and relevant protocol modifications, such as:
    - Actions needed to facilitate patient recruitment;
    - Decisions to open or close participating trial sites.
- They will enforce the rules pertaining to access to the trial data as well as reports and publications of the results;
- They will remain in contact with the sponsor, the DSMB and the coordinating investigators, and will make sure investigators and other trial personnel have access to up-to-date information.

At the end of each meeting, a report containing the meeting minutes, signed by the Scientific Committee chair will be sent to the members of the scientific committee, DSMB Members and the director of ANRS.

13.1.2 Data Safety & Monitoring Board (DSMB)

Composition

The DSMB members will be selected in collaboration between the coordinating investigators and the ANRS before the beginning of the inclusion phase.

Meeting agenda

The DSMB will meet once at the beginning of the inclusion phase, and at least every 12 months until the end of the trial. The sponsor, the scientific committee or the DSMB may request to increase the frequency of these meetings.

Role

The DSMB is a consultative board for the scientific committee and to the sponsor. Its members will provide general advice on the progress of the trial, including the rate of inclusions, the quality of follow-up, the overall rate of drug-related adverse events, changes in biological markers, the overall incidence of primary outcomes, and the number of subjects needed.

They will help to make difficult decisions that require an independent assessment while the trial is underway. Advice may be needed regarding:

- Premature discontinuation of the trial (because the rate of adverse events is high, the trial is no longer feasible, or the available data are sufficient);
- Substantial changes to the protocol that becomes necessary during the inclusion or follow-up phases, or to account for new scientific information.

The DSMB will conduct and interpret intermediate analyses, if any.

At the end of each meeting, a written report containing the DSMB's opinion will be sent to the sponsor and the members of the scientific committee.

13.1.3 Decision Support Committee (DSC)

Roles of the DSC

The DSC will provide advices and recommendations to investigators regarding:
- Occurrence of tuberculosis or pregnancy during the study
- Any morbidity event occurring during the study
- Decision on ART management
- Any important clinical issue for which the investigators wish to share experience before taking a decision

Composition of the DSC

The DSC will consist of 1/ Two physicians specialized in HIV infection 2/ One physician specialized in TB infection 3/ One pharmacist specialized in PK 4/ The two principal investigators of the study. Other specialists could be called at DSC's request.

Organization of the DSC

The DSC will meet regularly and must be accessible on rapid request through phone calls, e-mails, private online forum, or any other means in case of morbidity event.
The investigators of each site will be responsible to prepare the documents for the meeting and to send it by e-mail at least two days before the meeting.
The responsibility of DSC is to provide a recommendation on a written document. One member of the DSC will be in charge of the written report. This report will be send to the methodological centre in UHS.

14COORDINATION, MONITORING, DATA MANAGEMENT

14.1.1 Coordination

The UHS Research Grant Management Office is the referent for the trial methodology and management. The UHS team is responsible, in coordination with the clinical, laboratory and administrative coordinators, for the overall trial management (preparation and organisation of the trial, monitoring, data management and analysis). The team will include the project coordinator, the two trial monitors, one Lab technician and one data manager.

- **Preparation and organisation of the trial**: the UHS team will finalize and review the Case Report Forms (CRF) with all the collaborators, prepare the recruitment procedures, and organize the trial reference documentation. The coordinating centre team and the clinical coordination team will prepare the operation manual describing in details the trial procedures for each collaborators (clinical and laboratory activities, treatment dispensation, data management).
- **Database**: The trial database will be developed and maintained by the coordinating centre in collaboration with NCHADS Data Management Unit. The data manager will also be in charge of the data entry and implementation of data quality insurance plans. H/She has to prepare daily monitoring reports and the data file necessary for the trial analysis.
- **Data analysis and analysis report**: will be coordinated at the UHS coordinating centre.
- **Reporting**: the operational team will be responsible for finalizing:
    - the necessary reports and presentations for the Scientific Advisory Board and the DSMB meetings;
    - the trial yearly progress reports; The operational team will bring its support in preparing any communications on the trial (poster, oral presentation, papers).

14.1.2 Trial documents

Essential trial documents will be retained at the coordinating centre for 15 years. Data will be kept on a secured database installed on a server at the coordinating centre.

14.1.3 Data management

14.1.3.1 Data collection

Data on participants will be collected on duplicated CRF during the trial. A unique CRF will be assigned for each patient. The patient will only be identified by a unique anonymous code. An operation manual will be provided to help the clinical monitors fill out the CRF. All the information required by the protocol should be provided and any omissions require explanation.

The trial monitor from the coordinating centre will come on a regular basis to check for completeness, accuracy and legibility of data reported on the CRF. He/she will bring back the validated CRF to the coordinating centre for data entry.

14.1.3.2 Data entry and checking

Data will be entered at the coordinating centre (UHS). The trial database will be developed by a database developer which will closely work with the coordination team.

After entry, the database will be checked for consistency. If any inconsistency or question on the data, the coordinating centre monitor will go back to the clinical monitors at sites for clarification during their monitoring visit. The corrections will be entered and followed in the data base.

14.1.4 Monitoring

Monitoring will be conducted according to the Good Clinical Practice (ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996) to guarantee the good quality of the research and safeguard the health and the rights of the patient.

14.1.4.1 On site

The on-site trial activities (patient management; drug management and dispensation; trial monitoring) will be done under the responsibility of the **clinical coordinators**, based at the NCHADS in Phnom Penh. They will be responsible for coordinating all clinical activities for the trial:

- Recruitment, training and management of the clinical monitors;
- Organising and supporting clinical patient follow-up on site;
- Supervision of trial drug management;
- Member of the steering committee;

On each investigational site, a physician known as the "**clinical monitors**" will have the medical responsibility to conduct the trial according to the protocol. They will be responsible, under the supervision of the **clinical coordinator**, in organizing the trial follow-up and management on site:

- Organisation of patient screening, enrollment and follow-up;
- Report clinical and biological data in the Case Report Form (CRF) according to the most updated Methodology onsite MOP that will be provided;
- Report and document all Serious Adverse Events and sent follow-up report when necessary;
- Communication and coordination with the Decision Support Committee(DSC) and coordinating centre;
- Preparation and facilitation of the monitoring visit;

The clinical monitor must give the coordinating centre monitor access to relevant hospital or clinical records, to confirm their consistency with the CRF entries. No information about the identity of the subjects should appear on the CRF. The CRF must be completed within the week following the patient's visit. All CRF must be signed by the physician responsible of the patient follow-up. CRF will be considered as the source document for all the study sites regarding all the informations it contains.

14.1.4.2 Monitoring activities

Monitoring activities will be coordinated by the coordination center. The trial monitors will visit the site regularly during the study:

- Check the adherence to the protocol and to Good Clinical Practice (patient

informed consent, protocol visit and blood test schedule…);
- Assist in the trial organisation and management on site (communication between collaborators, treatment or material availability, tracing laboratory samples follow-up and result in collaboration with the lab technician);
- Check the completeness and the accuracy of patient data on the CRF;
- Collect and check the Serious Adverse Events reporting, documentation and follow-up, and send the forms to the sponsor;
- Evaluate the progress of enrolment.

15STATISTICAL ANALYSES

15.1.1 Calculation of number of patients needed

According to data available with the ANRS 139 TRIO and ANRS 143 NEAT studies, we could expect that at least 80% of patients will be in virological success after 6 months and we wish to conclude that treatment will be effective for more than 60% of patients
With a sample size of 45 patients, we could conclude that success rate is at least 60% if the total number of failure does not exceed 12 (alpha 0.05, power 90%, Fleming method with one stage).
Among the 3500 patients on PI-based regimen, and according to the results of the 2PICAM study, we could expect than 5% of patients followed in Cambodian sites could be enrolled in the study (175 patients) and one third of them (60 patients) will need third-line regimen at inclusion.
With a 10% refusal ratio, we anticipate to enroll 54 patients for third-line regimen while 100 patients will continue second-line regimen.

15.1.2 Analysis plan

- **Description of the subjects characteristics at inclusion** (including sociodemographic characteristics, medical history, CD4 cell count and plasma viral load). These variables will be described by their median, interquartile range, mean, standard deviation, or frequencies (%), as appropriate.

- **Primary outcome**

The percentage, and its 95% confidence interval, of patients with plasma HIV-1 RNA < 40 copies/mL at 6 months will be given, in a FDA snapshot analysis (patients who had stopped treatment and patients lost to follow-up were considered in virological failure).
An analysis stratified on the level of plasma HIV-RNA at inclusion will also be performed.
Comparisons of the percentage of subjects with plasma HIV-1 RNA <40 copies/mL at 6 months, by the characteristics at inclusion, will be done by a Chi2 test or Fisher exact test, as appropriate.

- **Secondary outcomes**

The immune restoration: The level of CD4 cell count reached at 6 months and 12 months will be described by mediane, interquartile range, mean and standard deviation. The percentage of subjects with a CD4 level > 350 cells/mm^3 and > 500 cells/mm^3 will also be given at each of these times.
The results will be given overall, and by group (according to whether subjects switched or not at M6 from DRV/r 600/100 twice daily to DRV/r 800/100 once daily).
The increase in CD4 cell count will also be analyzed by the difference of the value at M6 with that at inclusion, and then by the difference between M12 and M6 (median, interquartile interval, mean and standard deviation).
The analysis will be performed on the available data (without any imputation of missing data).
A sensitivity analysis will be also carried out, with data censored at treatment discontinuation.

Patients with IRIS: The percentage and its 95% confidence interval, of subjects with IRIS will be given.

Treatment discontinuation during the first year: The probability of discontinuation of treatment and its 95% confidence interval, as well as the median time to the occurrence of treatment discontinuation, will be determined using a Kaplan Meier analysis, to take into account censored data due to lost of follow-up. The analysis will be performed overall, and by group, the time of follow-up since inclusion will be taken into account in the analysis. An analysis will also be performed among those who switched at 6 months, with time of follow-up since M6 that will be considered in the analysis.

Occurrence of grade 3-4 adverse events (ANRS grading table): The percentage and its 95% confidence interval of subjects who had presented at least once a grade 3-4 adverse event will be given.
The incidence rate of grade 3-4 adverse event and its 95% confidence interval will also be determined, overall, and by group.
The type of side effects will be detailed, overall , and by group

Adherence of third-line regimen combination: The percentage and its 95% confidence interval of subjects with adherence > 90% during one year will be given.

Frequency of switch from DRV/r 600/100 twice daily to DRV/r 800/100 once daily at 6 months: The percentage and its 95% confidence interval of subjects who switched at 6 months will be given.

Plasma darunavir concentration: The plasma darunavir concentration will be described (median, interquartile interval, mean, standard deviation) at week 4 in all subjects, at week 30 in the subjects having switched at M6 DRV/r from 600/100 twice daily to 800/100 once daily, and in case of occurrence of coinfection tuberculosis during follow-up, at 2 weeks after Rifampicin initiation.

Effectiveness of switching DRV/r from 600/100 twice daily to 800/100 once daily : The percentage and its 95% confidence interval, of subjects with plasma HIV-RNA < 40 copies/mL at 12 months, among those switched from 600/100 twice daily to 800/100 once daily, will be given.

16SCIENTIFIC COMMUNICATION

All written or oral communications of the study's results must receive the approval of the coordinating investigators and of the scientific committee of the study.

The coordinating centre will realize data analysis. This analysis will lead to a report, submitted to the scientific committee for approval. This report will help to prepare scientific publications whose final draft must be approved by the scientific committee (SC).

SC shall have sole competence to include – if necessary – additional researchers to the papers related to the research project. All rules related to submission/publication, defined by ANRS, will be followed.

All publications will include the name of sponsor as follows ("Inserm-ANRS. The French National Institute for Health and Medical Research- ANRS [France REcherche Nord&Sud Sida-hiv

Hépatites] is the sponsor of the project") followed by the ANRS study number (ANRS 12374 + Acronym), as well as the investigators, the composition of SC

In case of ancillary studies, results will be published after approval by SC. In addition, these results will be published only after the publication of the main results obtained during the research project. The main project will be quoted (ANRS 12374). Results obtained through ancillary studies will be also transmitted to Inserm-ANRS for information.

17ETHICS AND LEGAL CONSIDERATIONS

- **17.1. Ethics**

This research project will be conducted with regard to fundamental ethical principles that are described in the updated version of the Declaration of Helsinki (64th World Medical Association [WMA] General Assembly, Fortaleza, Brazil, October 2013), and in the ANRS ethics charter for research in developing countries (July 2017) (http://www.anrs.fr/Ressources-et-publications/Publications/Publications-ANRS/Charte-d-ethique-de-la-recherche-dans-les-pays-en-developpement).

- **17.2. Policies and legal aspects**

This research project will be also conducted in accordance with national regulations and laws in Cambodia, and according to E6 Good Clinical Practice (GCP).
The protocol, information sheet, and informed consent (**appendix 1 and 2**) will receive the approval from the National Ethics Committee for Health Research (NECHR).
The research will be performed according to the present protocol. All researchers and investigators participating to this project will respect the protocol, especially in obtaining informed consent (see below).

- **17.3. Information and consent**

The consent of each potential participant is a prerequisite before starting any sampling or before obtaining any specific information related to the research project. The informed consent must be signed by each participant after giving full research description:

- What is being studied?
- What is the procedure/protocol?
- Who is sponsoring the study?
- What are the risks and burdens?
- What are the benefits?
- Whom to contact with questions/concerns

Each potential participant will be given time to think about the information before making a decision.
Each subject must fully understand that they have the full freedom to accept or refuse to participate in the study. Once one subject is included in the research project, he has to understand that he can also withdraw from it whenever he wants without any problems/consequences and he will continue to benefit from the regular medical care and check-up.
When one person gives his/her consent for participating to the study, he (she) will write his (her) last name and first name, date and sign the informed consent. In case of children, the informed consent will be filled, dated and signed by one parent or the legal guardian.
Each signed informed consent will be kept in a safe manner and in a safe place (MMC) for a total duration of 15 years after the end of the research project.

- **17.4. Data confidentiality**

All information collected from enrolled subjects will be strictly confidential and anonymized. During the implementation and by the end of the research, information collected among participants must be de-identified and names, personal addresses must not be indicated.

For this purpose, each participant will receive an anonymous identification (ID) number.

- **17.5. Type of collected data during the research project**

All data obtained through this research project will be recorded in a database at MMC (UHS). All the computer data will be treated in accordance with the Data Protection Act of 6th January 1978 (law n°78-17 Data Protection [DP] Officer) that was modified on 6th August 2004 (law 2004-801 DP Officer), with the implementing decree numbered 2005-1309 on 20th October 2005. We will follow this procedure in order to be in agreement with the treatment of personal data obtained through medical research programs.

- **17.6. Final report**

MMC will write the final report, in partnership with principal investigators.
This final report will be established within one year following the end of the research and will be transmitted to ANRS.

- **17.7. Archiving system**

Forms and data related to the research project are key documents. They can be useful to demonstrate that researchers and investigators respect GCP and current laws/legislation. Consequently, all these documents will be archived by MMC and ANRS during 15 years after the end of the research program.
Informed consents will be kept in a safe manner at MMC in sealed envelopes on which ID numbers of the participants will be indicated, as well as name and signature of the coordinating investigators.
No documents must be destroyed without prior authorization from ANRS.

18ACCESS TO DATA AND SPECIMENS

All research data and all collected samples will be under the responsibility of the MMC and coordinating investigators.
In case of request by other research teams to use results obtained during the research and/or to use stored samples, these teams will write a proposal and send it to the principal investigators, the scientific committee and the NECHR for approval.

After the dissolution of the SC, data and samples will be under the responsibility of ANRS and the coordinating investigators. In case of request by other research teams to use results obtained during the research and/or to use stored samples, these teams will write a proposal and send it to ANRS, which will take a decision in agreement with coordinating investigators and NECHR.

19DUTIES OF INVESTIGATORS

According to GCP aimed to achieve high quality of the research, each investigator must:

- To respect participants' rights and to ensure subjects' welfare,
- To ensure his availability as well as availability of his team,
- To ensure that enrollment will be feasible according to the research protocol,
- To organize technical infrastructures for the implementation of sampling, filling in of questionnaires and archiving of documents/records during the research study and 15 years after the end of the research,
- To collect and archive in a safe way signed informed consents,
- To ensure that researchers are following the protocol and to allow completed questionnaires to be regularly sent to MMC,
- To accept a possible audit of the research project carried out by ANRS itself or by other agencies if necessary.

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21 ANNEXES

Annex 1: Composition of the scientific committee
Annex 2: Treatments that could not be used because of potential drug-drug interactions
Annex 3: Information sheet of the study
Annex 4: Consent form of the study
Annex 5: Information sheet of PK analysis
Annex 6: Consent form of PK analyses

Annex 1: composition of the scientific committee

Name *(alphabetical order)*	Field of competence	Institution
Investigators		
Pr Cécile GOUJARD	HIV infection	CHU Bicêtre, APHP
Dr LY Penhsun	HIV infection	NCHADS
Dr PHENG Phearavin	Methodology and statistic	UHS
Dr SAMRETH Sovannarith	HIV infection	NCHADS
Dr Olivier SEGERAL	HIV infection	UHS
Dr MOM Chandara	Virologist	NCHADS
Dr Janin NOUHIN	Virologist	IPC
Pr CHOU Monidarin	Pharmacologist	UHS
Dr Anne Marie TABURET	Pharmacologist	CHU Bicêtre
Dr Remonie SENG	Methodology and statistic	CHU Bicêtre
External experts		
Dr Laurent Ferradini	HIV infection	WHO
Dr Joseph HARWELL	HIV infection	CHAI
Pr F Xavier BLANC	TB infection	CHU Nantes
Dr Nicolas ROUVEAU	Resource limited setting unit	ANRS
Dr Stephany PONG	Pharmacovigilance	ANRS

Annex 2: Treatments that could not be used because of potential drug-drug interactions

With DRV/r

- amiodarone, quinidine, bepridil, lidocaine systémique
- carbamazépine, phénobarbital, phénytoine
- rifampicine/rifampine, itraconazole ou kétoconazole > 200 mg/j, voriconazole
- astémizole, terfénadine
- dihydroergotamine, ergometrine, ergonovine, ergotamine, methylergonovine
- simvastatine, lovastatine
- millepertuis et produits contenant l'Hypericum perforatum
- pimozide, sertindole
- midazolam, triazolam
- cisapride

With DTG

- dofetilide
- Phenytoin, phenobarbitol and carbamazepine
- millepertuis
- concomitant administration with Al/Mg based antacids should be avoided or should be administered 2h before or 6h after antacids
- metformine: may increase metformin levels so that blood sugar levels need to be monitored. Dose should be limited to 1000 mg daily when initiating either dolutegravir or metformin and adjust dose carefully.

Dolutegravir, Darunavir/ritonavir and Optimized NRTI recycling as a third-line antiretroviral regimen in Cambodia – ANRS 12374

NB : this information sheet will be translated in khmer, reviewed with representatives of PLWHIV and back translated in English.

Information sheet
Version 1.0 – October 19th, 2017
approved by the National Ethics Committee for Health Research of Cambodia on
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Sponsor: **ANRS,** France REcherche Nord & sud Sida-hiv Hépatites
Coordinating investigators: **Pr Cécile GOUJARD (CHU Kremlin Bicêtre) – Dr LY Penhsun (NCHADS)**

This information sheet is made to help you to take the decision to participate or not in this study.

You are free to answer "yes" or "no" to the question: do you wish to participate to this study?

You have the right to take time, to discuss about this study and to ask all the questions that you wish

If you don't want to participate to this study, you will continue to receive the best possible care

You can change of mind at any moment and ask to stop the participation to the study. We just ask you to inform investigators as soon as possible.

GLOSSARY and DEFINITION:

- **Adherence:** the fact to take the treatment every day at the same time without missing dose

- **ART:** antiretroviral therapy = drugs active against HIV; according to the target involved in virus destruction, several families are available as :

- **NRTI (Nucleoside reverse-transcriptase inhibitor):** example: retrovir, tenofovir, abacavir
- **NNRTI (Non Nucleoside reverse-transcriptase inhibitor):** example: efavirenz, viramune
- **PI (Protease inhibitor):** example: lopinavir, atazanavir, darunavir
- **Integrase inhibitor:** example: raltegravir, dolutegravir

- **ARV: antiretroviral**

- **Genotype resistance test:** test to know if your virus is resistant to one or several drugs

- **Line regimen:**

- **Fist line regimen:** the first treatment received by the patient.
- **Second line regimen:** the second treatment received if the first one is not effective
- **Third line regimen:** the third treatment received if the second one is not effective

- **Pharmacogenetics:** this is a test to know whether unexpected adverse event could be due to a high amount of drug in your body
- **Viral load**: The viral load measures the quantity of virus circulating in the blood.

- **WHO: World Health Organisation**

What is a health research study?

A health research study is a way to find out new information about a disease and /or the treatment of the disease.

Why your doctor proposed you to participate in this study?

You are suffering of HIV infection and you have received several different drugs as recommended by the national guidelines. Your current treatment is a second line regimen composed of 3 antiretroviral drugs (ART) and one of those drugs is a protease inhibitor but the viral load is not controlled despite adherence counseling.
Without treatment the viral load is high.
The objective of the ART is to suppress the viral load (it becomes "undetectable").
A viral load could be detectable for many reasons:

- the beginning of the treatment is too recent
- the treatment is not correctly taken
- the treatment is not correctly absorbed by the body
- the treatment is not enough strong and the virus has developed resistance to one or several drugs

The most regular reason is a difficulty with treatment's dose. For that reason, you have received 3 months of adherence counseling to be sure that your treatment is correctly taken. Despite this adherence counseling, the viral load remains detectable meaning that you current treatment is not enough efficient. That is the reason why, we propose you to participate to this study, in order to possibly start a new ARV treatment call "Third line regimen".

What is the aim of the study?

The aim of this study is to assess the effectiveness of a third-line regimen including 2 new drugs, darunavir (DRV/r) and dolutegravir (DTG) combined to optimized NRTI recycling, in Cambodian HIV-infected adults, who failed a protease inhibitors (PI)-based second-line regimen after 3 months of boosted adherence counseling (BAC), and evidence of virus resistance to atazanavir (ATV) and/or resistance to all NRTI.
To reach this objective, we plan to enroll 54 participants in one year and to follow them during one year. The total duration of the study is, so, two years.
A genotypic resistance test will be done thanks to a blood exam to detect the presence of HIV resistances to one or several drugs.
If yes, you will be proposed to participate to the study and begin this new treatment.
If no, your doctor will decide the best therapeutic option (to continue your current treatment or to change one drug in case of intolerance) with adherence counseling support and you could not be enrolled in the study. You will continue to receive the support of care and treatment as recommended by the HIV national program.

Who can participate to the study?
The patients who have:

- >= 15 years old the day of inclusion
- With HIV-1 infection
- No pregnancy or desire of pregnancy for the women
- Failing a NNRTI-based first-line regimen
- Failing a PI-based second-line regimen after 3 months of adherence boosting with HIV RNA viral load > 1000 copies/mL and evidence of virus resistance to the current treatment
- Agree to participate in the study after oral and written explanation and sign the Informed consent form, at the latest the day of the inclusion

Who cannot participate to the study?
The patients who have:

- History of antiretroviral treatment including darunavir and integrase inhibitor
- Active pregnancy (and desire of pregnancy)
- Opportunistic infection in acute phase at inclusion including tuberculosis
- Advanced cirrhosis (Child-Pugh score B or C)

- Creatinine clearance < 50 ml/mn
- Any concomitant medical condition that, according to the clinical site investigator would contraindicate participation in the study
- Concurrent participation in any other clinical study without written agreement of the two study teams

Participation to the study:

You have full freedom in accepting or refusing to participate in this study.

If you refuse to participate in this study, you can still benefit from the current care provided by this center/hospital based on the HIV National Program, and your medical care will not be affected by your refusal.

If you accept to participate in this study, you will sign the consent form that will also be signed by the heath care provider who offered you to participate in this study.

Visits

- Pre-inclusion visit

During the first visit, we will collect information about personal and familial medical history, perform clinical examination and we will collect 25 mL of blood (5 tubes) to perform the biological tests including genotype resistance test to detect if the virus is resistant or not to your current ARV treatment. For women, we will also collect urine sample to perform a pregnancy test.

You will not participate to the study if this first evaluation shows that:

1) You have an acute infection, or a severe liver disease, or a renal insufficiency or an active pregnancy. In case, the medical problem is solved, it could be possible to you to participate in a second step.
2) The virus is still sensitive to the current treatment,

In that case, you will continue to receive the support of care and treatment as recommended by the HIV national program.

You will participate to the study:

- If the first evaluation doesn't detect any medical condition described above
- And confirms that the virus is resistant to atazanavir AND/OR resistant to both retrovir, abacavir and tenofovir: you will receive the new treatment, call third-line regimen, and which include at least two new drugs, darunavir and dolutegravir

In that case, a new consultation will be planed to start the new ARV treatment

- Inclusion visit

During the inclusion visit, the medical investigator will check the results of the pre-inclusion visit tests and verify that you meet all inclusion criteria and exhibit none of the non-inclusion criteria.

During this visit, we will perform clinical examination and we will collect 20 mL of blood (4 tubes) to perform the biological tests including HBV and HCV serology and glycemia and lipid profiles.

You will receive an adherence counselling and the treatment for one month.

- Follow-up visits for the first 6 months

The total duration of the study is one year and you will have a monthly consultation during the first 6 months + one consultation after 2 weeks of treatment. These consultations are necessary to detect any side effect of the treatment and to help you in case of difficulty to take the treatment. A blood collection will be done after 4, 8 and 12 weeks of treatment: 15 mL (3 tubes) for visits week 4 and 12 and 10 mL (2 tubes) for visits week 8.

If you miss any of these visits, you will be contacted at home or by phone by the study personal, unless you explicitly refuse such visits or phone calls.

Between study visits, you may come to the hospital whenever you have health problem. If needed, the doctor will undergo additional tests and specific treatment for your health care.

If you have one of these 4 symptoms - persistent cough (several weeks), fever, loss of weight and night sweats – you must contact your doctor to report him and further exams could be done.

- Visit week 24

After 6 months of treatment, a specific evaluation will be done including a viral load. During this visit, we will collect 20 mL of blood (4 tubes) to perform the biological tests including the viral load. The objective is that the quantity of virus in your blood will be undetectable:

In that case, the investigator will proposes you to switch from DRV/r 600/100 twice daily to DRV/r 800/100 once daily and to continue other drugs as usual. A new ART-related adherence counseling will be performed to explain the new dose. Plasma HIV-RNA will be performed one month later to confirm the maintenance of undetectable viral load.

If the HIV RNA viral load is still detectable at week 24, the investigator will not change the ART regimen and you will be addressed for systematic monthly adherence counseling during 3 months.

- Visits weeks 36 and 48

You will be systematically asked about your symptoms and drugs intakes, receive a clinical exam, an ART-related adherence counseling and a complete evaluation of adverse events.

Plasma HIV RNA will be performed:

- If you switched to DRV once daily, a reversal switch to DRV twice daily will be done if HIV RNA is > 40 copies/mL on two consecutive analyses

- If you not switched to DRV once daily because of uncontrolled HIV RNA at week 24, a GRT will be performed if HIV RNA is > 1000 copies/mL. If HIV RNA ranges from 40 to 1000 copies/mL, adherence counseling will be done.

Treatment

- Darunavir

Darunavir is a new generation protease inhibitor effective on virus known to be resistant to other protease inhibitors and recommended by WHO. Darunavir is always associated to ritonavir in order to increase the concentration of the drug in the blood. Darunavir could be administered twice daily or once daily. For patients with at least 2 resistance mutations for protease inhibitor, it is recommended to begin the treatment twice daily. For that reason, you will begin the treatment with 600 mg twice daily. But if your viral load is controlled after 6 months, we will propose you to switch to 800 mg once daily. In all cases, tablets must be taken with food.

Darunavir could have side effects. The most frequent are diarrhea, nausea, headaches and rash. More serious adverse effects that have been reported include an uncommon but severe hypersensitivity (allergic) reaction with rash and possible effects on the liver. This list is non exhaustive and you must report all side effects to your doctor, even if it’s not include in this list.

Darunavir could also present interaction with other drugs. For that reason, a list of forbidden drugs will be deliver and you must ask the authorization to your doctor before taking any new treatment.

- Dolutegravir

Dolutegravir is part of a new class of drugs, called integrase inhibitor, for which effectiveness has been reported in case of resistance to others drugs. Dolutegravir is administered once daily and could be taken with or without food. Dolutegravir is recommended by WHO.

Dolutegravir could have side effects. The most frequent are diarrhea, nausea, and headaches. Some psychiatric side effects could occur as depression, anxiety and difficulty to sleep. More serious adverse effects that have been reported include an uncommon but severe hypersensitivity (allergic) reaction with rash and possible effects on the liver. This list is non exhaustive and you must report all side effects to your doctor, even if it’s not include in this list.

Dolutegravir could also present interaction with other drugs. For that reason, a list of forbidden drugs will be delivered and you must ask the authorization to your doctor before taking any new treatment.

What happens if there is a problem?

In case of a problem, you should report it to your health care provider.
As a research sponsor, the ANRS purchase liability insurance for damage. This insurance guarantees compensation in case you experience any harm as the result of your involvement in this study including side effects of treatment.

Constitution of a biobank

Your biological samples (blood) will be frozen and kept anonymously in the freezers in the laboratory Rodolphe Merieux in University of Health Sciences of Phnom Penh, Cambodia and will be used in accordance with the protocol. They might be used for other purposes that the ones directly related to this study including genetic research studies, provided that explicit authorization from the National Authorities and from the sponsor will be obtained.

Pharmacokinetic analyses

We could propose you to participate to a pharmacokinetic sub-study. You are free to refuse to participate to this sub-study and you will continue to receive the follow-up of the main study. If you accept, analysis of concentration of dolutegravir and darunavir/ritonavir present in your blood will be conducted in a laboratory of the University of Health Sciences. A specific information sheet and consent form will be given to you.

If you have an unexpected adverse event with ART regimen, a pharmacogenetic test could be performed to better understand the reason of this adverse event. You are free to refuse pharmacogenetic test. If you are agree, you must answer “yes” in the consent form. In that case, a supplementary blood sample will be collected (one tube of 5 mL).

What are the advantages and disadvantages of participating?

Advantages

- You could receive new drugs, effective for resistant virus
- You could expect to have an undetectable viral load
- You could improve your immunity and so, decrease the risk of infections
- You will benefit the very closely monitored medical care with additional clinical and biological examination
- You will be reimbursed for the transportation fees used to come to the hospital for your protocol visits

Possible risks and disadvantages

- You will have to come more frequently to the hospital for the purpose of the study.
- Inconvenient could be associated with the drawing of blood. That includes light-headedness, bleeding and/or bruising at the puncture site and minor infection at the vein puncture site.
- The drugs can produce side effects (as explained above)
- It is possible that the treatment doesn’t work as expected.

For your safety, several Committees will meet regularly to examine all information related to the study.

Withdrawal

You can withdraw from this study whenever you wish without having to give any explication for your decision or having any consequences on your medical follow up. Moreover, your health care provider can stop your study participation if she/he thinks it is necessary. National Health Authorities or the Scientific Committee who monitor this study may also decide to end it.
If you withdraw from the study, you can express the will for your data to be removed from the database and your laboratory samples be destroyed. If you do not express such will, the study team could use data and samples collected prior to the date of your consent withdrawal.

Alternatives to Participating

If you do not wish to take part in the research, you will be provided with the established standard treatment available at the ART sites.

What happens when the study ends?

After this study ends, your medical care will continue at the same hospital and under the same condition as before through the HIV National Program. You could continue the same treatment delivered by the HIV National Program.

Confidentiality

All your personal information collected during the study period (data related to clinical assessment, biological testing) will be kept under an identification study code, which will not allow your identification. These data will be registered and coded in a computerized database. The health care providers and scientists have access to your medical record on the condition that they respect its confidentiality. When results of this study will be published, your identity will be kept confidential.

Expenses and compensations

You will not pay any costs related to this study: the costs of the biological and radiological diagnosis, of hospitalization and transportation expenses for protocol visits will be covered by the study during the entire duration of your follow-up.
Your participation is entirely voluntary and you will not receive any financial compensation.

Contact for further information

During the study period, you can ask any questions or request additional information from your health care provider or the person in charge of the study at your hospital or Health Centre. You have access to all the results of this research during and at the end of the research study.

Dr/ Mr/ Mrs …… Phone number: ……

Dolutegravir, Darunavir/ritonavir and Optimized NRTI recycling as a third-line antiretroviral regimen in Cambodia – ANRS 12374

NB : this information sheet will be translated in khmer, reviewed with representatives of PLWHIV and back translated in English.

Consent form for pharmacokinetic analyses
Version 1.0 – October 19th, 2017
approved by the National Ethics Committee for Health Research of Cambodia on
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Sponsor: **ANRS,** France REcherche Nord & sud Sida-hiv Hépatites
Coordinating investigators: **Pr Cécile GOUJARD (CHU Kremlin Bicêtre) – Dr LY Penhsun (NCHADS)**

I, (full name)…….……., the undersigned, declare that I have read or have been read the information sheet attached with this form and I have clearly understood the objectives, advantages and disadvantages of the study.
I had the opportunity to ask all questions and discuss this research study with the health care provider who proposed me to participate, whose name and signature are shown below, as well as with his/her staff.
They answered all my questions in an understandable language. The risk and benefits have been explained to me. I believe that I have not been unduly influenced by any team member to participate in the research study by any statement or implied statements. A time for thought is possible if I wish to take time before making my decision.
I understand that I may be given, if I wish, a copy of this consent form after signing it. I understand that my participation in this clinical study is voluntary, that I may choose to refuse to participate, that, if I accept, I may withdraw my consent in any time with no penalty or disadvantage to my routine care and that if I withdraw my consent, I have the right to ask that my personal data and samples would be removed from the study.
I understand that my samples and data might be used for further researches provided authorization from the National Ethics Committee and including genetic analyses.

Therefore, I fully agree to participate in this study. ❑**Yes** ❑ **No**
I agree to be contacted by phone or at home in relation to this study. ❑**Yes** ❑ **No**

I agree that my stored samples would be further used, for other studies approved by the National Ethics Committee ❑**Yes** ❑ **No**

I agree that my stored samples would be further used for genetic research studies ❑**Yes** ❑ **No**

I agree that one of my stored blood sample be used for a pharmacogenetic test which could be performed whether I happen to have an unexpected adverse effect with the new ARV regimen? ❑**Yes** ❑ **No**

I understand that information regarding my personal identity will be kept confidential and coded. I authorize the inspection of my medical records by the team in charge of the study. ❑**Yes** ❑ **No**

By signing this consent form, I have not waived any of the legal rights that I have as a participant in a research study.

Participant signature _____ Date |__|__| / |__|__| / |__|__|__|__|

I, Dr. / Mr/ Mrs ……..……., the undersigned, have fully explained the relevant details of this research to the participant named above and believe that the participant have understood and has knowingly given his(her) consent.

I solemnly promise I will respect all the terms and conditions mentioned in this consent form, kept full confidentiality, and respect the individual's rights and freedom as well as the requirements of the scientific work.

Investigator Signature_____ Date|__|__| / |__|__| / |__|__|__|__|

Dolutegravir, Darunavir/ritonavir and Optimized NRTI recycling as a third-line antiretroviral regimen in Cambodia – ANRS 12374

NB : this information sheet will be translated in khmer, reviewed with representatives of PLWHIV and back translated in English.

Information sheet for Pharmacokinetic analyses
Version 1.0 – October 19th, 2017
approved by the National Ethics Committee for Health Research of Cambodia on
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Sponsor: **ANRS,** France REcherche Nord & sud Sida-hiv Hépatites
Coordinating investigators: **Pr Cécile GOUJARD (CHU Kremlin Bicêtre) – Dr LY Penhsun (NCHADS)**

This information sheet is made to help you to take the decision to participate or not in this sub-study for pharmacokinetic analyses.

You are free to answer "yes" or "no" to the question: do you wish to participate to this sub-study?

You have the right to take time, to discuss about this sub-study and to ask all the questions that you wish

If you don't want to participate to this sub-study, you will continue to receive the follow-up of the main study

You can change of mind at any moment and ask to stop the participation to the sub-study. We just ask you to inform investigators as soon as possible.

Why your doctor proposed you to participate in this sub-study?

You have accepted to participate in a study entitled "dolutegravir, darunavir/ritonavir and Optimized NRTI recycling as a third-line antiretroviral regimen in Cambodia" and you will be treated for your HIV infection with antiretroviral drugs including dolutegravir and darunavir/ ritonavir. The HIV drug activity and tolerability depends on the drug concentration in your blood. We would like to understand precisely how your body absorbs and eliminates dolutegravir and darunavir/ritonavir. Analysis of concentration of dolutegravir and darunavir/ritonavir present in your blood will be conducted in a laboratory of the University of Health Sciences. We suggest you take part in a study that will last ten hours, one day at your convenience one month after initiation of treatment.

Role in the sub-study

The day before your visit to the hospital, you will take your dolutegravir or darunavir/ritonavir and other medicines prescribed by your doctor. On the morning of your arrival in the hospital, you will not take any medicine but you will bring them to the hospital (with the dolutegravir or darunavir/ritonavir that you did not take). A nurse will tell you when to take these medications.

To facilitate blood sampling and introduce a small needle in your vein only once, a catheter will be placed and then a first blood sample (4mL x 2 tubes) will be drawn. You will then take your medication with the nurse and samples of 4 mL x 2 tubes will be drawn at 1h, 2h, 6h, and 10h after taking the drugs.

Risk

Inconvenient could be associated with the drawing of blood. That includes light-headedness, bleeding and/or bruising at the puncture site and minor infection at the vein puncture site. Overall, certified medical doctors or nurses will perform these collection methods. During these 10 hours, you will be under medical observation and we ask you to stay in your hospital room. A surveillance or medical check-up will be done during your stay. A breakfast and lunch will be served.

Compensation

The cost of transportation to the hospital, room and meals will be borne by the study. A sum of 20 USD will be given to compensate for the day you will spend in the hospital.

Frozen samples

Some biological samples will be frozen and kept anonymously in the freezers in the laboratory Rodolphe Merieux in University of Health Sciences of Phnom Penh, Cambodia. They might be used for other purposes that the ones directly related to this study including genetic research studies, provided that explicit authorization from the National Authorities and from the sponsor will be obtained.

Contact for further information

During the study period, you can ask any questions or request additional information from your health care provider or the person in charge of the study at your hospital or Health Centre. You have access to all the results of this research during and at the end of the research study.

Dr/ Mr/ Mrs …… Phone number: ……

Dolutegravir, Darunavir/ritonavir and Optimized NRTI recycling as a third-line antiretroviral regimen in Cambodia – ANRS 12374

NB : this information sheet will be translated in khmer, reviewed with representatives of PLWHIV and back translated in English.

Consent form
Version 1.0 – October 19th, 2017
approved by the National Ethics Committee for Health Research of Cambodia on
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Sponsor: **ANRS,** France REcherche Nord & sud Sida-hiv Hépatites
Coordinating investigators: **Pr Cécile GOUJARD (CHU Kremlin Bicêtre) – Dr LY Penhsun (NCHADS)**

I, (full name)…….……., the undersigned, declare that I have read or have been read the information sheet for pharmacokinetic analyses attached with this form and I have clearly understood the objectives, advantages and disadvantages of this sub-study.
I had the opportunity to ask all questions and discuss this research sub-study with the health care provider who proposed me to participate, whose name and signature are shown below, as well as with his/her staff.
They answered all my questions in an understandable language. The risk and benefits have been explained to me. I believe that I have not been unduly influenced by any team member to participate in the research sub-study by any statement or implied statements. A time for thought is possible if I wish to take time before making my decision.
I understand that I may be given, if I wish, a copy of this consent form after signing it. I understand that my participation in this clinical sub-study is voluntary, that I may choose to refuse to participate, that, if I accept, I may withdraw my consent in any time with no penalty or disadvantage to my routine care and that if I withdraw my consent, I have the right to ask that my personal data and samples would be removed from the study.
I understand that my samples and data might be used for further researches provided authorization from the National Ethics Committee and including genetic analyses.

Therefore, I fully agree to participate in this study. ❑**Yes** ❑ **No**
I agree to be contacted by phone or at home in relation to this study. ❑**Yes** ❑ **No**

I agree that my stored samples would be further used, for other studies approved by the National Ethics Committee ❑**Yes** ❑ **No**

I agree that my stored samples would be further used for genetic research studies ❑**Yes** ❑ **No**

I understand that information regarding my personal identity will be kept confidential and coded. I authorize the inspection of my medical records by the team in charge of the study. ❑**Yes** ❑ **No**

By signing this consent form, I have not waived any of the legal rights that I have as a participant in a research study.

Participant signature _____ **Date** |__|__| / |__|__| / |__|__|__|__|

I, Dr. / Mr/ Mrs ……..……., the undersigned, have fully explained the relevant details of this research to the participant named above and believe that the participant have understood and has knowingly given his(her) consent.

I solemnly promise I will respect all the terms and conditions mentioned in this consent form, kept full confidentiality, and respect the individual's rights and freedom as well as the requirements of the scientific work.

Investigator Signature_____ Date|__|__| / |__|__| / |__|__|__|__|