Résumé du rapport final
ANRS 12180 REFLATE TB

Name of Sponsor/Company: The French National Institute of Health and Medical Research - French National Agency for Research on AIDS and Viral Hepatitis (Inserm-ANRS)	**Individual Study Table Referring to Part of the Dossier** **Volume: NA** **Page: NA**	**(For National Authority Use only)**
Name of Finished Product: raltegravir, efavirenz, emtricitabine, tenofovir		
Name of Active Ingredient: raltegravir, efavirenz, emtricitabine, tenofovir		

Title of Study: Phase II open-label randomized multicenter trial to compare the efficacy and safety of two different doses of raltegravir and efavirenz, all in combination with tenofovir and lamivudine, in naive HIV- 1-infected patients receiving rifampin for active tuberculosis : ANRS 12 180 REFLATE TB Trial

Investigators:

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Publications (references)

• Raltegravir for the treatment of patients co-infected with HIV and tuberculosis (ANRS 12 180 Reflate TB): a multicentre, phase 2, non-comparative, open-label, randomised trial
Beatriz Grinsztejn, Nathalie De Castro, Vincent Arnold, Valdiléa G Veloso, Mariza Morgado, José Henrique Pilotto, Carlos Brites, José Valdez Madruga, Nêmora Tregnago Barcellos, Breno Riegel Santos, Carla Vorsatz, Catherine Fagard, Marilia Santini-Oliveira, Olivier Patey, Constance Delaugerre, Geneviève Chêne, Jean-Michel Molina, for the ANRS 12 180 Reflate TB study group*
Lancet Infect Dis. 2014 Apr 9

• A randomized trial to estimate efficacy and safety of 2 doses of raltegravir and efavirenz for treatment of HIV-TB co-infected patients: ANRS 12 180 REFLATE TB trial.
B. Grinsztejn, N. De Castro, V. Arnold, V. Veloso, M. Morgado, JH. Pilotto, C. Brites, JV. Madruga, N. Barcellos, BR Santos, C. Vorsatz, C. Grondin, M. Santini-Oliveira, O. Patey, C. Delaugerre, G. Chêne, J-M. Molina and the ANRS 12 180 Reflate TB study group. XIX International AIDS Conference July 26, 2012 Abstract #:THLBB01

• Efficacy and Safety of Raltegravir vs. Efavirenz for the Treatment of HIV-TB Patients:
48-Week Results of the ANRS 12 180 Reflate TB trial.
Beatriz Grinsztejn, Nathalie De Castro, Vincent Arnold, Valdilea Veloso, José Henrique Pilotto, Carlos Brites, Carla Vorsatz, Carine Grondin, Geneviève Chêne and Jean-Michel Molina
and the ANRS 12 180 REFLATE TB Trial Group. CROI 2013 Atlanta 2013, Poster Board #: 853

Studied period (years): 2.9 (date of first enrolment: 13 August 2009) (date of last completed: 03 May 2012)	**Phase of development:** II

Objectives:

Primary objective :
To estimate the antiviral efficacy of two doses of raltegravir and one dose of efavirenz at week 24, in HIV-1 naive patients co-infected with active tuberculosis (TB) treated with rifampin.

Secondary objectives :
• To assess in each arm, each component of antiviral efficacy, separately
• To assess in each arm:
- virologic success at the threshold of 50 copies/ml at week 48 and at the threshold of 400 copies/ml at week 24 and week 48,
- evolution of HIV RNA and HIV DNA (total and 2LTR circular) from baseline to week 48
- emergence of genotypic resistance in patients with virologic failure
- evolution of CD4 cell counts from baseline to week 48
- progression to HIV disease progression or death
- treatment tolerance (grades 3 or 4)
- success of TB treatment
- anti-TB resistance
- raltegravir and efavirenz trough concentrations overtime

Sub-studies objectives :
• To study the pharmacokinetic interactions between raltegravir at the doses of either 400 mg bid and 800 mg bid doses and rifampin.
• To assess the incidence of immune reconstitution inflammatory syndrome (IRIS) and to identify potential predictors of IRIS
• To assess the relationship between genetic polymorphism and either antiretroviral plasma concentrations, or antiviral efficacy and tolerance

Methodology:

Phase II, multicenter, open-label, randomized trial in HIV-1-TB co-infected patients, naïve from antiretroviral therapy and receiving anti-tuberculosis treatment with rifampin, to evaluate the efficacy and safety of raltegravir given either at a dose of 400 or 800 mg bid compared to efavirenz, each in combination with emtricitabine and tenofovir.
Patients at day 0 have received between 2 and 8 weeks of rifampin-based TB treatment. The remaining duration of rifampin-based TB treatment in this trial was therefore of at least 16 weeks (for a minimal total duration of rifampin-based TB treatment of 24 weeks).

Number of patients (planned and analysed):
- planned : 150
- analysed : 153 (51 in each arm)

Diagnosis and main criteria for inclusion:

Inclusion criteria :

- Signed informed consent form
- Adult patients (at least 18 years old)
- Plasma HIV RNA > 1000 copies/ml
- HIV1-infection confirmed by ELISA and Western blot or Immunofluorescence (patient can be randomized while waiting for the serology results if plasma HIV RNA > 1000 copies/ml)
- ART naïve patients or ART for less than 3 months and more than 6 months ago (including single dose nevirapine for prevention of mother to child transmission (PMTCT); an HIV resistance genotype showing no mutation to NNRTI and tenofovir or lamivudine was required.
- For women of childbearing age, negative urinary test for pregnancy and to accept contraceptive methods: condom use and intra-uterine device when possible or declare no wish of pregnancy in the coming year.
- Confirmed or probable TB (WHO guidelines for HIV infected patients):

- Pulmonary TB:

sputum smear-positive: One sputum smear examination positive for AFB AND culture positive for M. tuberculosis OR One sputum smear examination positive for AFB AND radiographic abnormalities consistent with active pulmonary TB.

sputum smear-negative: Sputum smear examinations negative for AFB and sputum culture positive for M. tuberculosis OR At least 2 sputum examinations negative for AFB and radiographic abnormalities consistent with active tuberculosis OR Decision by clinician to treat with a full course of anti-TB treatment.

- Extra-pulmonary TB: One specimen from an extra-pulmonary site culture-positive for M.tuberculosis or smear positive for AFB OR Histological or strong clinical evidence consistent with active TB OR
Decision by clinician to treat with a full course of anti-TB treatment

- TB treatment including rifampin started since 2 to 8 weeks before W0
- For French patients, affiliation to the National Health Care System

Non-inclusion criteria:

- HIV-2 infection (single or with HIV-1)
- Woman who was pregnant or likely to become so, was breastfeeding or refused to use contraception
- ALT>2,5N, Hb <7g/dl, neutrophils < 750/mm3, platelet<50 000/mm3, bilirubin >5N, lipase >3N
- Creatinine clearance <60ml/min as assessed by the Cockcroft method
- Ongoing psychiatric pathology or any condition (including, but not limited to, the consumption of alcohol or drugs) which have might, in the investigator's opinion, compromise the safety of treatment and/or patient compliance with the protocol
- Concomitant treatments including phenytoin or phenobarbital (compounds interacting with UGT1A1)
- Prior TB with a *mycobacterium tuberculosis* strain resistant to rifampin.
- TB treatment started for more than 8 weeks before W0

Test product, dose and mode of administration, batch number:

Once eligibility criteria were checked, patients were randomised in one of the three following arms and received from week 0 to week 48, the three drugs together:

Arm 1: tenofovir (245 mg 1 tablet qd)/lamivudine (one 300 mg tablet qd in France and two 150 mg tablets qd in Brazil) + efavirenz (600 mg, once a day)

Arm 2: tenofovir (245 mg 1 tablet qd)/lamivudine (one 300 mg tablet qd in France and two 150 mg tablets qd in Brazil) + raltegravir (400 mg, twice daily, 1 tablet bid)

Arm 3: tenofovir (245 mg 1 tablet qd)/lamivudine (one 300 mg tablet qd in France and two 150 mg tablets qd in Brazil) + raltegravir (800 mg, twice daily, 1 tablet bid) at least up to 24 weeks. One month after stopping rifampin, the dose of raltegravir should be reduced to 400 mg.

Duration of treatment: From week 0 to week 48.

Reference therapy, dose and mode of administration, batch number: NA

Criteria for evaluation:

Primary endpoint (efficacy and safety combined)

The primary endpoint was the proportion of patients in success at week 24 with success defined as:

- Plasma HIV-1 RNA below 50 copies/ml at week 20, confirmed at week 24
- Absence of permanent discontinuation of either efavirenz, raltegravir or rifampin (before the end of anti-TB treatment) for any reason
- Absence of death
- Still follow-up at week 24

Secondary endpoints (efficacy and safety combined)

Each criterion of the primary endpoint was separately considered as a secondary endpoint:

- Proportion of patients with virologic response with the following definitions:
- Plasma HIV-1 RNA <50 copies/ml at week 20, confirmed at week 24
- Rate of strategy discontinuation and treatment changes
- Proportion of death
- Proportion of patients lost to follow-up

Efficacy secondary endpoints:

- Proportion of patients with virologic response with the following definitions:
- Plasma HIV-1 RNA <50 copies/ml at week 48
- Plasma HIV-1 RNA <400 copies/ml at week 24 and at week 48
- Evolution in HIV-1 RNA and DNA from baseline to week 48
- Rate of viral resistance mutations in the plasma at the time of virologic failure and in comparison with HIV-1 RNA mutations at W0
- CD4 cell counts changes from baseline to week 48
- Rate of success of TB treatment
- Anti-TB resistance rate
- Raltegravir and efavirenz trough concentrations overtime

Safety secondary endpoints:

- Frequency, type and time to a new AIDS-defining event or death
- Frequency, type, time to grade 3 or 4 adverse events

The sub-studies endpoints were:

- Evolution of pharmacokinetic parameters of raltegravir between week 4 (with rifampin), 1 month after rifampin discontinuation and before dose decrease in the raltegravir 800 mg arm), 1 month after switch to raltegravir 400mg only for patients included in the raltegravir 800 mg arm.
- Rate and predictors of immune reconstitution inflammatory syndrome (IRIS)
- Relationship between genetic polymorphism of genes involved in the metabolization and transport of antiretroviral drugs and plasma concentrations, antiviral efficacy and tolerance

Statistical methods:

Sample size :

The objective of the trial was to select a regimen with a success rate of at least 70%, which could then be tested in a phase III trial in patients with tuberculosis. This objective was based on data published by Markowitz et al. with the combination of raltegravir + TDF + 3TC among naive subjects, which suggest that a proportion of virologic response of 85 to 95% could be achieved at 24 weeks with this combination. The number of subjects to enrol was calculated to give a power of at least 80% to select a regimen which a proportion of virologic response at week 24 was high, at least 70%, based on the primary efficacy endpoint. We expected an observed proportion of virologic response at week 24 of at least 85% and we wished to be able to conclude that the proportion of virologic response at week 24 with the regimen was at least 70% with a power of 80%. With 49 patients per arm, we would have been able to conclude with $\alpha = 5\%$ (one-sided test) and a power of 80%, that the proportion of virologic response at week 24 was at least 70% if the number of failures did not exceed 9. This calculation was based on the Fleming method. We planned to include 50 patients per arm.

Analyses :

The primary efficacy analysis was a intention-to-treat analysis, which included all randomised patients who received at least one dose of efavirenz or raltegravir. The proportion of patients reaching the primary outcome with its 95 confidence interval (CI) was estimated in each arm and the lower bound of the confidence interval compared to 70%. A per protocol analysis was also performed to describe the true efficacy of each combination in those continuing their initial therapy. The per protocol population censored patients who have stopped efavirenz or raltegravir.

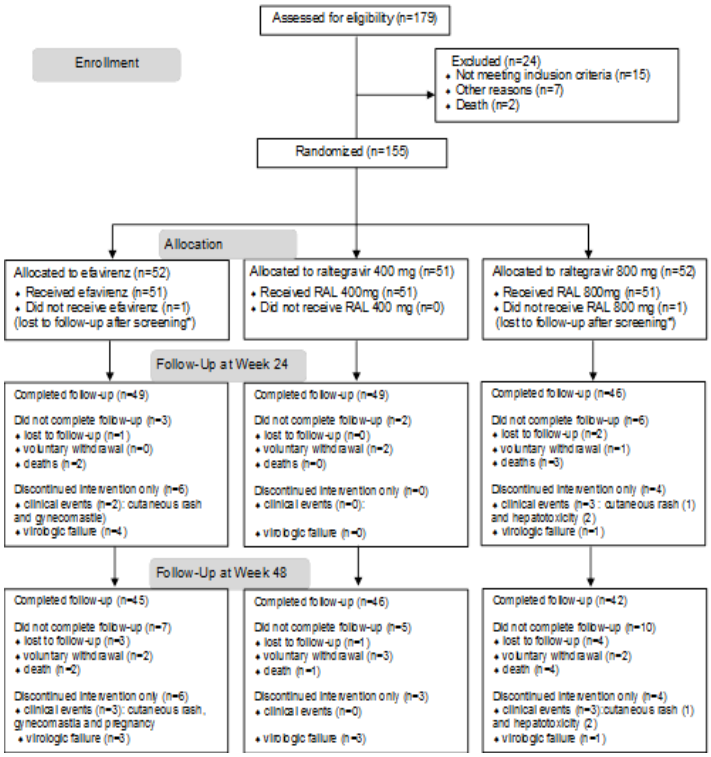
Secondary analyses included estimations of the proportion of patients with HIV-1 RNA levels of less than 50 or 400 copies/ml at each visit up to week 48, the proportion of patients with virologic failure, the change from baseline in CD4 cell counts, the proportion of patients with an incident AIDS-defining disease, tuberculosis treatment outcomes and the proportion of tuberculosis with grade 3 to 4 paradoxical IRIS. Safety and TB outcomes were assessed by the report of adverse events using the ANRS grading scale and WHO case definition of TB cure and success (WHO, 2007), respectively.

Summary - Conclusions

From July 2009 to June 2011, 179 patients were screened and 155 randomized but 2 patients never received allocated regimen and were not included in analyses. 153 patients were analysed, randomized in raltegravir (RAL) 400 (n=51), RAL 800 (n=51) and efavirenz (EFV) (n=51) arms, respectively.

133 (87%) completed follow-up at 48 weeks (see reasons of study and intervention discontinuation in the following trial profile).

ANRS 12 180 REFLATE TB Trial profile



At baseline, 73% were male, median age was 38 years, median baseline CD4 cell count was 140 cells/µL (with 20% of patients having less than 50 cells/µL), median HIV-1 RNA level was 4.9 $\log_{10}$ cp/ml (with 46% of patients having more than 100.000 copies/ml).

Tuberculosis location was pulmonary in 43% of patients and pulmonary and extra-pulmonary in 45% of patients. Mycobacteriosis was bacteriologically confirmed in 75 cases (49%), 73 had *Mycobacterium tuberculosis*, one had *M. bovis* and one had *M. avium*. Among cultures with susceptibility testing (n= 56), 6 had streptomycin resistance, 6 isoniazid resistance and none had rifampin resistance.

Baseline characteristics were overall well balanced across all treatment arms.

Efficacy results:

At week 24, virologic suppression was achieved in 39 patients allocated raltegravir 400 mg bid (76%, 95% Confidence Interval [CI]: 65 to 88), 40 patients raltegravir 800 mg bid (78%, 95%CI: 67 to 90) and 32 patients efavirenz (63%, 95%CI: 49 to 76). The lower bound of the 95% confidence interval remained below the predefined margin of 70% in all three arms, demonstrating that the response rate was slightly lower than anticipated.

At week 48, virologic suppression was achieved in 39 (76%, 95%CI: 65 to 88), 32 (63%, 95%CI: 49 to 76) and 34 (67%, 95%CI: 54 to 80) patients, respectively.

Three patients allocated efavirenz and 3 raltegravir 800 mg bid discontinued study drugs because of adverse events, one of whom developed liver failure and underwent a liver transplantation.

The per-protocol analysis on available data censoring patients who discontinued efavirenz or raltegravir for reasons other than virologic failure provided results consistent with those of the intention-to-treat analysis. Using a higher threshold of 400 copies/ml of HIV-1 RNA, viral suppression rates were higher and similar across treatment arms, accounting for the slower decrease in HIV-1 RNA levels with efavirenz.

Antiretroviral resistance associated mutations were available for 30 of 39 (77%) patients who presented with virologic failure over the 48 weeks of follow-up. A similar low proportion of patients in the two raltegravir arms developed integrase inhibitors and NRTI resistance.

Median increase in CD4 cell counts from baseline to week 48 was +216, +239 and +212 cells/mm^3 in the efavirenz, raltegravir 400 mg and raltegravir 800 mg arms, respectively. Tuberculosis treatment success rate (cured or treatment completed) was about 90% in all three arms. The median duration of tuberculosis treatment in this trial was around 6 months in the three arms.

Safety results:

Seven patients died during the study and none of the deaths was related to study drugs.

The proportion of patients with serious adverse events was much the same in all three arms (see Table below). However, the occurrence of treatment-related serious adverse events was lower in the raltegravir 400 mg arm than in the two others arms. One patient in the raltegravir 800 mg arm developed liver failure that was evaluated as being related to tuberculosis treatment by investigator and being possibly related to tuberculosis treatment and to antiretroviral drugs by the sponsor. This patient underwent a liver transplant and after transplantation, raltegravir was resumed at the standard dose of 400 mg bid without further toxicity.

The proportion of patients with grade 3 to 4 tuberculosis IRIS was low in all three arms.

The proportion of patients with grade 3 to 4 laboratory abnormalities did not differ among the three arms.

The occurrence of new AIDS-defining illnesses did not differ among treatment arms, 4 in the efavirenz arm and 2 in each of the two raltegravir arms.

Table: Treatment-emergent adverse events, serious adverse events, and adverse events of interest in the ANRS 12 180 REFLATE TB Trial

AE: adverse event; ARV: antiretroviral treatment; IRIS: immune reconstitution inflammatory syndrome; ULN: upper limit of normal range

	Efavirenz N=51		**Raltegravir 400 N=51**		**Raltegravir 800 N=51**		**Total N=153**	
Any adverse event (AE), n patients (%)	46	(90)	46	(90)	47	(92)	139	(91)
Serious AE, n patients (%)	19	(37)	17	(33)	17	(33)	53	(35)
Serious AE related to ARV, n patients (%)	10	(20)	6	(12)	8	(16)	24	(16)
Any event leading to drug discontinuation, n patients (%)	3	(6)	0	(0)	3	(6)	6	(4)
*- hepatotoxicity **	*0*		0		*2*		*2*	
- cutaneous rash	*1*		0		*1*		*2*	
- gynecomastia	*1*		0		*0*		*1*	
- pregnancy	*1*		0		*0*		*1*	
** (to ARV or anti-TB drugs)*								
AE grade 3 or 4, n patient (%)	19	(37)	17	(33)	17	(33)	53	(35)
Grade 3 or 4 IRIS	5	(10)	2	(4)	4	(8)	11	(7)
Death	2	(4)	1	(2)	4	(8)	7	(5)
Laboratory adverse event, any, n (%)	49	(96)	49	(96)	44	(85)	142	(92)
Laboratory grade 3 or 4, n patients (%)	10	(20)	13	(25)	9	(17)	32	(21)
- neutrophil count < 750 cells /mm^3	*3*		*5*		*5*		*13*	
- aspartate amino-transferase >5 ULN	*3*		*3*		*3*		*9*	
- alanine amino-transferase >5 ULN	*3*		*1*		*1*		*5*	
- haemoglobin <7g/dl	*1*		*2*		*1*		*4*	
- alkaline phosphatase >5 ULN	*2*		*0*		*1*		*3*	
- platelets <50 000 cells/mm^3	*0*		*2*		*1*		*3*	
- bilirubin >5 ULN	*2*		*0*		*0*		*2*	
- creatinine >3 ULN	*1*		*0*		*0*		*1*	
- glycemia >16.5 mmol/l	*0*		*1*		*0*		*1*	

Conclusions

Raltegravir at the dose of 400 mg bid was well tolerated and could be considered as a valuable alternative to efavirenz in patients co-infected with TB receiving rifampin. This should be further evaluated in a larger phase III trial.

Date of report: 15/09/2023

Signature:

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