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

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Summary

Background Concurrent treatment of HIV and tuberculosis is complicated by drug interactions. We explored the safety and efficacy of raltegravir as an alternative to efavirenz for patients co-infected with HIV and tuberculosis.

Methods We did a multicentre, phase 2, non-comparative, open-label, randomised trial at eight sites in Brazil and France. Using a computer-generated randomisation sequence, we randomly allocated antiretroviral-naive adult patients with HIV-1 and tuberculosis (aged ≥18 years with a plasma HIV RNA concentration of >1000 copies per mL) to receive raltegravir 400 mg twice a day, raltegravir 800 mg twice daily, or efavirenz 600 mg once daily plus tenofovir and lamivudine (1:1:1; stratified by country). Patients began study treatment after the start of tuberculosis treatment. The primary endpoint was virological suppression at 24 weeks (HIV RNA <50 copies per mL) in all patients who received at least one dose of study drug (modified intention-to-treat analysis). We recorded death, study drug discontinuation, and loss to follow-up as failures to achieve the primary endpoint. We assessed safety in all patients who received study drugs. This study is registered in ClinicalTrials.gov, number NCT00822315.

Findings Between July 3, 2009, and June 6, 2011, we enrolled and randomly assigned treatment to 155 individuals; 153 (51 in each group) received at least one dose of the study drug and were included in the primary analysis. 133 patients (87%) completed follow-up at week 48. At week 24, virological suppression was achieved in 39 patients (76%, 95% CI 65–88) in the raltegravir 400 mg group, 40 patients (78%, 67–90) in the raltegravir 800 mg group, and 32 patients (63%, 49–76) in the efavirenz group. The adverse-event profile was much the same across the three groups. Three (6%) patients allocated to efavirenz and three (6%) patients allocated to raltegravir 800 mg twice daily discontinued the study drugs due to adverse events. Seven patients died during the study (one in the raltegravir 400 mg group, four in the raltegravir 800 mg group, and two in the efavirenz group): none of the deaths was deemed related to study treatment.

Interpretation Raltegravir 400 mg twice daily might be an alternative to efavirenz for the treatment of patients co-infected with HIV and tuberculosis.

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Introduction

In patients with HIV, tuberculosis is the most common life-threatening opportunistic infection and is a leading cause of death. Concurrent treatment of HIV and tuberculosis decreases mortality,[1–3] reduces tuberculosis relapse,[4] and decreases community transmission of both tuberculosis and HIV.[5,6] Antiretroviral treatment should, therefore, be started early in all patients with active tuberculosis, irrespective of their WHO clinical stage or CD4 cell count.[7]

However, despite the increasing number of antiretroviral drugs developed for the treatment of HIV infection, few options are available for patients co-infected with tuberculosis because of drug interactions. Rifampicin is the cornerstone of tuberculosis treatment, and is a potent inducer of hepatic cytochrome P450 3A4 enzymes, the main metabolic pathway of most non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors. Induction of these enzymes leads to increased clearance, reduced drug exposure, and potentially suboptimum clinical efficacy. Efavirenz, an NNRTI metabolised mainly through the cytochrome P450 2B6 pathway, also has pharmacokinetic interaction with rifampicin, which does not necessitate dose adjustment, and is the preferred antiretroviral to be used in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) for the treatment of patients with both HIV and tuberculosis.[7] Common side-effects of efavirenz are neuropsychiatric adverse events and rash, which can lead to treatment discontinuation.[8] Additionally, primary NNRTI-resistance mutations could jeopardise the efficacy of efavirenz, and its use is controversial during the first trimester of pregnancy.[9–11] Alternatives to efavirenz are therefore needed for the treatment of HIV in patients with tuberculosis.

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Raltegravir, a strand-transfer HIV integrase inhibitor, has shown potent antiviral activity and good tolerability in patients with HIV.[12] In the long-term follow-up of the phase 3 STARTMRK study in treatment-naive patients,[13] raltegravir had better virological and immunological efficacy and had a more favourable safety profile when compared with efavirenz. Raltegravir is not metabolised by the cytochrome P450 enzymes, but by uridine 5′-diphospho (UDP)-glucuronosyltransferase 1A1, an enzyme that is also induced by rifampicin. When raltegravir is given with rifampicin, and is used at the standard dose of 400 mg twice a day, findings from pharmacokinetic studies in healthy volunteers have shown a 40% decrease in plasma raltegravir area under the concentration-time curve, and a 61% decrease in plasma raltegravir trough concentration.[14] Increasing the raltegravir dose to twice the standard dose (800 mg twice a day) compensates for the effect of rifampicin on the area under the concentration-time curve, although raltegravir trough concentrations remain 53% lower than expected.[14] Therefore, both the US Food and Drug Administrations (FDA) and the European Medicines Agency approved the raltegravir package insert to recommend for raltegravir dosing to be increased from a standard 400 mg twice a day to 800 mg twice a day for patients taking concomitant rifampicin. Despite this recommendation, clinical experience with the combination of raltegravir and rifampicin is restricted, and the efficacy and safety of high-dose raltegravir during tuberculosis treatment has not been assessed.[15–17] We assessed the efficacy and safety of two raltegravir doses in antiretroviral-naive adults receiving rifampicin-based treatment for HIV and tuberculosis co-infection.

Methods

Study design and participants

The French National Agency for Research on AIDS and Viral Hepatitis (ANRS) 12180 Reflate TB trial was a multicentre, randomised, parallel-group, phase 2, 48 week study, done at eight clinical sites, six in Brazil and two in France. We enrolled adult patients (aged 18 years or older) with previously untreated HIV-1 infection and a plasma HIV RNA concentration of greater than 1000 copies per mL, who had been receiving a rifampicin-based treatment for pulmonary or extra-pulmonary tuberculosis for 2–8 weeks. Patients who had received previous antiretroviral treatment for less than 3 months (including single-dose nevirapine for prevention of mother-to-child transmission) were also eligible for inclusion, provided they had received antiretroviral treatment more than 6 months before enrolment, and that baseline HIV testing showed no mutations associated with resistance to NNRTIs, tenofovir, or lamivudine. Women who were pregnant (established by urinary pregnancy test) or breastfeeding were not eligible for inclusion, nor were those who refused to use contraception (condom or intrauterine device) or those with HIV-2 infection, alanine aminotransferase concentrations of more than 2·5 times the upper limit of normal, bilirubin concentrations of more than five times the upper limit of normal, lipase concentrations of more than three times the upper limit of normal, creatinine clearance of less than 60 mL per min (Cockcroft formula), haemoglobin of less than 7 g/dL, absolute neutrophil count of less than 750 cells per µL, platelet count of less than 50 000 per µL, ongoing psychiatric disease, or any disorder (including, but not limited to, the consumption of alcohol or psychoactive drugs) that the enrolling clinician thought would compromise the safety of treatment or patients' compliance with the protocol. Individuals on concomitant treatment including phenytoin or phenobarbital (compounds interacting with UDP-glucuronosyltransferase 1A1) or who had prior tuberculosis infection with a rifampicin-resistant *Mycobacterium tuberculosis* strain were also not eligible. The upper threshold for alanine aminotransferase concentrations was lower in this study than in previous trials in HIV and tuberculosis co-infection (usually less than five times the upper limit of normal) to minimise the risk of liver toxicity because we were assessing a high dose of raltegravir with unknown safety.

All participants provided signed informed consent before or at the time of the screening visit. The protocol was approved by national and local ethics committees in Brazil (Comissão Nacional de Ética em Pesquisa [CONEP] and Comitê de Ética em Pesquisa [CEP] at IPEC/FIOCRUZ) and France (Comité de Protection des Personnes de Paris Ile de France I). We did this trial in accordance with Good Clinical Practices, the ANRS Ethical Chart for Research in Developing Countries, the Brazilian regulatory requirements for clinical trials, and the ethical principles of the Declaration of Helsinki.

Randomisation and masking

Using a computer-generated sequence, we randomly allocated eligible patients (1:1:1; stratified by country) to receive either raltegravir 400 mg twice a day, raltegravir 800 mg twice a day, or efavirenz as the standard of care. One trial statistician (Celine Colin, Reflate study group) generated the randomisation sequence, another (CG) did the analyses. This randomisation list was kept confidential to the site investigators. Randomisation was managed centrally at the clinical trial units at Institut National de la Santé et de la Recherche Médicale (INSERM) via the e-CRF (Capture System; Clinsight-Ennov, Paris, France). Treatment allocation was communicated to the site investigators sequentially, for consecutive enrolment of patients so that antiretroviral treatment could be started at the baseline visit with the assigned treatment. There was no masking in this study and we did not use a placebo to mask the raltegravir dose allocated to patients.
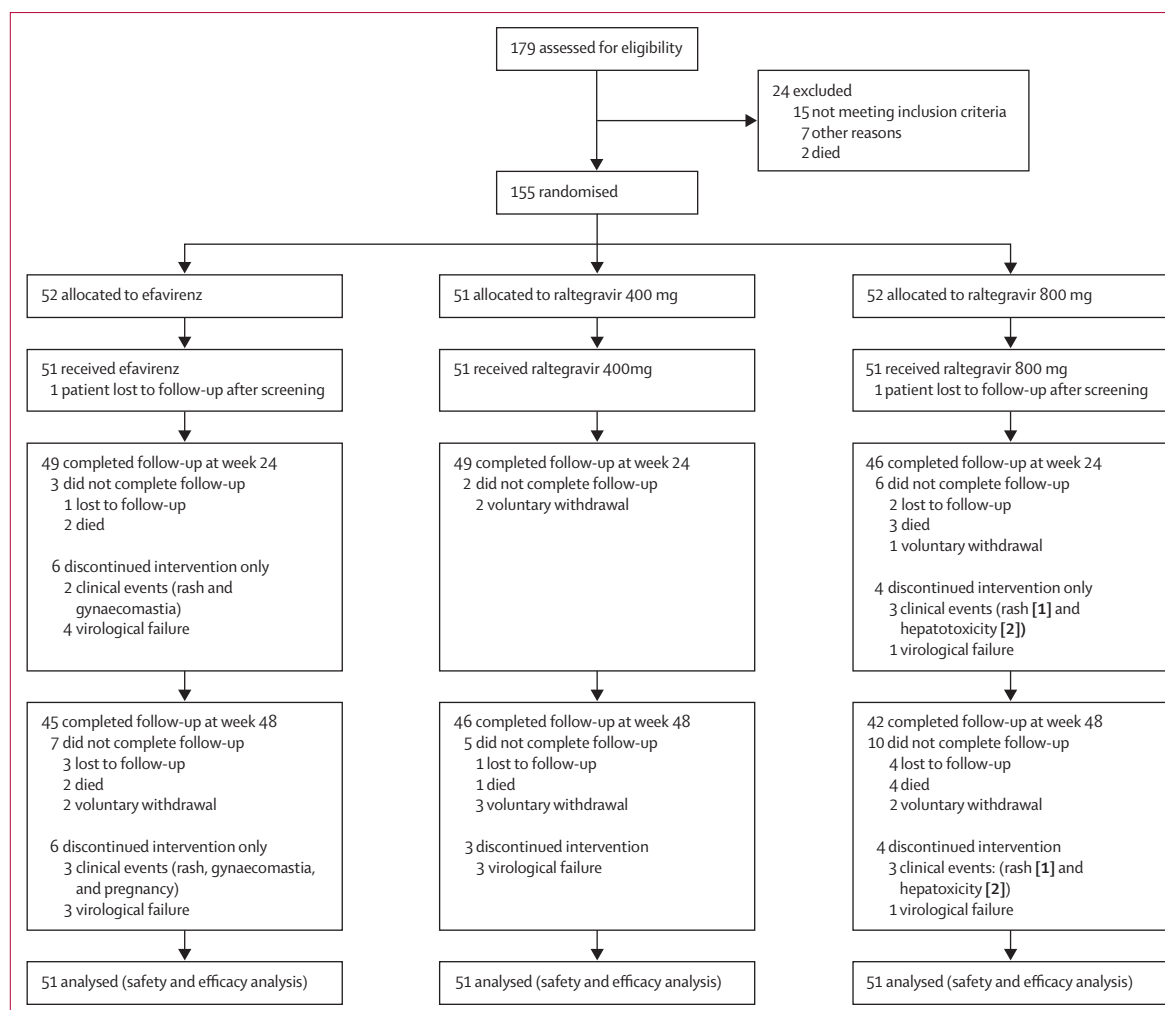
Figure 1: Trial profile

Procedures

All patients received a standard tuberculosis treatment regimen with WHO prequalified drugs on a fasting state with isoniazid, rifampicin, pyrazinamide, and ethambutol for the first 2 months, followed by isoniazid and rifampicin for the subsequent 4 months. In case of renal, skeletal, or CNS tuberculosis, the duration of the maintenance regimen could be extended and the total duration of tuberculosis treatment in the trial was left to the investigator's discretion. Rifampicin was given at the dose of 10 mg per kg per day. Antiretroviral treatment was started after 2–8 weeks of tuberculosis treatment to allow enough time in the study for concomitant treatment with rifampicin and antiretroviral drugs.

Participants in the efavirenz group received 600 mg per day of efavirenz (one tablet), 300 mg per day of lamivudine (one 300 mg tablet in France, two 150 mg tablets in Brazil), and 245 mg per day of tenofovir disoproxil fumarate (one tablet). Patients were instructed to take all drugs at the same time with food, preferably at bedtime, to reduce CNS adverse events with efavirenz. Patients in the raltegravir groups received either the standard dose of one 400 mg tablet twice a day, or the double 800 mg dose twice a day (two 400 mg tablets twice a day), in combination with 300 mg of lamivudine and 245 mg of tenofovir disoproxil fumarate. Patients were instructed to take raltegravir with food to increase its bioavailability. Efavirenz and lamivudine were provided by the Brazilian National HIV/AIDS Program. In France, efavirenz was obtained from Bristol Myers Squibb (Rueil Malmaison, France), and lamivudine from ViiV Health Care (Marly le Roi, France). Tenofovir disoproxil fumarate was donated by Gilead (Foster City, CA, USA), and raltegravir by Merck (Philadelphia, PA, USA), in both countries. Patients enrolled in the high-dose raltegravir group were required to switch to the standard dose of 400 mg twice a day of raltegravir 1 month after rifampicin discontinuation, but not before week 24. The protocol allowed substitution of tenofovir and lamivudine with other NRTIs in case of intolerance. Co-trimoxazole

prophylaxis was recommended for patients with CD4 counts less than 200 cells per µL.

We did clinical examination and laboratory analyses at screening and inclusion (baseline) visits, and at visits at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, and 48. Patients were diagnosed with confirmed or probable tuberculosis according to WHO guidelines for patients with HIV, and started tuberculosis treatment at clinics before referral to the trial site.[18]

Confirmed tuberculosis was defined by the detection of acid-fast bacilli in a sputum smear or a positive culture from a sputum sample, a lymph node aspirate, or a sample from another sterile site. Probable tuberculosis required a clinician's assessment that signs and symptoms warranted empirical tuberculosis treatment. Tuberculosis could be either pulmonary or extrapulmonary.

Smears and cultures from sputum or extrapulmonary specimens were done at the screening visit, if not already available. Chest radiographs were also done at the screening visit, unless already available at the time of the tuberculosis diagnosis. In patients with prior tuberculosis, resistance testing for rifampicin was done on available strains. During follow-up, sputum microscopy and chest radiographs were done, according to the national guidelines in each country, and at least week 12.

Hepatitis B (defined as detection of hepatitis B surface antigen) and hepatitis C (defined as detection of hepatitis C virus specific antibodies) infection status were assessed at the screening visit. HIV infection was confirmed at the screening visit by detection of HIV-specific antibodies by ELISA and western blot or immunofluorescence. We measured plasma HIV RNA concentrations with the COBAS Taqman HIV test (version 2.0; Roche Diagnostics, Meylan, France) in France, and the VERSANT HIV-RNA 3.0 assay (bDNA; Bayer, Berkeley, CA, USA) in Brazil. We assessed CD4 cell counts at baseline and all consecutive visits by flow cytometry.

We assessed the presence of resistance mutations to NRTIs, NNRTIs, and integrase inhibitors in patients with virological failure by sequencing the reverse transcriptase and integrase genes, and reporting mutations by use of the consensus technique of the ANRS AC11 Resistance Group, or the Trugene HIV-1 genotyping assay (Siemens Healthcare, Saint Denis, France), both at the time of confirmed virological failure and at baseline, using stored plasma specimens.

We measured full blood cell counts, alanine and aspartate aminotransferase, lipase, creatinine, alkaline phosphatase, and total bilirubin concentrations, and did urinary pregnancy tests at screening visits and at each follow-up visit for women of childbearing potential. Fasting glucose, total cholesterol, HDL and LDL cholesterol, and triglycerides were measured at baseline and weeks 12, 24, and 48.

We monitored adherence to antiretroviral drugs using the ANRS self-report adherence questionnaire based on a 4 day recall period before the visit. We assessed the intensity of adverse events by the ANRS Scale for Grading Adult Adverse Events (grade 1 defined as mild, grade 2 as moderate, grade 3 as severe, and grade 4 as life-threatening).[19] We defined serious adverse events as any untoward medical occurrence that, at any dose, resulted in death, was life-threatening, needed hospital admission or an extended hospital stay, resulted in disability or incapacity, or resulted in a congenital abnormality or birth defect. We also regarded grade 3 or 4 clinical and laboratory adverse events as serious adverse events.

Outcomes

The primary outcome was the proportion of patients with a plasma HIV RNA below 50 copies per mL at week 20, confirmed at week 24, with missing data and treatment discontinuation (efavirenz, raltegravir, or rifampicin before the end of tuberculosis treatment) counted as failures. This approach is consistent with an approach based on the time to loss of virological response (TLOVR) algorithm, recommended by the FDA. If viral load data from weeks 20 or 24 were missing and a patient's viral load at week 16 was below 50 copies per mL, we recorded treatment success.

	Efavirenz (N=51)	Raltegravir 400 mg (N=51)	Raltegravir 800 mg (N=51)	Total (N=153)
Country				
Brazil	48 (94%)	49 (96%)	48 (94%)	145 (95%)
France	3 (6%)	2 (4%)	3 (6%)	8 (5%)
Men	39 (76%)	35 (69%)	38 (75%)	112 (73)
Age (years)	35 (29–45)	37 (31–44)	38 (33–43)	38 (31–44)
Ethnic origin				
Black	15 (29%)	14 (27%)	21 (41%)	50 (33%)
Mixed	15 (29%)	16 (31)	23 (45%)	54 (35)
White	21 (41%)	21 (41)	7 (14)	49 (32)
Weight (kg)	62 (52–66)	60 (51–69)	57 (50–67)	60 (51–66)
Body-mass index (kg/m²)	21 (19–23)	21 (19–23)	20 (17–23)	21 (19–23)
History of antiretroviral treatment*	2 (4%)	2 (4%)	2 (4%)	6 (4%)
CD4 cells per µL	129 (45–308)	115 (50–213)	166 (80–367)	140 (58–302)
CD4 cell count <50 per µL	14 (27%)	12 (24%)	5 (10%)	31 (20)
HIV RNA in log₁₀ copies per mL	5·0 (4·5–5·5)	4·9 (4·4–5·4)	4·9 (4·2–5·4)	4·9 (4·4–5·4)
HIV RNA ≥100 000 copies per mL	26 (51%)	20 (39%)	24 (47%)	70 (46%)
Tuberculosis location				
Pulmonary only	20 (39%)	23 (45%)	23 (45%)	66 (43)
Pulmonary and extrapulmonary	26 (51)	20 (39%)	23 (45%)	69 (45%)
Extrapulmonary only	5 (10%)	8 (16%)	5 (10%)	18 (12)
Bacteriologically confirmed cases	23 (45%)	27 (53%)	25 (49%)	75 (49%)
Time between antituberculosis and antiretroviral drugs (weeks)	5·7 (4·9–7·0)	6·0 (5·0–7·1)	5·9 (5·0–6·7)	5·9 (5·0–7·0)
Hepatitis B or C co-infection	2 (4%)	8 (16%)	6 (12%)	16 (10%)

Data are n (%) or median (IQR). *Antiretroviral treatment for less than 3 months and more than 6 months before screening.

Table 1: Baseline characteristics

Secondary outcomes included virological suppression at week 48 (with the same definition as for the primary outcome), measured as the proportion of patients with plasma HIV RNA below 50 copies per mL and 400 copies per mL during follow-up; emergence of resistance-associated mutations in patients with virological failure defined as a plasma HIV RNA rebounding above 400 copies per mL; or an increase of more than 1 $\log_{10}$ of HIV RNA at or after week 8 and confirmed 2–4 weeks later; changes from baseline in CD4 cell counts; occurrence of AIDS-defining events or death; tuberculosis treatment outcomes according to WHO definitions;[18] occurrence of adverse events and serious adverse events; and paradoxical tuberculosis immune reconstitution inflammatory syndrome.[20] Cases of immune reconstitution inflammatory syndrome were reviewed by an independent events validation committee. Adverse events terms were adopted from the Medical Dictionary for Regulatory Activities (MedDRA US version 12.1).

Statistical analysis

We aimed to identify whether the success rate of the two raltegravir doses tested exceeded 70% at 24 weeks, which is the average response rate reported with efavirenz-based regimens in patients with HIV and tuberculosis co-infection, for further assessment in a phase III trial.[3,21] Assuming a recorded proportion of virological success at week 24 of 85%, we calculated that, with 49 patients per group, we would be able to conclude with an α of 5% (one-sided test) and a power of 80% that the proportion of virological success at week 24 would be at least 70% if the number of failures did not exceed nine. This calculation was based on the Fleming method.[22] We increased the proposed sample size to 50 patients per group to account for loss to follow-up. This study was an estimation study only, and it was not powered for formal efficacy comparison between raltegravir and efavirenz. Data were reviewed by the independent data monitoring committee every 6 months.

	Efavirenz	Raltegravir 400 mg	Raltegravir 800 mg	Total
Primary endpoint (week 24)				
Intention to treat (HIV RNA <50 copies per mL)	32/51 (63%; 49–76)	39/51 (76%; 65–88)	40/51 (78%; 67–90)	111/153 (73%; 65–80)
Per protocol (HIV RNA <50 copies per mL)	42/49 (86%; 76–96)	43/49 (88%; 79–97)	43/47 (91%; 84–99)	128/145 (88%; 83–94)
Snapshot (HIV RNA <50 copies per mL)	34/51 (67%; 54–80)	41/51 (80%; 69–91)	39/51 (76%; 65–88)	114/153 (75%; 68–81)
Secondary endpoint (week 24) Intention to treat (HIV RNA <400 copies per mL)	39/51 (76%; 65–88)	41/51 (80%; 69–91)	42/51 (82%; 72–93)	122/153 (80%; 73–86)
Secondary endpoint (week 48)				
Intention to treat (HIV RNA <50 copies per mL)	34/51 (67%; 54–80)	39/51 (76%; 65–88)	32/51 (63%; 49–76)	105/153 (69%; 61–76)
Per protocol (HIV RNA <50 copies per mL)	41/45 (91%; 83–99)	41/46 (89%; 80–98)	35/42 (83%; 72–95)	117/133 (88%; 82–93)
Snapshot (HIV RNA <50 copies per mL)	37/51 (73%; 60–85)	39/51 (76%; 65–88)	32/51 (63%; 49–76)	108/153 (71%; 63–78)
Intention to treat (HIV RNA <400 copies per mL)	37/51 (73%; 60–85)	41/51 (80%; 69–91)	33/51 (65%; 52–78)	111/153 (73%; 65–80)

Data are n/N (%; 95% CI).
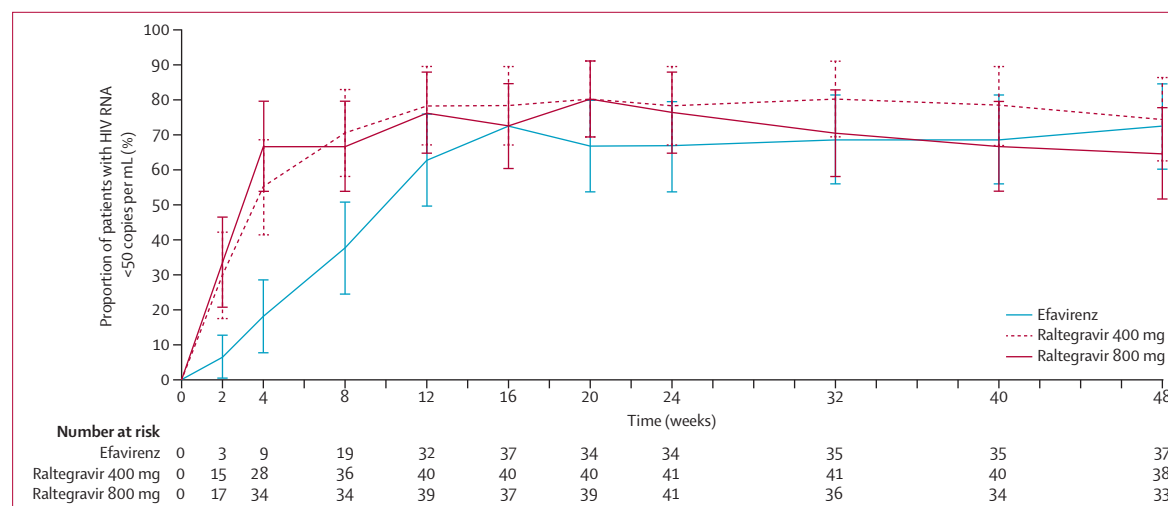
Table 2: Efficacy outcomes

Figure 2: Virological response
Error bars are 95% CIs.

The primary efficacy analysis was a modified intention-to-treat analysis, which included all randomly allocated patients who received at least one dose of efavirenz or raltegravir. We calculated the proportion of patients with virological suppression at week 24 with 95% CIs for every group. We also did sensitivity analyses using a per-protocol analysis on available data, censoring patients who discontinued study drugs prematurely for reasons other than death or virological failure (ie, who withdrew from the study, were lost to follow-up, or had no data available), and did a snapshot analysis (the proportion of patients with HIV RNA of less than 50 copies per mL while staying on their allocated antiretroviral regimen in a time window of at most 4 weeks at weeks 24 and 48, with missing data counted as failures).

For the safety analysis, we reported the proportion of patients who had at least one grade 3–4 adverse event and one serious adverse event. We used SAS (version 9.1.3 and higher) for statistical analyses.

The study is registered in ClinicalTrials.gov, number NCT00822315.

Role of the funding source

The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. BG and GC had full access to all the data in the study, and JMM had the final responsibility for the decision to submit for publication.

Results

Between July 3, 2009, and June 6, 2011, we screened 179 patients, 171 in Brazil and eight in France, of whom 155 were randomly assigned treatment (we enrolled all eight patients from France): 52 to efavirenz, 51 to raltegravir 400 mg, and 52 to raltegravir 800 mg (figure 1). 153 patients (51 in each group) received at least one dose of the study drug and were included in the modified intention-to-treat analysis (figure 1). We completed follow-up of all patients on May 3, 2012.

At baseline, the number of patients with plasma HIV RNA concentrations of more than 100 000 copies per mL was slightly lower in the raltegravir 400 mg group than in the other two groups, the number of patients with CD4 cell counts below 50 cells per μL was slightly lower in the raltegravir 800 mg group than in the other two groups, and the number of patients with hepatitis B or C co-infection was lower in the efavirenz group than in the other two groups (table 1). Baseline characteristics were otherwise much the same between treatment groups (table 1).

75 patients had bacteriologically confirmed myco-bacteriosis (table 1), of whom 73 had *M tuberculosis*, one had *Mycobacterium avium*, and one had *Mycobacterium bovis*. Of the 56 cultures tested for drug susceptibility, six were streptomycin resistant, six wer isoniazid resistant, and none were rifampicin resistant.

In the modified intention-to-treat analysis at week 24, our primary endpoint, we saw no between-group difference in the number of patients who achieved virological suppression (HIV RNA <50 copies per mL; table 2). The lower bound of the 95% CIs was below the predefined margin of 70% in all three groups, showing that that the response rate was slightly lower than expected according to the study hypothesis. The per-protocol analysis on available data, censoring patients who discontinued efavirenz or raltegravir for reasons other than virological failure, provided similar response rates in all three groups (all lower 95% CI bounds >70%). Virological suppression rates at week 24 were slightly higher when we used a higher threshold of 400 copies per mL of HIV RNA, and we detected no between-group difference (table 2). In secondary endpoint analysis, there was again no between-group difference in viral suppression rates (HIV RNA <50 copies per mL) at week 48 (table 2). In analysis of the proportion of patients with HIV RNA concentrations lower than 50 copies per mL at each visit (figure 2), the virological response rate at week 48 was 73% (95% CI 60–85) in the efavirenz group, 75% (63–86) in the raltegravir 400 mg group, and 65% (52–78) in the raltegravir 800 mg group, with no between-group difference.

Genotypic resistance test results were available for 30 (77%) of 39 patients who had virological failure during the 48 weeks of follow-up. A similarly small proportion of patients in the two raltegravir groups developed resistance to either integrase inhibitors and NRTIs (table 3). Median

	Efavirenz (N=51)	Raltegravir 400 mg (N=51)	Raltegravir 800 mg (N=51)	Total (N=153)
Virological failures*	14 (27%)	12 (24%)	13 (25%)	39 (25%)
Resistance analysis population	9 (18%)	11 (22%)	10 (20%)	30 (20%)
Developed resistance to antiretroviral regimen	6 (12%)	5 (10%)	4 (8%)	15 (10%)
Any integrase resistance mutations	0	4	4	8
E92EQ	..	1	0	1
Y143R/C	..	1	2	3
N155H	..	2	2	4
Any non-nucleoside reverse transcriptase inhibitor resistance mutations	5	..	..	5
K103N	3†	..	..	3†
V106M	1	..	..	1
Y188L	1	..	..	1
Any nucleoside reverse transcriptase inhibitor resistance mutations	6	5	3	14
M184V/I	6	5	3	14
K65R	3	..	..	3
K70E	1	1	..	2
Others (thymidine analogue mutations)	1	1	..	2

Data are n or n (%). *Defined by a confirmed plasma HIV RNA concentration higher than 400 copies per mL or a confirmed increase of more than 1 $\log_{10}$ copies per mL at week 8 or later. †The *K103N* mutation was also detected in two patients in baseline samples analysed at the time of failure.

Table 3: Resistance data

increase in CD4 cell counts from baseline to week 48 was similar in all three groups (an increase of 216 [IQR 87–328] cells per μL with efavirenz, 239 [160–372] cells per μL with raltegravir 400 mg, and 212 [130–369] cells per μL with raltegravir 800 mg). Four patients in the efavirenz group and two in each of the raltegravir groups had a new AIDS-defining illness.

Overall, self-reported adherence to antiretroviral treatment was high and similar in all three groups at both week 24 (38 [95%] of 40 patients in the efavirenz group, 40 [87%] of 46 patients in the raltegravir 400 mg groups, and 32 [84%] of 38 patients in the raltegravir 800 mg group reported 100% adherence [no dose missed in the 4 days before the visit]) and week 48 (31 [94%] of 33 patients in the efavirenz group, 36 [92%] of 39 patients in the raltegravir 400 mg groups, and 27 [79%] of 34 patients in the raltegravir 800 mg group reported 100% adherence). Tuberculosis treatment success rate (cure or treatment completed) was about 90% in all three groups (table 4). Overall, the median duration of tuberculosis treatment was 6·2 months (IQR 6·0–7·2) and did not differ between the three groups.

The proportion of patients with serious adverse events was much the same in all three groups (table 5). However, the occurrence of treatment-related serious adverse events was lower in the raltegravir 400 mg group than in the efavirenz or raltegravir 800 mg groups. Also, fewer patients discontinued study drugs because of an adverse event in the raltegravir 400 mg group than in the efavirenz or the raltegravir 800 mg groups. One patient in the raltegravir 800 mg group had liver failure that was deemed to be related to the tuberculosis treatment, and underwent a liver transplant. After transplantation, raltegravir was resumed at the standard dose of 400 mg twice a day without further toxicity. The proportion of patients with grade 3 or 4 tuberculosis immune reconstitution inflammatory syndrome was low in all three groups (table 5). The proportion of patients with grade 3 or 4 laboratory abnormalities did not differ between the three groups. Seven patients died during the study (figure 1), and none of the deaths was thought to be related to the study drugs.

Discussion

We recorded no statistically significant between-group differences in patients treated with 400 mg or 800 mg of raltegravir or 600 mg of efavirenz at either week 24 or week 48. We know of no other randomised controlled trial exploring efficacy and safety of raltegravir in patients co-infected with HIV and tuberculosis (panel).

The slightly higher point estimates of efficacy at week 24 in the raltegravir groups using a threshold of 50 copies per mL were expected because the decrease in plasma HIV RNA is faster with integrase inhibitors than it is with NNRTIs. However, this rapid decrease in plasma viral load is not associated with clinical benefit;[12,13] and with a higher

	Efavirenz (N=51)	Raltegravir 400 mg (N=51)	Raltegravir 800 mg (N=51)	Total (N=153)
Treatment success	45 (88%)	46 (90%)	45 (88%)	136 (89%)
Cured	6 (13%)	8 (17%)	5 (11%)	19 (14%)
Treatment completed	39 (87%)	38 (83%)	40 (89%)	117 (86%)
Death	2 (4%)	1 (2%)	3 (6%)	6 (4%)
Default*	4 (8%)	3 (6%)	1 (2%)	8 (5%)
Treatment failure	0 (0%)	1 (2%)	1 (2%)	2 (1%)
Transferred to different centre	0 (0%)	0 (0%)	1 (2%)	1 (1%)

Data are n (%). *Patients whose tuberculosis treatment was interrupted for 2 consecutive months or more (including one patient with *Mycobacterium avium*).

Table 4: **Tuberculosis treatment**

	Efavirenz (N=51)	Raltegravir 400 mg (N=51)	Raltegravir 800 (N=51)	Total (N=153)
Any adverse event	46 (90%)	46 (90%)	47 (92%)	139 (91%)
Serious adverse events	19 (37%)	17 (33%)	17 (33%)	53 (35%)
Serious adverse event related to antiretroviral treatment	10 (20%)	6 (12%)	8 (16%)	24 (16%)
Blood or lymphatic disorders	1	3	5	9
Immune system disorders	3	2	4	9
Hepatobiliary and gastrointestinal disorders	3	0	2	5
Cardiovascular disorders	1	1	1	3
Infections	1	0	0	1
Skin disorders	1	0	0	1
Any event leading to drug discontinuation	3 (6%)	0	3 (6%)	6 (4%)
Hepatotoxicity	0	0	2	2
Cutaneous rash	1	0	1	2
Gynaecomastia	1	0	0	1
Pregnancy	1	0	0	1
Grade 3–4 adverse event	19 (37%)	17 (33%)	17 (33%)	53 (35%)
Grade 3–4 immune reconstitution inflammatory syndrome	5 (10%)	2 (4%)	4 (8%)	11 (7%)
Death	2 (4%)	1 (2%)	4 (8%)	7 (5%)
Meningitis	1	0	2	3
Septic shock	1	0	1	2
Tuberculosis worsening	0	1	0	1
Unknown cause	0	0	1	1
Laboratory adverse event (any grade)	49 (96%)	49 (96%)	44 (85%)	142 (92%)
Laboratory grade 3–4	10 (20%)	13 (25%)	9 (18%)	32 (21%)
Neutrophil count <750 cells per μL	3	5	5	13
Aspartate aminotransferase >5 ULN	3	3	3	9
Alanine aminotransferase >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 per μL	0	2	1	3
Bilirubin >5 ULN	2	0	0	2
Creatinine >3 ULN	1	0	0	1
Glycaemia >16·5 mmol/L	0	1	0	1

Data are number of events or number of patients (%). ULN=upper limit of normal.

Table 5: **Treatment-emergent adverse events, serious adverse events, and adverse events of interest**

threshold at 400 copies per mL for virological suppression, we detected no between-group difference in antiretroviral activity.

At week 48, virological suppression was slightly, but not significantly higher in the standard-dose raltegravir group than in the double-dose raltegravir and the efavirenz groups. This outcome was not due to a better antiviral activity of the raltegravir 400 mg twice-daily dose, but rather to a better tolerability profile and also possibly to better adherence. Indeed, the number of patients who did not achieve a viral load of less than 50 copies per mL in the intention-to-treat analysis was similar in all three groups, suggesting that despite the interaction with rifampicin, the standard dose of raltegravir provided potent and durable antiviral activity similar to that of efavirenz. Our results are supported by data from the pharmacokinetic sub-study suggesting that the interaction between raltegravir and rifampicin is lower than expected in patients with HIV receiving

tuberculosis treatment, with no change in raltegravir's area under the concentration-time curve, and only a 31% decrease in trough concentration.[23]

The antiviral activity of raltegravir and efavirenz in this trial seemed lower than in previous studies in antiretroviral-naive patients.[12,13] However, the rate of virological suppression in our trial was similar to that reported in patients with HIV and tuberculosis co-infection receiving efavirenz-based regimens. Indeed, in the CARINEMO-ANRS 12146 study,[21] 199 (70%) patients achieved an HIV RNA concentration of less than 50 copies per mL at week 48. Similarly, virological response rate at week 48 in the ACTG A 5221 trial was 74% (596 of 806 patients), although a higher threshold of 400 copies per mL was used.[3]

CD4 cell counts increase and the occurrence of AIDS-defining events were also similar in all three groups during follow-up. Fewer patients died in the standard-dose raltegravir group than in the high-dose raltegravir group, although fewer patients in the high-dose group had low CD4 cell counts at baseline, but differences were not statistically significant.

All antiretroviral regimens were associated with very good tuberculosis treatment outcomes (although only about half were bacteriologically confirmed; table 4), and few severe or life-threatening events of immune reconstitution inflammatory syndrome occurred, probably because of the higher baseline CD4 cell counts and the longer time between initiation of tuberculosis treatment and antiretroviral treatment in this study than in others.[1–3]

The standard dose of raltegravir in this study seemed to be well tolerated, at least as well as efavirenz and the double-dose of raltegravir. The proportion of patients with grade 3 or 4 alanine aminotransferase and aspartate aminotransferase concentration increases was much the same in all three groups. Also, no patient discontinued treatment for adverse events in the standard-dose raltegravir group and the number of serious drug-related serious adverse events were similar in all three groups. Both patients who had hepatotoxicity in this study were in the double-dose raltegravir group—one of these patients eventually had liver failure and received a liver transplant. Although this patient resumed raltegravir at the standard dose without further toxicity, the role of high-dose raltegravir in the occurrence of this serious event could be a contributing factor. Liver toxicity overall was probably underestimated in this trial because we enrolled only patients with an alanine aminotransferase concentration below 2·5 times the upper limit of normal.

In view of the potent antiviral activity of standard-dose raltegravir in combination with tenofovir and lamivudine in this trial of patients with HIV treated for tuberculosis, its favourable safety profile, its convenience and low cost compared with a double-dose regimen, this regimen is a potential first-line regimen in patients who cannot use

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Panel: Research in context

Systematic review

We searched PubMed for articles published in English between Jan 1, 1970, and Feb 22, 2014, with the following search string: ("tuberculosis"[Text Word]) AND "raltegravir"[Text Word]) OR ("tuberculosis"[Text Word] AND "integrase inhibitor"[Text Word]). We identified no randomised trial that compared raltegravir-based and efavirenz-based antiretroviral treatment in patients co-infected with HIV and tuberculosis treated with rifampicin. We identified only two studies reporting outcomes of patients co-infected with HIV and tuberculosis receiving a raltegravir-based regimen and rifampicin-containing tuberculosis treatment.[15,16] In the first study,[15] two patients with HIV-2 received rifampicin and raltegravir at the double dose of 800 mg twice a day and the treatment was reported to be well tolerated and effective with suppression of viral replication below 50 copies per mL in one patient. In the second study,[16] eight patients received treatment, four of whom had not previously received antiretroviral treatment. All patients received raltegravir at the dose of 800 mg twice a day and treatment was reported to be well tolerated. Viral replication was suppressed in all eight patients.[16] Both studies refer to our clinical trial to lend support to the recommended dose increase of raltegravir in patients co-infected with HIV and tuberculosis receiving a rifampicin-based treatment.

Interpretation

To the best of our knowledge, our trial is the first to assess the safety and efficacy of two doses of raltegravir in combination with tenofovir and lamivudine in patients co-infected with HIV and tuberculosis receiving a rifampicin-based treatment. This trial was a phase 2 study not powered for comparisons between doses, instead aiming to assess the efficacy and safety of two doses of raltegravir (standard dose of 400 mg twice daily and double dose of 800 mg twice daily) in a randomised study with a standard-of-care group receiving efavirenz-based treatment. The efficacy of all three regimens was acceptable and provided similar virological response rates to those reported in other trials in patients with both HIV and tuberculosis. Also the safety of the three regimens was good and similar, although we enrolled patients with alanine aminotransferase concentrations below 2·5 times the upper limit of normal. According to these results, the standard dose of raltegravir seems to be as good as the recommended double dose in patients with HIV and tuberculosis, with a lower cost and a lower pill burden, and might be a better alternative to efavirenz in patients unable to tolerate efavirenz or who have a contraindication to efavirenz. These findings should be substantiated in a larger phase 3 comparative study.

efavirenz. However, because of the small size of the study, these results need further assessment in a larger phase 3 trial before raltegravir at a dose of 400 mg twice a day could be regarded as a valuable alternative to efavirenz in patients with HIV and tuberculosis receiving rifampicin-based treatment.

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