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STANDARD DOSE RALTEGRAVIR OR EFAVIRENZ BASED ANTIRETROVIRAL TREATMENT FOR HIV-1-INFECTED ADULTS WITH TUBERCULOSIS: A PHASE 3, RANDOMIZED, OPEN-LABEL, NON-INFERIORITY TRIAL

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ABSTRACT

Background:

In HIV-infected adults with tuberculosis, antiretroviral therapy options are limited due to drug-drug interactions with rifampin. A phase 2 trial previously suggested that raltegravir 400 mg twice daily or efavirenz 600 mg once daily may have similar virologic efficacy in patients on rifampin. We conducted a phase 3 trial to confirm these findings.

Methods:

ANRS 12300 Reflate TB2 was an open-label, randomized, non-inferiority trial in Côte d'Ivoire, Brazil, France, Mozambique and Vietnam. Antiretroviral-naïve HIV1-infected adults with tuberculosis and receiving a standard tuberculosis treatment regimen were randomized using computerized random numbers to receive either raltegravir 400mg twice daily or efavirenz 600mg once daily both in combination with tenofovir and lamivudine. The primary endpoint was virologic success at week 48 (plasma HIV-1 RNA <50 copies/mL, FDA snapshot algorithm). The pre-specified non-inferiority margin was 12%. Safety measured as grade 3 and 4 adverse events and adherence to ART measured by pill count ratio were among the secondary outcomes. (Registration number: NCT02273765)

Findings:

Overall, 230 patients were randomized in each arm. At baseline, the median CD4+ cell count was 103/mm³ and the median plasma HIV-1 RNA 5.5 Log₁₀ copies/mL. Tuberculosis was bacteriologically-confirmed in 310 (68.0%) participants. At week 48, 140 (60.9%) participants on raltegravir and 150 (66.1%) on efavirenz achieved virologic success (difference: -5.2%; 95% CI -14.0 to +3.6; non-inferiority not shown). The proportions of patients experiencing grade 3 and 4 adverse events were 58/229 (25.3%) and 66/230 (28.7%) in the raltegravir and efavirenz arms, respectively. The proportion of patients with a pill count ratio <95% was 42.3% (94/222) on raltegravir and 27.0% (60/222) on efavirenz (p<0.0001).

Interpretation:

In HIV-1 infected patients on rifampin, the non-inferiority of raltegravir as compared to efavirenz was not demonstrated. Adherence to raltegravir was poorer, which may have contributed to lower virologic efficacy. Raltegravir was well tolerated and could be considered as an option only in selected patients.

Funding: ANRS, Ministry of Health in Brazil, and Merck and Co.

INTRODUCTION

Tuberculosis remains a major cause of morbidity and mortality in human immunodeficiency virus type 1 (HIV-1)-infected individuals, with 862,000 cases and 251,000 deaths reported by the World Health Organization (WHO) in 2018.^{1,2} In antiretroviral therapy (ART)-naïve HIV-1-infected adults with tuberculosis, initiation of ART, while reducing mortality, may be challenging due to treatment-related adverse events, drug-drug interactions and risk of immune reconstitution inflammatory syndrome (IRIS), which can be difficult to manage in severely ill individuals.³⁻⁸

Drug-drug interactions between antiretrovirals and rifampin, the cornerstone of anti-tuberculosis treatment, and a strong cytochrome P450 A3 inducer, limit ART options in HIV-infected individuals with tuberculosis. Many studies have shown that efavirenz is less affected by the interaction with rifampin, with good virologic outcomes.⁸⁻¹³ However, efavirenz may not always be used for reasons such as neurological tolerance and transmitted drug-resistance.

Integrase inhibitors have a good safety profile and could be alternatives to efavirenz in patients with tuberculosis. However, they also present significant drug-drug interaction with rifampin. Dolutegravir, the preferred first-line antiretroviral in low and middle-income countries, is recommended at a double dose for patients with tuberculosis based on pharmacokinetic data in healthy volunteers and on results of one non comparative trial.¹⁴⁻¹⁶ Likewise, raltegravir is recommended at double doses based on pharmacokinetic data in healthy volunteers.¹⁷

The ANRS 12180 Reflate TB phase 2 trial suggested that, in patients with tuberculosis receiving raltegravir at a standard dose, the interaction with rifampin had minimal impact on virologic efficacy.^{18, 19} A similar proportion of patients taking efavirenz 600 mg once daily and raltegravir 400 mg twice daily-based ART achieved virologic success at 24 and 48 weeks. In addition, the associated pharmacokinetic sub-study showed only a modest reduction in raltegravir trough concentrations and area under the curve in the raltegravir 400 mg twice daily arm when co-administered with rifampin.^{18,19} Following these preliminary results, we sought to confirm in a phase 3 trial whether raltegravir at a standard 400 mg twice-daily dose could be a suitable alternative to efavirenz for antiretroviral treatment of naïve HIV-1-infected patients with tuberculosis.

METHODS

Study design and participants

We conducted a phase 3, multicenter, open-label, non-inferiority, randomized trial in five countries (Brazil, Côte d'Ivoire, France, Mozambique, and Vietnam) aiming to compare a raltegravir-based regimen (at a standard dose of 400 mg twice daily) to an efavirenz-based regimen in terms of virologic success at week 48.

We enrolled ART-naïve HIV-1 infected adults (≥ 18 years old) with tuberculosis receiving anti-tuberculosis treatment initiated within the past 8 weeks. We excluded patients with HIV-2 infection, tuberculous meningitis, pregnancy or breastfeeding, rifampin-resistant *Mycobacterium tuberculosis* strain, impaired hepatic function (icterus or alanine aminotransferase (ALT) > 5 times the upper limit of normal (ULN)); creatinine clearance < 60 mL/min; hemoglobin < 6.5 g/dL (see the Appendix page 5 for full eligibility criteria). We randomly assigned (1:1) participants to receive either raltegravir or efavirenz, both in association with tenofovir disoproxil fumarate (TDF) and lamivudine.

The protocol was approved by relevant National and Local Ethics Committees in all participating countries (see protocol in Supplementary material). All participants provided signed informed consent before enrolment. An independent data monitoring committee reviewed efficacy and safety data during the trial.

Randomization and masking

We randomly assigned (1:1) participants to receive either raltegravir 400 mg twice daily (standard dose), or efavirenz 600 mg once daily both in association with tenofovir disoproxil fumarate (TDF) and lamivudine. The randomization list was prepared by the trial statistician before the beginning of the trial, with the SAS® software (version 9.1.3), using computerized random numbers. Randomization was blocked and stratified by country. This randomization list was kept confidential to site investigators who obtained automated treatment assignment centrally from the international coordinating Clinical Trial Unit (Mereva INSERM U1219, Bordeaux, France), via the e-CRF. There was no masking in this study.

Treatments

All patients received a standard tuberculosis treatment regimen (on a fasting state) with isoniazid (4-6 mg/kg/day), rifampicin (8-12 mg/kg/day), pyrazinamide (20-30 mg/kg/day), and ethambutol (15-20 mg/kg/day) for two months (intensive phase), followed by isoniazid and rifampin for four months (maintenance phase). In case of skeletal or central nervous system (CNS) tuberculosis, maintenance phase could be extended and the total duration of tuberculosis treatment in the trial was left to the investigator's discretion.

Participants initiated either raltegravir 400 mg twice daily or efavirenz 600 mg once daily, both in association with tenofovir disoproxil fumarate 300 mg once daily and lamivudine 300 mg once daily, after two to eight weeks of tuberculosis treatment as recommended by the WHO.¹²⁰ Patients were instructed to take raltegravir with food in order to increase its bioavailability. The protocol allowed substitution of tenofovir and lamivudine

by other NRTIs in case of intolerance. Antiretrovirals were provided by National HIV/AIDS Programs or social insurance in France, at the exception of raltegravir that was donated by Merck and Co. Cotrimoxazole prophylaxis was provided according to local recommendations (see the protocol in the Supplementary material).

Endpoints

The primary endpoint was virologic success at week 48 defined as plasma HIV-1 RNA <50 copies/mL on study drugs per the Food and Drug Administration (FDA) Snapshot algorithm.²⁰ Permanent discontinuations of raltegravir or efavirenz were considered as strategy discontinuations. Secondary endpoints were proportion of patients with HIV RNA <50 copies/mL at each visit, change in CD4+ T-cell counts from baseline to week 48; virologic failure defined as confirmed plasma HIV-1 RNA \geq 200 copies/mL at week 24 or a rebound above 200 copies/mL at any time in those who previously suppressed; emergence of resistance-associated mutations; occurrence of new AIDS-defining events, non-AIDS severe illnesses, and grade 3 and 4 adverse events; tuberculosis treatment outcomes; frequency of paradoxical tuberculosis-associated IRIS, and adherence to ART. We measured ART intake based on a pill count adherence ratio calculated over the 48 weeks of follow up, as well as over the first and last 24 weeks (on and off antituberculosis treatment). Pill count adherence ratio was defined as ((total number of pills given - total number of pills returned)/total number of pills needed to cover the period) and we defined poor adherence as a pill count adherence ratio <95%.²¹

Detailed trial procedures are provided in the protocol and statistical analysis plan (Supplementary material).

Follow up

Clinical and laboratory assessments were performed at all study visits (Appendix page 6).

Patients were diagnosed with confirmed or probable tuberculosis according to WHO guidelines, and started anti-tuberculosis treatment at clinics before referral to the trial site. Smear microscopy, Xpert® MTB/RIF (Cepheid, Sunnyvale, Ca. USA), and mycobacterial cultures on expectorated sputum and relevant extrapulmonary samples obtained at the time of tuberculosis diagnosis were collected, or performed at the screening visit, if not available. Chest radiographs were also performed at the screening visit, unless performed recently for tuberculosis diagnosis. Follow-up sputum smear microscopy and culture, and chest radiographs were performed, per National Guidelines, and at least at week 8. Patients were tested for hepatitis B (detection of hepatitis B surface antigen), and hepatitis C (detection of hepatitis C virus specific antibodies), at the screening visit.

Plasma HIV-1 RNA levels were measured at weeks 0, 4, 12, 24, 32, 40, and 48, using the COBAS Taqman HIV-

1 assay v2.0® (Roche Diagnostics, Meylan, France) in France, Côte d'Ivoire, Mozambique, and Vietnam, and the VERSANT HIV-RNA 3.0® (bDNA) assay (Bayer, Berkeley, CA) in Brazil . Genotypic resistance mutations were assessed in patients experiencing virologic failure by sequencing the reverse transcriptase and integrase genes at the time of virological failure and at baseline, and reporting mutations as recommended by the ANRS AC11 Resistance Group (www.hivfrenchresistance.org).

Statistical Analysis

Assuming a 70% virologic success rate at week 48 in both study arms, a sample size of 230 participants in each arm would provide 80% power to demonstrate non-inferiority at a one-sided α of 2.5%. Non-inferiority would be established if the lower bound of the 95% binomial confidence interval for the treatment difference (raltegravir-efavirenz) was greater than -12%. The primary non-inferiority analysis used both the intention-to-treat and the on-treatment population defined as patients continuing allocated treatment, and patients who discontinued allocated treatment because of death or virologic failure. We performed a sensitivity analysis adjusting for country, the only stratification factor, using logistic regression and a non-inferiority margin of 0.592 on the odds ratio. No interim analysis was planned unless requested by the independent data monitoring committee.

In a post-hoc analysis, we analyzed virologic success at week 24 (HIV1 RNA<50 copies/mL) and virologic success at week 48 with 200 and 1000 copies/mL thresholds. We performed sub-group analyses of the differences in proportion of patients reaching the primary endpoint by treatment for baseline subgroups based on baseline CD4+ T-cell count, baseline HIV-1 RNA, age, sex, BMI, country. We performed analysis for secondary endpoints in the intention-to-treat population and we included all patients receiving at least one dose of the assigned treatment regimen in the safety analysis (safety population). We analyzed data with the SAS software (version 9.4M3).

Role of the funding source

This trial was funded by the National French Agency for AIDS Research (ANRS), the Brazilian Ministry of Health in Brazil, and Merck and Co.; ANRS 12300 REFLATE TB2 ClinicalTrials.gov number, NCT02273765.

The funders had no role in the analysis of the data nor in the manuscript writing.

NDC, OM, CC, DL, XA, BG, VV, CD and JMM had access to all the data reported in the present study; all results were presented to all other authors and members of the scientific committee.

RESULTS

Between September 28, 2015 and January 5, 2018, 460 participants were randomly assigned to raltegravir or efavirenz (230 in each arm) (Figure 1). A total of 457 patients were considered in the intention-to-treat analysis and 410 in the on-treatment analysis. Overall, patient baseline characteristics were balanced across trial arms (Table 1). The median CD4+ T-cell count was 103 (IQR 38-239) per cubic millimeter. The median plasma HIV-1 RNA was 5.5 (IQR 5.0–5.8) Log₁₀ copies/mL and 157/457 (34.4%) patients had HIV-1 RNA above 500,000 copies/mL. Tuberculosis was bacteriologically-confirmed in 310/457 (67.8%) participants.

In the intention-to-treat analysis, 140/230 (60.9%) patients in the raltegravir arm and 150/227 (66.1%) in the efavirenz arm had a plasma HIV-1 RNA <50 copies/mL at week 48 (Table 2). The difference in week 48 success rate between the raltegravir and efavirenz arms was -5.2% (95%CI -14.0 to 3.6), thus not meeting the pre-specified criterion for non-inferiority. Non-inferiority was not demonstrated either in the on-treatment analysis (Table 2) nor in the sensitivity analyses stratified on the country (table S1, Appendix page 8). Sub-group analyses are presented in Figure S1 (Appendix page 9).

At week 24, 133/230 (57.8%) patients (95%IC 51.4-64.2) in the raltegravir arm and 130/227 (57.3%) patients (95%IC 50.8-63.7) in the efavirenz arm had HIV-1 RNA <50 copies/mL under the allocated treatment (Figure 2A). Overall, 83/114 (72.8%) patients with baseline HIV-1 RNA <100,000 copies/mL, 123/183 (67.2%) patients with HIV-1 RNA 100,000-499,000 copies/mL and 83/157 (52.9%) patients with HIV-1 RNA ≥500,000 copies/mL achieved HIV-1 RNA <50 copies/mL at week 48. The evolution of virologic success over time according to baseline HIV-1 RNA and study arm is presented in Figure 2B.

In post-hoc analyses considering different virologic outcomes at week 48, 159/230 (69.1%; 95%CI 63.2-75.1) and 163/227 (71.8%; 95%CI 66.0-77.7) patients had HIV-1 RNA <200 copies/mL in the raltegravir and efavirenz arms, respectively, and 164/230 (71.3%; 95%CI 65.5-77.1) and 166/227 (73.0%; 95%CI 67.4-78.9) had HIV-1 RNA <1000 copies/mL in the raltegravir and efavirenz arms, respectively.

Seventy-five patients met the definition of virologic failure during follow-up: 42/230 (18.3%) in the raltegravir arm and 33/227 (14.5%) in the efavirenz arm. Amplification of integrase and reverse transcriptase genes was unsuccessful in 10/42 (23.8%) and 1/42 (2.4%) patients in the raltegravir arm and 7/33 (21.2%) and 1/33 (3.0) in the efavirenz arm, respectively. In the raltegravir arm 26/41 (63.4%) patients had drug-associated mutations

versus 24/32 (75.0%) in the efavirenz arm (TableS2, Appendix page 10). Resistance to tenofovir was detected in 2/41 (5.0%) patients in the raltegravir arm and in 11/32 (34.0%) in the efavirenz arm, resistance to raltegravir was detected in 12/32 (38.0%) patients in the raltegravir arm, and resistance to efavirenz was detected in 22/32 (69.0%) patients in the efavirenz arm. Dolutegravir remained active in 8/12 patients with resistance to raltegravir.

The median increase in CD4+ T-cell counts from baseline to week 48 was +183/mm³ in the raltegravir arm and +172/mm³ in the efavirenz arm.

The median pill count adherence ratio over 48 weeks of follow-up was 96.9% (IQR 89.7%-100.0%) and 100.0% (IQR 94.3%-104.5%) in the raltegravir and the efavirenz arms, respectively (p-value<0.0001). Ninety-four (42.3%) and 60 (27.0%) patients had a pill count adherence ratio <95% in the raltegravir and efavirenz arms, respectively (p-value<0.0001). The proportion of patients with poor adherence increased after week 24 in both arms (Table 4).

The median duration of tuberculosis treatment was 26 (IQR: 26-27) weeks and did not differ between arms. Tuberculosis treatment success was achieved in 203/227 (89.4%) and 206/230 (90.9%) patients in the efavirenz and raltegravir arms, respectively (Table S3 Appendix, page 12).

Twenty-six patients out of 457 patients (5.7%) died during follow-up: 14 in the efavirenz arm and 12 in the raltegravir arm. The majority of deaths [21 out of 26 (80.8%)] occurred within the first 24 weeks of the study [11/26 (42.3) before week 8 and 10/26 (38.5) between week 8 and week 24]. Causes of death are detailed in table S4 (Appendix page 13). Grade 3 or 4 adverse events occurred in 58/229 (25.3%) and 66/230 (28.7%) of patients in the raltegravir and efavirenz arms, respectively (Table 3). Grade 3 or 4 tuberculosis-associated IRIS occurred in 8/229 (3.5%) and 12/230 (5.2%) patients in the raltegravir and efavirenz arms, respectively.

DISCUSSION

We did not demonstrate the non-inferiority of a raltegravir 400 mg twice daily-based antiretroviral regimen compared to an efavirenz 600 mg once daily-based regimen in terms of virologic success at week 48 in ART-naïve HIV-infected adults treated for tuberculosis. Virologic success rates using a 50 copies/mL threshold were 60.9% on raltegravir and 66.1% on efavirenz, thus lower than we had hypothesized based on previous studies evaluating antiretroviral strategies in patients with tuberculosis.^{9,10}

To our knowledge this is the first phase 3 comparative randomized trial to date comparing an integrase inhibitor-

based to an efavirenz-based regimen in HIV-1 infected patients treated for tuberculosis in low and middle-income countries. In the non-comparative ANRS 12180 Reflate TB trial, we previously showed higher virologic success rates at week 48 in patients receiving raltegravir while on tuberculosis treatment, with success rates of 76% and 67% in the raltegravir 400 mg twice daily and efavirenz arms, respectively.¹⁸ The INSPIRING non-comparative randomized trial evaluated dolutegravir given twice daily and efavirenz in adults with a median CD4 T-cell count of 208 cells per cubic millimeter and mostly pulmonary tuberculosis. Virologic success rates at week 48 were 75% (52/69) and 82% (36/44) in the dolutegravir and efavirenz arms, respectively.¹⁶

Taken together, the results of Reflate TB2 and INSPIRING suggest that integrase inhibitor-based regimens, despite high anti-viral potency in patients without tuberculosis, result in a 5 to 7% lower success rate at week 48 than efavirenz based regimens in patients with tuberculosis.^{23,24}

Our results contrast with raltegravir registration trials that enrolled participants with less advanced disease and without tuberculosis co-infection in high or middle-income countries. In the STARTMRK trial, virologic suppression rates reached 90.9% and 89.2% on raltegravir and efavirenz-based regimens, respectively.²³ Conversely, the lower virologic success rates observed in our study are consistent with results from the NAMSAL trial that enrolled adults in Cameroon with a median HIV-1 RNA of 5.3 Log₁₀ copies/mL.²⁵ It showed virologic success rates of 74.5% and 69.0% on dolutegravir 50 mg once daily and efavirenz 400 once daily, respectively, that were lower than expected from previous studies on dolutegravir in antiretroviral-naïve patients as the ADVANCE study.²⁶ The main factor explaining these results was higher baseline viral loads.²⁵

We observed a similar impact of high baseline viral loads in our study with only 52.9% of patients with baseline HIV-1 RNA \geq 500,000 copies/mL reaching virologic success at week 48. The impact seemed notably higher in the raltegravir arm, with only 45.3% of those with baseline HIV-1 RNA \geq 500,000 copies/mL achieving virologic success as compared to 75.0% of those with baseline HIV-1 RNA <100,000 copies/mL. This may also explain why we observed lower success rates than in our previous phase 2 study where median baseline HIV-1 RNA was 4.9 Log₁₀ with a lower proportion of patients with HIV-1 RNA above 100,000 copies/mL.¹⁸

Despite similar rates of virologic failure and similar proportions of patients showing any resistance to antiretrovirals in both study arms, we observed a lower proportion of tenofovir resistance in patients with virologic failure in the raltegravir arm as compared to those in the efavirenz arm. The number of patients with dolutegravir-associated resistance mutations in patients with virologic failure in the raltegravir arm was also limited, therefore preserving future use of dolutegravir-based second line regimens.

The main limitations of our study are that we did not plan drug dosages nor detailed quality-of-life sub-study to

better describe psychological or social factors that may hamper treatment adherence. The interaction between antiretrovirals and rifampin does not seem, however, to explain our results. As a matter of fact, we found no difference between trial arms in terms of virologic suppression at week 24, at a time when most patients still take both antiretroviral and antituberculosis medications. This is consistent with results from our previous study in Brazilian HIV-infected individuals showing a lower impact of drug-drug interactions with rifampin on raltegravir pharmacokinetic parameters than expected, and similar virologic success rates in patients taking raltegravir 400 mg twice daily or efavirenz.^{18,19}

Adherence to treatment, a key contributor to virologic success, was globally poorer in the raltegravir arm dosed twice daily as compared to the efavirenz arm dosed once daily, and may have contributed to the results observed in this study.²⁷ A meta-analysis suggested that in ART-naïve patients twice daily treatment dosing was associated with reduced adherence but that the negative impact on virologic success was rather related to pill burden.²⁸ It is therefore unclear why adherence decreased in our study after week 24, when pill burden decreased following the discontinuation of anti-tuberculosis drugs, and whether recovery from tuberculosis and increase in wellbeing led participants to be less adherent to their treatment.

Both antiretroviral strategies were safe. Only few patients discontinued treatment due to adverse events. Two cases of severe hepatotoxicity in patients taking raltegravir 800 mg twice daily with tuberculosis treatment in our previous trial had raised concerns on hepatic tolerance of high-dose raltegravir. However, in the present study, only 3.9% of patients in both arms experienced hepatic toxicity. Other severe adverse events, including severe cases of tuberculosis-associated IRIS were also uncommon.

Integrase inhibitor-based ART has progressively become the preferred first-line antiretroviral regimen in international guidelines.¹⁴ The results of our study suggest, however, that integrase inhibitor-based regimens may not be as potent as expected in patients with tuberculosis due to adherence issues. Indeed, the twice daily dosage seems to have disadvantaged the raltegravir-based regimen, as compared to the once daily efavirenz regimen. Preliminary programmatic data from Botswana showed 90% virologic success at week 12 or 24 using a 400 copies/mL detection threshold in patients taking dolutegravir 50 mg twice or once daily.²⁹ However, programmatic virologic data at week 48 with a 50 copies/mL detection threshold is still lacking. Pending the availability of such data as well as results from one other trials enrolling patients co-infected with tuberculosis, the Reflate TB2 study is the only large phase 3 trial providing information on integrase inhibitor based therapy in this population. In the context of the dolutegravir roll-out, virologic response and adherence to the twice daily dosing for patients with tuberculosis needs to be monitored very closely by national HIV programs. Indeed,

emergence of high-level resistance to dolutegravir is rare but has been previously described in the context of drug-drug interaction with rifampin.³⁰

In conclusion, despite promising virological and pharmacokinetic data from our previous phase 2 study, this phase 3 trial failed to demonstrate the non-inferiority of raltegravir 400 mg twice daily when compared to efavirenz in HIV-1 infected adults with advanced HIV disease and tuberculosis. Our data support that efavirenz 600 mg once daily should still be considered an option for ART patients with HIV and tuberculosis co-infection. In these patients with advanced disease, adherence to ART and baseline viral load seem to have played an important role in virologic response, this needs to be further understood. Raltegravir that was well tolerated could be considered as an option only in selected patients.

PANEL: RESEARCH IN CONTEXT

Evidence before the study

The interaction between antiretroviral drugs and rifampicin, reduces treatment options for HIV-infected patients receiving tuberculosis treatment, making antiretroviral therapy (ART) options very limited. The non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz is less affected by the interaction with rifampicin and has been the drug of choice for many years. Tolerance issues and transmitted NNRTIs-resistance has prompted the search for alternatives to efavirenz-based regimens to treat patients co-infected with HIV and tuberculosis.

We searched PubMed for randomized controlled clinical trials published in English between Jan 1, 2010, and July 8, 2020, with the following search terms: (“tuberculosis” AND “raltegravir” AND “HIV”) OR (“tuberculosis” AND “integrase inhibitor” AND “HIV”). Our search found no comparative controlled trial but two non-comparative randomized trials.

The ANRS 12180 Reflate TB trial was a phase 2 trial comparing raltegravir-based and efavirenz-based antiretroviral therapy in patients co-infected with HIV and tuberculosis treated with rifampin, with standard (400 mg twice daily) or double dose (800 mg twice daily) raltegravir during antituberculosis treatment. The interaction with rifampin in patients receiving the standard dose of raltegravir had a minimal impact on virologic efficacy as patients taking efavirenz 600 mg once daily, raltegravir 400 mg twice daily or 800 mg twice daily had similar virologic response at W24 and W48. The pharmacokinetic parameters reduction in the raltegravir 400 mg twice daily arm was lower than expected and the safety of the three regimens was good and similar in the three arms. Based on these results, we designed the Reflate TB 2 phase 3 open label comparative randomized trial to confirm these results.

Another integrase inhibitor, dolutegravir, is now recommended by the WHO as the preferred first line ART and is replacing efavirenz in low and middle income countries. For patients with tuberculosis, one non-comparative randomized study showed that virologic response with dolutegravir was similar to that of efavirenz in patients with pulmonary tuberculosis and CD4 counts above 50 cells/mm³.

Added value of this study

To our knowledge, the Reflate TB 2 study is the only phase 3 comparative randomized clinical trial assessing the efficacy of an integrase inhibitor based antiretroviral regimen in the context of HIV and tuberculosis co-infection. Despite promising results from the previous phase 2 study, we failed to demonstrate at week 48 the

non-inferiority of the standard dose of raltegravir (400 mg twice daily) compared to efavirenz (600mg once daily). Our results showed that virologic response was lower than expected in both arms, especially in patients with high levels of HIV-1 RNA; adherence was also lower in both arms after week 24, but with a larger negative impact of the twice daily dosing of the integrase inhibitor regimen. There were no major safety issues in both arms.

Implications of the available evidence

Despite its negative results, the Reflate TB 2 study provides important data in the field of HIV and tuberculosis co-infection. We have shown that efavirenz should still be considered an option for ART in HIV and tuberculosis co-infection. However, raltegravir 400mg could be an acceptable alternative in selected patients. Our results also raise concerns about the use of twice daily dosing of integrase inhibitors regimens in the context of dolutegravir roll out in countries with high tuberculosis burden.

Declaration of Interests

Nathalie De Castro has received a research grant from Gilead (Voice program 2015).

Jean-Michel Molina has acted as a consultant, participated in advisory boards, has received speaker fees and has been an investigator for clinical trials for Janssen, ViiV Healthcare, Gilead Sciences, Bristol-Myers Squibb, Abbott Laboratories, Boehringer Ingelheim, and Merck, Sharp & Dohme. He has also received research grants from Merck. Constance Delaugerre participated in advisory boards for ViiV Healthcare, Gilead Sciences, BMS, and Merck, and has also received research grants from Gilead, and MSD.

All other authors declared no conflicts of interest.

Authors' contribution

NDC, OM, DL, XA, BG, and JMM conceived and designed the study. BG and NDC led the study at international level. NDC, OM, CC accessed and verified the data. VV and BG led the study in Brazil. EM and SE led the study in Côte d'Ivoire. NDC and JMM led the study in France. NB and CK led the study in Mozambique. GDC and DL led the study in Vietnam. OM coordinated study implementation at international level, RE coordinated study implementation in Brazil, JBN coordinated study implementation in Côte d'Ivoire, IT coordinated study implementation in Mozambique, AD coordinated study implementation in Vietnam. CD coordinated the virologic analyses. NDC, OM, BG, JMM, CC, CD, and DL contributed to the interpretation of

the results. EM, SE, NB, CK, GDC, SW, RE, VV, BG, NDC, JMM implemented the study and enrolled participants. CC did the statistical analysis. CC, OM prepared the report. NDC wrote the first draft and all authors reviewed and approved the final version of the report and the manuscript.

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We thank all the patients who participated to the trial.

Data sharing statement :

Reflate-TB2 data will not be shared publicly. Data could be made available by the sponsor (ANRS) to any researcher interested in getting the Reflate-TB2. Deidentified participant data would be made available with a data dictionary and shared under a data Transfer Agreement. Reflate-TB2 data can be requested at the following email address: nathalie.de-castro@aphp.fr .

Study protocol, statistical analysis plan and informed consent form are available with the present manuscript.

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Figure 1: Study flow chart

Figure 2A: Viral suppression (HIV-1 RNA < 50 copies/mL) under allocated therapy during follow-up, ANRS 12300 REFLATE TB2 trial (intention-to-treat)

Figure 2A legend:

/: percentage; CI: confidence interval; mL: milliliter;

All percentages are calculated on the ITT population: 227 in efavirenz arm and 230 in raltegravir arm.

Figure 2B: Viral suppression (HIV-1 RNA < 50 copies/mL) under allocated therapy according to baseline viral load, ANRS 12300 REFLATE TB2 trial (intention-to-treat)

Figure 2B legend:

/: percentage; CI: confidence interval; mL: milliliter;

All percentages are calculated on the ITT population: 227 in efavirenz arm and 230 in raltegravir arm.

Table 1. Characteristics of patient at baseline Raltegravir arm

	Efavirenz arm (N=227)	Raltegravir arm (N=230)
Age (years)	37 (30 - 43)	34 (28 - 42)
Female sex	90 (39.6)	92 (40.0)
Body mass index (kg/m ²)*†	19.1 (17.5 - 20.8)	19.1 (17.6 - 21.2)
CD4+ T-cell count (cells per mm ³)	108 (35 - 238)	99 (39 - 239)
≤200 cells per mm ³	154 (67.8)	159 (69.1)
≤50 cells per mm ³	77 (34.1)	75 (32.6)
Plasma HIV-1 viral load (Log ₁₀ copies per mL)	5.5 (5.0 - 5.9)	5.5 (5.0 - 5.8)
≥100,000 copies per mL	165 (72.7)	175/227 (77.1)
≥500,000 copies per mL	82 (36.1)	75/227 (33.0)
Time since first HIV-positive test (days)	22 (15 - 33)	21 (15 - 31)
On cotrimoxazole prophylaxis	201 (88.5)	201 (87.4)
Previous tuberculosis disease treated	3 (1.3)	3 (1.3)
Current anatomical site of tuberculosis disease		
Pulmonary only	159 (70.0)	154 (67.0)
Extra-pulmonary only	43 (18.9)	44 (19.1)
Pulmonary and extra-pulmonary	25 (11.0)	32 (13.9)
Bacteriologically confirmed tuberculosis‡	159 (70.0)	151 (65.7)
Smear microscopy positive for acid-fast bacilli	113 (49.8)	95 (41.3)
Xpert MTB/RIF test positive	132 (58.1)	134 (58.3)
Culture positive for mycobacterium tuberculosis	114 (50.2)	114 (49.6)
Probable (non-bacteriologically confirmed) tuberculosis‡	66 (29.1)	76 (33.0)
Urine lipoarabinomannan positive	18 (7.9)	15 (6.5)
Time on tuberculosis treatment at enrolment (days)	20 (15 - 27)	20 (15 - 28)
Alanine aminotransferase level (U/L)	23 (15 - 37)	24 (15 - 38)
Creatinine clearance (mL/min/1.73m ²)	98 (77 - 118)	103 (85 - 132)
Hemoglobin level (g/dL)	9.9 (8.2 - 11.4)	9.8 (8.7 - 11.1)
Positive for hepatitis B virus surface antigen	21 (9.3)	24 (10.4)
Positive for hepatitis C virus antibodies	7 (3.1)	2 (0.9)

Data are n (%) or median (IQR). *Data were available for 226 participants in the efavirenz arm and 227 participants in the raltegravir arm

†Body-mass index is the weight in kilograms divided by the square of the height in meters‡As defined by the WHO guidelines;

Table 2. Primary endpoint at week 48

	Efavirenz arm	Raltegravir arm	Difference (95% CI*)
Intention-to-treat population	(N=227)	(N=230)	
Virologic success (HIV-1 RNA <50 copies per mL)**	150 (66.1)	140 (60.9)	-5.2% (95% CI-14.0% to 3.6%)
Virologic non response	51 (22.5)	67 (29.1)	
HIV-1 RNA ≥ 50 copies per mL	32 (14.1)	46 (20.0)	
Discontinued due to lack of efficacy	9 (4.0)	13 (5.7)	
Discontinued due to other reasons [†] and last available HIV-1 RNA ≥50 copies per mL	10 (4.4)	8 (3.5)	
No data in the week 48 window	26 (11.5)	23 (10.0)	
Discontinued study/study drug due to adverse events or death	18 (7.9)	12 (5.2)	
Discontinued study/study drug for other reasons.	7 (3.1)	11 (4.8)	
On study but missing data in window.	1(0.4)	0 (0.0)	
On-treatment population	(N=204)	(N=206)	
Virologic success (HIV-1 RNA <50 copies per mL)**	150 (73.5)	139 (67.5)	-6.0% (95% CI-14.9% to 2.8%)
Virologic non response	41 (20.1)	58 (28.2)	
No data in the week 48 window	13 (6.4)	9 (4.4)	

Data are n or n (%).

*95% binomial confidence interval

**Federal Drug Administration (FDA) snapshot algorithm

†Other reasons include subjects who discontinued study drug due to investigator's discretion, withdrawal of consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy.

Table 3. Clinical outcomes

	Efavirenz arm (N=230)		Raltegravir arm (N=229)	
AIDS-defining illnesses (CDC)	17	13 (5.7)	10	10 (4.4)
HIV-associated non-AIDS illnesses	24	21 (9.1)	9	8 (3.5)
All grade IRIS	39	38 (16.5)	26	25 (10.9)
All grade drug-induced adverse reactions	38	30 (13.0)	25	25 (10.9)
Leading to allocated treatment permanent discontinuation	3	3 (1.3)	2	2 (0.9)
Type of drug-induced adverse reaction				
Hepatotoxicity*	9	9 (3.9)	9	9 (3.9)
Hypersensitivity	2	2 (0.9)	1	1 (0.4)
Renal failure	7	7 (3.0)	0	0
Rash	2	1 (0.4)	0	0
Grade 3 and 4 events adverse events	75	66 (28.7)	58	58 (25.3)
IRIS	14	14 (6.1)	10	10 (4.4)
Drug-induced adverse reactions	26	22 (9.6)	24	24 (10.5)
Other	35	30 (13.0)	24	24 (10.5)
Median weight gain at week 48 (IQR) – kg		7 (3 - 11)		9 (6 - 14)

Data are N, n (%). N= Number of events; n=number of patients; %=percentage of patients with at least one event

CDC: centers for disease control; IRIS: immune reconstitution inflammatory syndrome

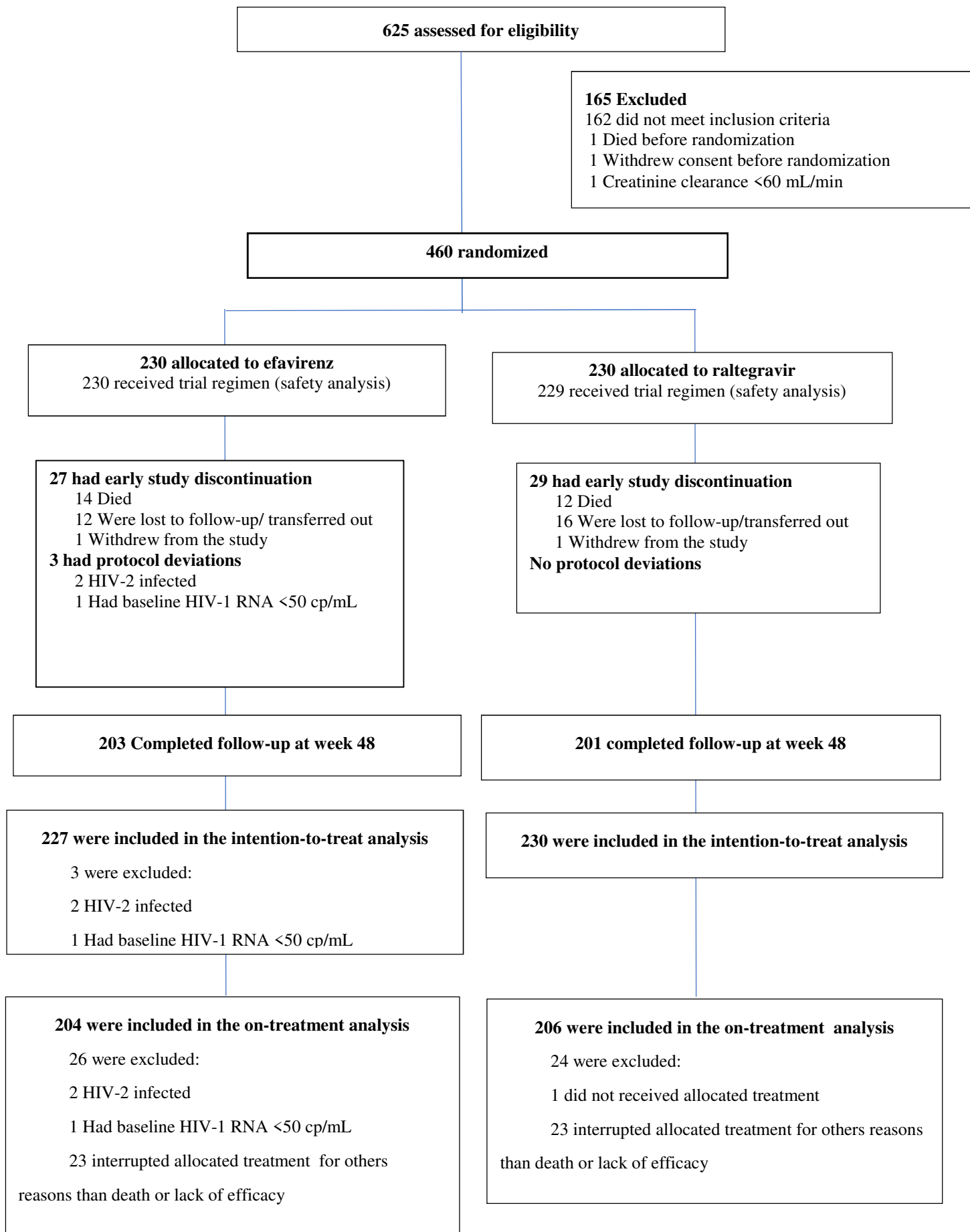
*10 grade 3 or 4 transaminase elevations, 2 grade 3 or 4 bilirubin elevations, 2 grade 2 transaminases elevation, 1 grade 2 bilirubin elevation, 1 grade 4 alkaline phosphatase

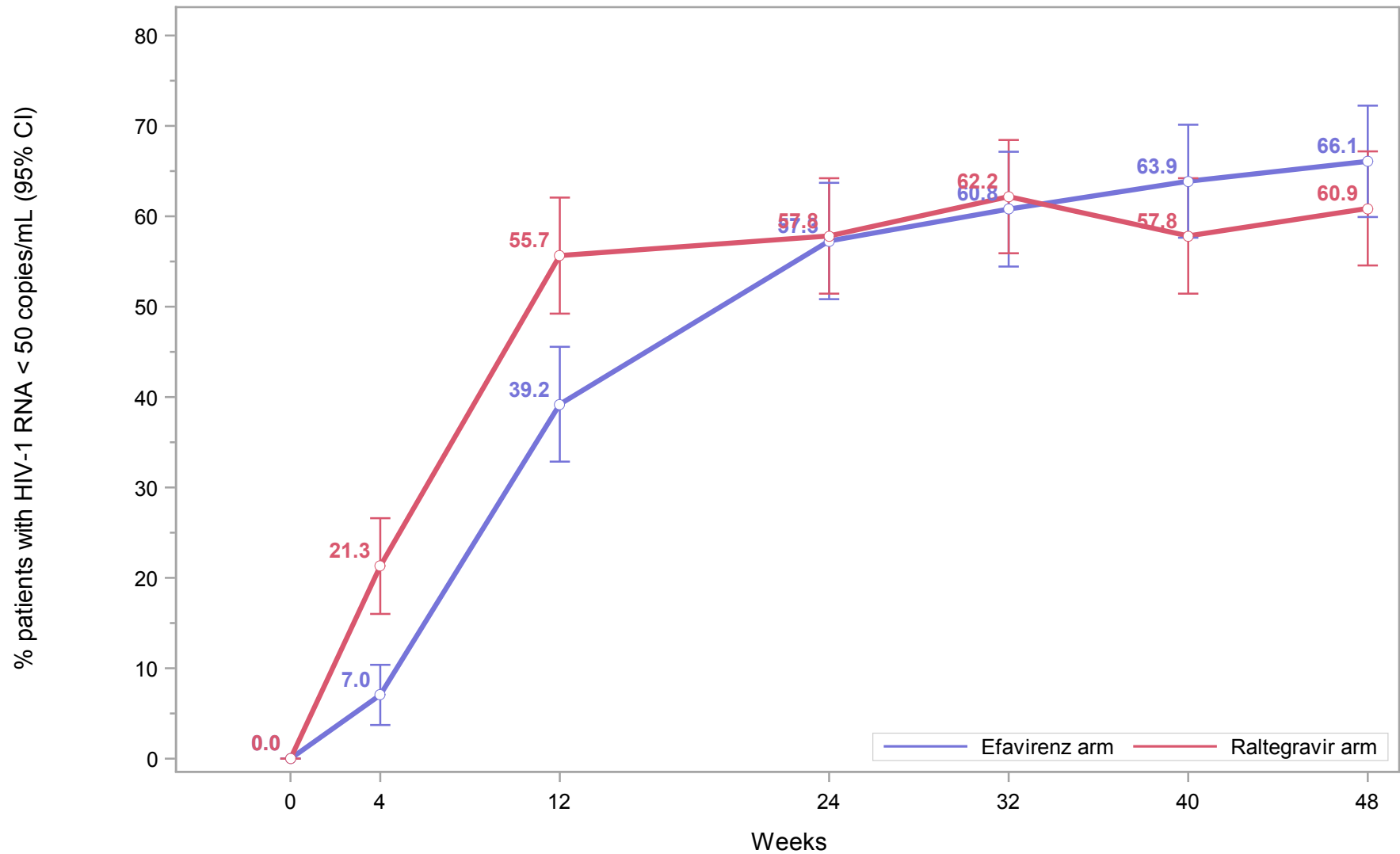
Table 4 : Pill count adherence ratio throughout the study (W0-W48), from week0 to week24 and week24 to week 48;for patients with available data

	Efavirenz arm	Raltegravir arm	P value
W0-W 48 study period	n=222	n=222	
Pill count adherence ratio (%)	100.0 (94.3%-104.5%)	96.9 (89.7-100.0)	P<0.0001
Pill count adherence ratio<95%	94 (42.3)	60 (27.0)	
W0-W24 study period	n=222	n=221	
Pill count adherence ratio (%)	100.6 (95.2-103.0)	98.8 (92.9-100.3)	P<0.0001
Pill count adherence ratio<95% (n, %)	50 (22.5)	72 (32.6)	
W24-W48 study period	n=199	n=208	P<0.0001
Pill count adherence ratio (%)	100.0 (93.7-106.5)	97.4 (84.8-100.9)	
W24-W48 pill count adherence ratio<95% (n, %)	55 (27.6%)	85 (40.9%)	

Data are n (%) or median (IQR)

Figure 1: Study flow chart





Patients with HIV-1 RNA < 50 copies/ml under allocated therapy

Efavirenz arm	0	16	89	130	138	145	150
Raltegravir arm	0	49	128	133	143	133	140

