

Nevirapine versus efavirenz for patients co-infected with HIV and tuberculosis: a randomised non-inferiority trial



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Summary

Background In countries with a high incidence of HIV and tuberculosis co-infection, nevirapine and efavirenz are widely used as antiretroviral therapy but both interact with antituberculosis drugs. We aimed to compare efficacy and safety of a nevirapine-based antiretroviral therapy (started at full dose) with an efavirenz-based regimen in co-infected patients.

Methods We did a multicentre, open-label, randomised, non-inferiority trial at three health centres in Maputo, Mozambique. We enrolled adults (≥ 18 years) with tuberculosis and previously untreated HIV infection (CD4 cell counts < 250 cells per μL) and alanine aminotransferase and total bilirubin concentrations of less than five times the upper limit of normal. 4–6 weeks after the start of tuberculosis treatment, we randomly allocated patients (1:1) with central randomisation, block sizes of two to six, and stratified by site and CD4 cell count to nevirapine (200 mg twice daily) or efavirenz (600 mg once daily), plus lamivudine and stavudine. The primary endpoint was virological suppression at 48 weeks (HIV-1 RNA < 50 copies per mL) in all patients who received at least one dose of study drug (intention-to-treat population); death and loss to follow-up were recorded as treatment failure. The non-inferiority margin for the difference of efficacy was 10%. We assessed efficacy in intention-to-treat and per-protocol populations and safety in all patients who received study drug. This study is registered with ClinicalTrials.gov, number NCT00495326.

Findings Between October, 2007, and March, 2010, we enrolled 285 patients into each group. 242 (85%) patients in the nevirapine group and 233 (82%) patients in the efavirenz group completed follow-up. In the intention-to-treat population, 184 patients (64.6%, 95% CI 58.7–70.1) allocated nevirapine achieved virological suppression at week 48, as did 199 patients (69.8%, 64.1–75.1) allocated efavirenz (one-sided 95% CI of the difference of efficacy 11.7%). In the per-protocol population, 170 (70.0%, 63.8–75.7) of 243 patients allocated nevirapine achieved virological suppression at week 48, as did 194 (78.9%, 73.2–83.8) of 246 patients allocated efavirenz (one-sided 95% CI 15.4%). The median CD4 cell count at randomisation was 89 cells per μL . 15 patients substituted nevirapine with efavirenz and six patients substituted efavirenz with nevirapine. 20 patients allocated nevirapine (7%) had grade 3–4 increase of alanine aminotransferase compared with 17 patients allocated efavirenz (6%). Three patients had severe rash after receipt of nevirapine (1%) but no patients did after receipt of efavirenz. 18 patients in the nevirapine group died, as did 17 patients in the efavirenz group.

Interpretation Although non-inferiority of the nevirapine-regimen was not shown, nevirapine at full dose could be a safe, acceptable alternative for patients unable to tolerate efavirenz.

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Introduction

Tuberculosis is the main opportunistic infection and a leading cause of death in people living with HIV. Antiretroviral therapy reduces mortality in patients co-infected with HIV and tuberculosis and should be started during the first 8 weeks of tuberculosis treatment, irrespective of the patient's CD4 cell count.¹ Nevirapine and efavirenz are non-nucleoside reverse transcriptase inhibitors (NNRTIs) recommended by WHO as first-line antiretroviral therapy.¹ Nevirapine is the most commonly used drug in resource-poor countries with a high HIV burden because of the convenience and affordability of generic fixed-dose combinations.

Rifampicin is a key component of tuberculosis treatment but also a potent inducer of some forms of hepatic cytochrome P450, leading to enhanced NNRTI drug

clearance and, consequently, reduced drug exposure. Nevirapine biotransformation pathways are more sensitive to induction than are those of efavirenz, and nevirapine-based regimens therefore have a greater risk of subtherapeutic NNRTI concentrations.^{2–5} The reduction in nevirapine concentration is most pronounced during the first 2 weeks of antiretroviral therapy, when it is typically prescribed at half dose (200 mg lead-in dose) to prevent hypersensitivity before a steady state concentration has been reached.⁶ To avoid this problem, WHO guidelines recommend efavirenz rather than nevirapine for patients co-infected with HIV and tuberculosis.¹ However, efavirenz has other difficulties, primarily its toxic effects on the CNS that can necessitate discontinuation of early treatment.⁷ Moreover, because of efavirenz's potential teratogenicity, use during the first

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trimester of pregnancy is controversial.^{18,9} For national HIV programmes, fixed-dose combinations containing efavirenz (efavirenz-lamivudine-tenofovir and efavirenz-tenofovir-emtricitabine) are less affordable than are fixed-dose combinations based on nevirapine.¹⁰

Assessment of the effects of giving rifampicin with nevirapine on virological outcome has yielded conflicting results in clinical studies of nevirapine given with a 2 week lead-in dose.^{11–14} These discrepancies led some authors to propose that, because cytochrome P450 enzymes in patients on rifampicin are presumably already induced at the time of antiretroviral therapy initiation, nevirapine should be started at full dose in these patients.^{15,16} However, efficacy and safety of this approach have not been assessed. In this study, we aimed to compare the efficacy and safety of nevirapine-based and efavirenz-based antiretroviral therapies in patients co-infected with HIV and tuberculosis, with initiation of nevirapine at full dose.

Methods

Study design and participants

The comparison of nevirapine and efavirenz for the treatment of HIV-tuberculosis co-infected patients (French Research Agency for HIV/AIDS and hepatitis [ANRS] 12146 CARINEMO) trial was an open-label, randomised, phase 3 non-inferiority trial done at three health centres in Maputo, Mozambique: José Macamo

Hospital, Mavalane Hospital, and Alto Maé Health Centre. We enrolled adults (≥ 18 years) with previously untreated HIV infection who had been receiving treatment for pulmonary or extrapulmonary tuberculosis for less than 4 weeks at tuberculosis or HIV outpatient clinics in three health areas of Maputo. We enrolled participants if they had a Karnofsky score of 60% or more (ambulatory patients), CD4 cell count of less than 250 cells per μL , a negative urine pregnancy test, alanine aminotransferase and total bilirubin concentrations of less than five times the upper limit of normal (ULN; grade <3), and absence of any grade 4 clinical or biological adverse event. Women who had previously received one dose of nevirapine or zidovudine–nevirapine for prevention of mother-to-child transmission of HIV were eligible for inclusion.

We followed good clinical practice guidelines and four ethics committees approved the study protocol: the Comité Nacional de Bio-Ética para a Saúde (Maputo, Mozambique), the Médecins Sans Frontières Ethics Review Board (Zurich, Switzerland), the Comité de Protection des Personnes (Saint Germain-en-Laye, France), and the Columbia University ethics review committee (New York, NY, USA). All participants provided signed informed consent.

Randomisation and masking

4–6 weeks after starting tuberculosis treatment, we randomly allocated patients (1:1) to receive either nevirapine or efavirenz regimens. Randomisation was done centrally at Epicentre headquarters (Paris, France) and treatment allocation was communicated to the site investigators sequentially for consecutive enrolment of patients. The allocation sequence was computer-generated with block sizes of two to six (in steps of two), stratified by site and CD4 cell count (≤ 50 cells per μL vs >50 cells per μL). Randomisation lists were prepared by the trial statistician (EB) and concealed from the site investigators. Masking of investigators and patients to treatment allocation would have required use of placebo and was not feasible in this context. Before closure of the trial sites, aggregated data by treatment group were available only to the trial statistician and the independent data monitoring committee (IDMC).

Procedures

All patients received the standard national tuberculosis chemotherapy of a generic fixed-dose combination of once-daily tablets combining rifampicin (150 mg), isoniazid (75 mg), pyrazinamide (400 mg), and ethambutol (275 mg) for the first 2 months, followed by isoniazid (75 mg) and rifampicin (150 mg) for the subsequent 4 months (Lupin, Aurangabad, India), at a dose of 10 mg/kg (rifampicin), 5 mg/kg (isoniazid), 25 mg/kg (pyrazinamide), and 15 mg/kg (ethambutol). Antiretroviral therapy was started after patients received 2 weeks of counselling, which involved psychosocial

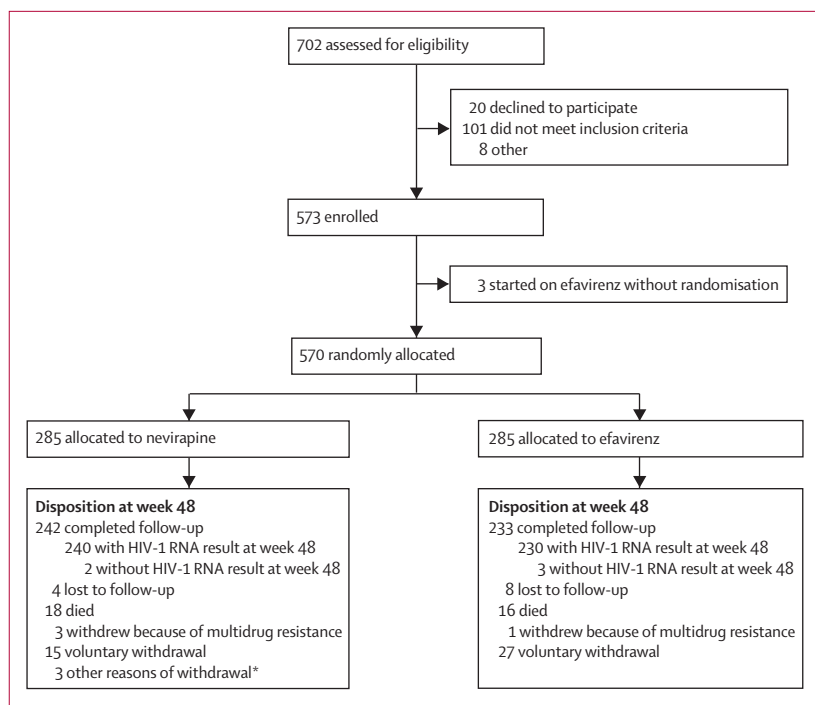


Figure 1: Study profile

*One patient was incarcerated during follow-up, one had an exacerbation of a chronic psychotic disorder that prevented retention in the trial, and one had baseline monoresistance to rifampicin and was referred to the national multidrug-resistant tuberculosis programme.

support and education about adherence to antiretroviral therapy and tuberculosis therapy. Participants in the nevirapine group received one tablet of fixed-dose combination nevirapine (200 mg), lamivudine (150 mg), and stavudine (30 mg; Cipla, Patalganga, India) twice-daily, which was replaced by nevirapine (200 mg), lamivudine (150 mg), and zidovudine (300 mg; Aurobindo, Heydarabad, India) in August, 2010, to comply with new national and international recommendations. Patients in the efavirenz group received one tablet per day of efavirenz (600 mg; Aurobindo, Andrah Pradesh, India) combined with one tablet twice-daily of the fixed-dose combination lamivudine (150 mg) and stavudine (30 mg; Cipla, Goa, India), replaced by lamivudine (150 mg) and zidovudine (300 mg; Cipla) in August, 2010. All drugs were WHO prequalified.¹⁷ The protocol allowed substitution of nevirapine by efavirenz in cases of severe hepatitis (alanine aminotransferase >5×ULN) or rash (grade ≥3), and substitution of efavirenz by nevirapine during the first trimester of pregnancy for women who became pregnant during follow-up. Tenofovir replaced stavudine or zidovudine in patients who developed lactic acidosis, as measured by lactic acid concentration in symptomatic patients, and in patients co-infected with hepatitis B and presenting with severe hepatitis. According to 2006 WHO and national guidelines, patients with HIV-1 RNA counts of more than 10 000 copies per mL on two consecutive measures and reinforcement of treatment adherence were switched to an adapted boosted protease inhibitor-based antiretroviral therapy after approval by the national antiretroviral committee. All patients received pyridoxine (50 mg per day) during tuberculosis treatment and 960 mg co-trimoxazole per day.

We did clinical examination and laboratory analyses at screening and inclusion visits, at weekly visits for the first 8 weeks after randomisation, and thereafter every 4 weeks. Patients were diagnosed with pulmonary tuberculosis and started tuberculosis treatment at clinics before referral to the trial site. Diagnosis of pulmonary tuberculosis was based on the results of two sputum smear-examination (on spot and early-morning specimens) or chest radiograph and response to an antibiotic trial for patients with smear-negative pulmonary tuberculosis. Extrapulmonary tuberculosis was diagnosed with cytohistopathology, biochemical, and radiographical assessment. For patients with pulmonary tuberculosis, two sputum samples were collected at the first trial screening visit within 2 weeks after start of tuberculosis treatment and were shipped to the reference laboratory at the Institute of Tropical Medicine (Antwerp, Belgium) for culture and drug-susceptibility testing. Sputum-microscopy was also done at 2, 4, and 6 months after start of tuberculosis treatment. We took chest radiographs and full blood counts at the screening visit for all patients.

We diagnosed hepatitis B (defined as detection of hepatitis B surface antigen and hepatitis B core antibody)

and hepatitis C (defined as detection of hepatitis C virus antibody with two ELISA tests and confirmation by the detection of hepatitis C virus-RNA at the Necker Hospital, Paris, France) at the inclusion visit. We measured plasma HIV-1 RNA with the Roche Cobas Amplicor HIV-1 monitor test v1.5 (Roche Diagnostics, Basel, Switzerland) at the inclusion visit and at weeks 12, 24, 36, and 48; CD4 cell count was assessed at screening visit, week 24, and week 48. Resistance mutations to nucleoside reverse transcriptase inhibitors and NNRTI were determined in all patients with HIV-1 RNA counts of more than 400 copies per mL at week 48 by sequencing the reverse transcriptase gene with the consensus technique of the

| | Nevirapine group (n=285) | Efavirenz group (n=285) |
|---|--------------------------|-------------------------|
| Site | | |
| Alto Maé | 100 (35%) | 101 (35%) |
| Mavalane | 112 (39%) | 111 (39%) |
| José Macamo | 73 (26%) | 73 (26%) |
| Sex, female | 125 (44%) | 114 (40%) |
| Age, years | 33 (29–41) | 33 (28–40) |
| Weight, kg | 51.7 (46.6–57.2) | 52.5 (47.5–58.8) |
| Body-mass index, kg/m ² | 18.7 (17.1–20.2) | 18.9 (17.6–20.3) |
| Karnofsky performance score | | |
| ≥80 | 249 (87%) | 261 (92%) |
| 60–70 | 36 (13%) | 24 (8%) |
| Pulmonary tuberculosis smear result | | |
| Positive | 99 (35%) | 121 (42%) |
| Negative or no microscopy results* | 127 (45%) | 97 (34%) |
| Extrapulmonary tuberculosis | 59 (21%) | 67 (24%) |
| Tuberculosis meningitis | 1 (<1%) | 0 |
| Pleural tuberculosis | 37 (13%) | 35 (12%) |
| Miliary tuberculosis | 9 (3%) | 10 (4%) |
| Lymph node tuberculosis | 9 (3%) | 15 (5%) |
| Abdominal tuberculosis | 2 (1%) | 3 (1%) |
| Tuberculosis pericarditis | 1 (<1%) | 0 |
| Bone tuberculosis | 0 | 2 (1%) |
| Disseminated tuberculosis | 0 | 3 (1%) |
| WHO stage 4 HIV infection other than extrapulmonary tuberculosis | 19 (7%) | 15 (5%) |
| Time between start of tuberculosis therapy and start of antiretroviral therapy, weeks | 4.9 (4.4–5.1) | 4.9 (4.4–5.1) |
| Laboratory findings | | |
| Alanine aminotransferase, ULN | 24.2 (15–39) | 23.7 (16.3–37.8) |
| Bilirubin, mg/dL | 0.44 (0.32–0.60) | 0.46 (0.33–0.63) |
| Haemoglobin, g/dL | 9.4 (8.4–10.2) | 9.4 (8.3–10.4) |
| CD4 count, cells per µL | 92 (44–148) | 86 (44–140) |
| CD4 count, <50 cells per µL | 81 (28%) | 81 (28%) |
| HIV-RNA, log ₁₀ copies per mL | 5.7 (5.1–6.1) | 5.5 (5.2–6.1) |
| HBV surface antigen | 59/284 (21%) | 63/281 (22%) |
| HCV antibody | 4/284 (1%) | 5/284 (2%) |

Data are n (%), median (IQR), or n/N (%). ULN=upper limit of normal. HBV=hepatitis B virus. HCV=hepatitis C virus.
*19 patients in the nevirapine group and 11 patients in the efavirenz group were not able to produce sputum specimen for microscopy test.

Table 1: Baseline characteristics of the intention-to-treat population

See Online for appendix

AC11 ANRS resistance group at the Necker Hospital (Paris, France). We measured alanine aminotransferase and total bilirubin concentrations at screening visits and at weeks 2, 4, 6, 8, 12, 16, 20, 24, 36, and 48. At every follow-up visit, we monitored adherence to antiretroviral therapy and tuberculosis treatment with an analogue visual scale, questionnaire, and pill count. In addition, we used the isoniazid urine test (BBL Taxo isoniazid test; Becton Dickinson, Franklin Lakes, USA) to assess tuberculosis treatment adherence.

We assessed intensity of adverse events with the ANRS table for grading adult adverse event (grade 1 was defined as mild, grade 2 as moderate, grade 3 as severe, and grade 4 as lifethreatening).¹⁸ We defined serious adverse events as any untoward medical occurrence that, at any dose, resulted in death, was life-threatening, required hospital admission or prolongation of hospital stay, resulted in disability or incapacity, or resulted in a congenital anomaly or birth defect. We obtained blood samples for measurement of nevirapine and efavirenz plasma concentration every 12 weeks. To verify the absence of major changes in metabolism of nevirapine caused by rifampicin, the IDMC requested a full pharmacokinetic analysis in the first 20 patients enrolled in the nevirapine group 4 weeks after co-administration with rifampicin and also 4 weeks after completion of tuberculosis treatment.¹⁹ The protocol was amended in January, 2010 to extend follow-up until week 96 for the last enrolled patients with

HIV-1 RNA and CD4 cell count measured at 72 weeks and 96 weeks (appendix). Results of the extended follow-up will be presented separately.

The primary outcome was virological suppression at week 48, defined as an HIV-1 RNA count of less than 50 copies per mL. Patients who died or were lost to follow-up before week 48 were categorised as treatment failures. Secondary outcomes were increase in CD4 cell count by more than 20% from baseline to week 48, occurrence of AIDS-defining events, end of tuberculosis treatment outcomes as per WHO definitions, occurrence of treatment-emergent adverse effects (TEAE), and paradoxical tuberculosis immune reconstitution inflammatory syndrome (IRIS) within 12 weeks of start of antiretroviral therapy.^{20,21} Members of the trial's scientific advisory board (RB and CM) validated causes of death and IRIS-tuberculosis. Adverse event terms were adopted from the medical dictionary for regulatory activities (MedDRA version 11.1).²²

Statistical analysis

We defined the non-inferiority margin for the difference in efficacy as 10%. Assuming a 70% efficacy in the efavirenz group²³ and a maximum difference of 10% in efficacy between two groups, a sample size of 260 patients per group was needed to determine non-inferiority with a power of 80% and an α level of 5% (one-sided test; nQuery Advisor version 6). We increased the proposed sample size by 10% to account for loss to follow-up.

Data were reviewed by the IDMC every 6 months. We did efficacy analyses for two populations: the intention-to-treat population, which included all randomised patients who received at least one dose of allocated drug; and the per-protocol population, excluding participants who discontinued treatment prematurely for reasons other than death or loss to follow-up, who had a treatment adherence of less than 80%, who had NNRTI substitution, or who did not have HIV-1 RNA results at week 48. We did a sensitivity analysis of efficacy in the intention-to-treat population, classifying treatment failures as patients

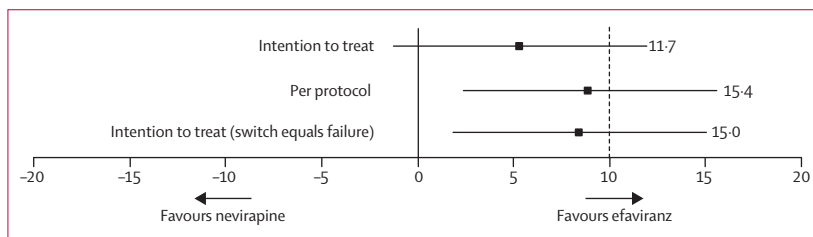


Figure 2: Overall success rates (non-inferiority analysis) in intention-to-treat and per-protocol populations Difference of success rates between efavirenz and nevirapine regimens; bars show 90% CI. Dotted line shows the non-inferiority margin of 10%.

| | Nevirapine group | | Efavirenz group | | Difference (%) | One-sided (95% CI) | p value |
|--|------------------|-------------------|-----------------|-------------------|----------------|--------------------|---------|
| | n/N | % (95% CI) | n/N | % (95% CI) | | | |
| Primary analysis* | | | | | | | |
| Intention to treat | 184/285 | 64.6% (58.7-70.1) | 199/285 | 69.8% (64.1-75.1) | 5.3% | 11.7 | .. |
| Per protocol | 170/243 | 70.0% (63.8-75.7) | 194/246 | 78.9% (73.2-83.8) | 8.9% | 15.4 | .. |
| Intention to treat (switch equals failure) | 171/285 | 60.0% (54.1-65.7) | 195/285 | 68.4% (62.7-73.8) | 8.4% | 15.0 | .. |
| Secondary analysis | | | | | | | |
| Death | 18/285 | 6.3% (3.8-9.8) | 16/285 | 5.6% (3.2-9.0) | .. | .. | 0.7236 |
| HIV1-RNA <400 copies per mL† | 187/243 | 76.9% (71.1-82.1) | 202/246 | 82.1% (76.7-86.7) | .. | .. | 0.1573 |
| CD4 gain ≥20% | 223/285 | 78.2% (73.0-82.9) | 213/285 | 74.7% (69.3-79.7) | .. | .. | 0.3233 |
| New AIDS-defining diseases | 19/285 | 6.7% (4.1-10.2) | 22/285 | 7.7% (4.9-11.4) | .. | .. | 0.6267 |

*Virological suppression at week 48. †In the per-protocol population.

Table 2: Efficacy outcomes

who had NNRTI substitution, including substitution because of pregnancy (switch equals failure analysis). We tested non-inferiority of the nevirapine regimen with the Blackwelder method by calculating the difference in efficacy between the efavirenz and nevirapine regimens and comparing the upper limit of the 90% CI (as specified in the sample-size calculation based on a one-sided test and a 5% α error) to the non-inferiority margin.²⁴ Therefore, to accept non-inferiority of the nevirapine regimen, the upper limit of the 90% CI needed to be equal or less than 10%. Secondary analyses included estimation of the proportion of patients with HIV-1 RNA levels of less than 50 copies per mL at weeks 12, 24, 36, and 48. For patients who had NNRTI substitution, we used only HIV-1 RNA results before substitution. Other secondary analyses included antiretroviral therapy efficacy at 48 weeks with an HIV-1 RNA detection limit of 400 copies per mL in the per-protocol population; the proportion of patients with an increase in CD4 cell count by 20% or more from baseline to week 48; the proportion of patients with an incident AIDS-defining disease; and end of tuberculosis treatment outcomes and the proportion of tuberculosis with paradoxical IRIS. For safety analysis, we report the proportion of patients who had at least one TEAE, major TEAE (grade ≥ 3), serious TEAE, or TEAE of interest (grade ≥ 3 hepatitis and rash) by treatment group. We report the proportion of patients with an increase of alanine aminotransferase (grade ≥ 2) during follow-up and by group. We compared proportions with χ^2 or Fisher's exact tests with two-sided p values. Data were analysed with Stata version 10.1.

This study is registered with ClinicalTrials.gov, number NCT00495326.

Role of the funding source

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

Results

We enrolled 573 patients between October, 2007, and March, 2010, and completed follow-up in February, 2011 (figure 1). Because of a temporary hold on inclusions placed by the IDMC in October, 2007, which was justified by the investigators' decision to abandon the 2 week nevirapine lead-in dose on the basis of preliminary results from a large South African prospective cohort,¹⁴ three patients were started on efavirenz regimen without randomisation. 43 (15%) of 285 patients randomly allocated nevirapine and 52 (18%) of 285 patients randomly allocated efavirenz did not complete 48 weeks of follow-up ($p=0.3118$).

In the nevirapine group, 17 patients discontinued follow-up before 12 weeks (13 deaths, three losses to follow-up, and one referral to treatment for multidrug-

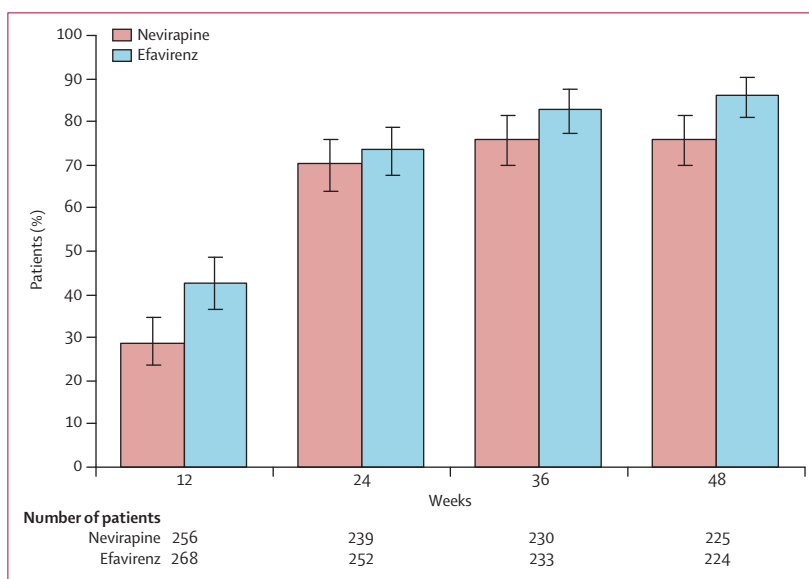


Figure 3: Patients with HIV-1 RNA counts less than 50 copies per mL during follow-up

resistant tuberculosis), 12 discontinued follow-up at 12–24 weeks (seven voluntary withdrawals, four referrals to treatment for multidrug-resistant tuberculosis, one death, and one referral to psychiatric treatment), and 14 discontinued follow-up after 24 weeks (eight voluntary withdrawals, four deaths, one loss to follow-up, and one incarceration). In the efavirenz group, 15 patients discontinued follow-up before 12 weeks (eight deaths, three losses to follow-up, three voluntary withdrawals, and one referral to treatment for multidrug-resistant tuberculosis); 20 discontinued follow-up at 12–24 weeks (11 voluntary withdrawals, five deaths, and four losses to follow-up) and 17 discontinued follow-up after 24 weeks (13 voluntary withdrawals, three deaths, and one loss to follow-up). Of 42 voluntary withdrawals, 18 moved to South Africa and 13 moved to another region in Mozambique for work reasons, ten refused to continue follow-up in the trial, and one was unable to participate because of drug addiction. Fewer patients withdrew voluntarily in the nevirapine group (15 patients [5%]) than in the efavirenz group (27 patients [9%]; $p=0.0544$). 15 patients substituted from nevirapine to efavirenz (14 because of toxic effects and one because of protocol deviation) and six patients substituted from efavirenz to nevirapine (four because of pregnancy and two because of neurological toxic effects).

Table 1 shows baseline characteristics of patients. Although not significantly different, slightly fewer patients had smear-positive pulmonary tuberculosis in the nevirapine group than the efavirenz group ($p=0.0584$). The median time between start of tuberculosis treatment and sputum collection for *Mycobacterium tuberculosis* culture was 14 days (IQR 8–20) for nevirapine and 12 days (7–18) for efavirenz. After exclusion of failure of specimen shipment (12 samples in the nevirapine group vs

14 samples in the efavirenz group), culture contaminated results (13 vs 15), and mycobacteria other than tuberculosis (one vs five), cultures were positive in 58 (29%) of 200 patients with pulmonary tuberculosis in the nevirapine group and 69 (38%) of 183 patients in the efavirenz group ($p=0.0707$).

Two patients were allocated the incorrect drug because of an incorrect stratification by CD4 cell count but were retained in the intention-to-treat population. After exclusion of patients who discontinued prematurely for reasons other than death or loss to follow-up (voluntary withdrawals, withdrawals due to multidrug resistance, or other reasons; figure 1), patients with NNRTI substitution, patients with antiretroviral therapy adherence lower than 80% (four patients in the nevirapine group vs two patients in the efavirenz group), and patients who completed follow-up but did not have an HIV-1 RNA measurement at week 48 (two vs three), we included 243 patients from the nevirapine group and 246 patients from the efavirenz group in the per-protocol analysis.

Antiretroviral therapy efficacy (HIV-1 RNA <50 copies per mL) at 48 weeks was 64.6% for nevirapine and 69.8% for efavirenz in the intention-to-treat population and 70.0% vs 78.9% in the per-protocol population (figure 2

and table 2). Non-inferiority of the nevirapine regimen was not shown. The one-sided 95% CI of the efavirenz-nevirapine efficacy difference exceeded the predefined 10% non-inferiority margin in intention-to-treat, per-protocol, and switch-equals-failure analysis (figure 2 and table 2). 15 patients who substituted nevirapine with efavirenz had virological suppression at week 48. Two of four patients who substituted efavirenz with nevirapine because of pregnancy had no virological suppression at week 48 and one had confirmed NNRTI resistance.

Although the proportion of patients with an HIV-1 RNA count of less than 50 copies per mL was lower in the nevirapine group than in the efavirenz group, the difference was not significant beyond 12 weeks (figure 3). Incidence of AIDS-defining illness, increase in CD4 cell count, and the proportion of patients at week 48 with an HIV-1 RNA count of less than 400 copies per mL did not differ between groups (table 2).

Antiretroviral resistance genotyping results (table 3) were available for 49 (79%) of 62 patients who had HIV-1 RNA levels of more than 400 copies per mL at week 48. All reverse transcriptase gene sequences corresponded to HIV-1 subtype C.

Tuberculosis treatment success (cured or completed) was more than 90% in both groups (table 4). 32 patients in the nevirapine group (11%) and 21 in the efavirenz group (7%) had paradoxical associated tuberculosis IRIS ($p=0.1039$).

The number of TEAEs was much the same in both groups (table 5). 18 patients in the nevirapine group died, as did 17 patients in the efavirenz group (one patient allocated efavirenz died without been randomly allocated). Cause of death was determined for 29 (83%) of 35 deaths and included tuberculosis (three deaths in the nevirapine group vs five in the efavirenz group), severe infection (three vs three), IRIS-tuberculosis (four vs none), IRIS-Kaposi (one vs one), Kaposi sarcoma (two vs two), wasting syndrome (none vs two), tumour of hypopharynx (none vs one), Guillain-Barré syndrome (none vs one), and car accident (one vs none). No deaths were attributed to the study drugs. The proportion of patients with an increase of alanine aminotransferase during follow-up was much the same in both groups (figure 4). One patient in the nevirapine group had Stevens-Johnson syndrome that resolved after discontinuation of nevirapine. More patients in the nevirapine group (14 patients) than in the efavirenz group (two) discontinued because of toxic effects ($p=0.002$; table 5). 11 patients received tenofovir during follow-up (four for severe hepatitis with hepatitis B co-infection and seven for lactic acidosis or severe neuropathy with anaemia).

Discussion

To our knowledge, our study is the largest randomised non-inferiority trial to compare the efficacy of nevirapine-based and efavirenz-based regimens in patients co-infected with HIV and tuberculosis, and the first to use

| | Nevirapine group | Efavirenz group | p value |
|----------------------------------|------------------|-----------------|---------|
| HIV-1 RNA >50 copies per mL | 56 | 31 | .. |
| HIV-1 RNA >400 copies per mL | 37 | 25 | .. |
| No sample | 2 | 7 | .. |
| No amplification | 2 | 2 | .. |
| Samples tested for resistance | 33 | 16 | .. |
| NNRTI resistance mutations* | 27 (82%) | 11 (69%) | 0.5073 |
| Etravirine resistance mutations* | 8 (24%) | 3 (19%) | 0.9465 |
| 184V mutation | 22 (67%) | 9 (56%) | 0.4781 |
| TAMs | 5 (15%) | 1 (6%) | 0.6696 |

TAM=tumour-associated macrophage. NNRTI=non-nucleoside reverse transcriptase inhibitors. ANRS= French Research Agency for HIV/AIDS and hepatitis. *NNRTI resistance mutations according to the ANRS algorithm.¹⁸

Table 3: Resistance data by study group at week 48

| | Nevirapine group (n=285) | Efavirenz group (n=288) |
|---------------------|--------------------------|-------------------------|
| Treatment success | 260 (91%) | 260 (90%) |
| Cured | 131 (46%) | 142 (49%) |
| Treatment completed | 129 (45%) | 118 (41%) |
| Death | 13 (5%) | 14 (5%) |
| Defaulter | 6 (2%) | 11 (4%) |
| Treatment failure | 1 (<1%) | 2 (1%) |
| Transferred* | 5 (2%) | 1 (<1%) |

Treatment outcomes did not differ between the two study groups. *Five patients were transferred to the national multidrug-resistant tuberculosis programme for treatment and one patient was incarcerated during follow-up.

Table 4: Tuberculosis treatment outcomes in the safety population

| | Nevirapine group (n=285) | Efavirenz group (n=288) |
|---|--------------------------|-------------------------|
| Treatment-emergent adverse events | 284 (>99%) | 280 (97%) |
| Major adverse event | 74 (26%) | 70 (24%) |
| Serious adverse events* with $\geq 1\%$ frequency | 53 (19%) | 53 (18%) |
| Blood and lymphatic system disorders | | |
| Anaemia | 7 (2%) | 9 (3%) |
| Leukopenia | 3 (1%) | 2 (1%) |
| Neutropenia | 4 (1%) | 2 (1%) |
| Gastrointestinal disorders | | |
| Diarrhoea | 5 (2%) | 3 (1%) |
| General disorders and administration-site conditions | | |
| Fatigue | 11 (4%) | 17 (6%) |
| Oedema | 2 (1%) | 3 (1%) |
| Immune system disorders | | |
| Immune reconstitution syndrome | 5 (2%) | 2 (1%) |
| Hypersensitivity | 3 (1%) | 0 |
| Infections and infestations | | |
| Abscess | 2 (1%) | 3 (1%) |
| Pulmonary tuberculosis | 0 | 3 (1%) [†] |
| Investigations | | |
| Increased alanine aminotransferase | 8 (3%) | 13 (5%) |
| Nervous system disorders | | |
| Headache | 4 (1%) | 2 (1%) |
| Respiratory, thoracic, and mediastinal disorders | | |
| Dyspnoea | 7 (2%) | 7 (2%) |
| Haemoptysis | 0 | 3 (1%) |
| Skin and subcutaneous tissue disorders | | |
| Rash | 4 (1%) | 0 |
| Adverse event of interest | | |
| Increased ALT grade ≥ 2 | 59 (21%) | 55 (19%) |
| Increased ALT grade ≥ 3 | 20 (7%) | 17 (6%) |
| Rash grade ≥ 2 | 21 (7%) | 24 (8%) |
| Rash grade ≥ 3 | 3 (1%) | 1 (<1%) |
| Rash grade ≥ 2 and increased ALT or bilirubin grade ≥ 3 | 4 (1%) | 3 (1%) |
| Rash grade ≥ 3 and increased ALT or bilirubin grade ≥ 2 | 3 (1%) | 1 (<1%) |
| Adverse event leading to NNRTI substitution | | |
| Hepatitis | 11 (4%) | 0 |
| Rash | 3 (1%) | 0 |
| Acute psychiatric disorders | 0 | 2 (1%) |

Hepatitis was graded as an increase of ALT or bilirubin of 1.25–2.50 \times ULN (grade 1), >2.50–5.00 \times ULN (grade 2), >5.00–10.00 \times ULN (grade 3), and >10.00 \times ULN (grade 4). NNRTI=non-nucleoside reverse transcriptase inhibitor. ALT=alanine aminotransferase. ULN=upper limit of normal. *By system organ class and preferred term according to Medical Dictionary for Regulatory Activities coding.²³ †Two recurrences and one death from tuberculosis.

Table 5: Treatment-emergent adverse events, serious adverse events, and adverse events of interest in the safety population

nevirapine without a lead-in dose. Non-inferiority of the nevirapine-regimen was not shown in our intention-to-treat or per-protocol populations. However, rates of

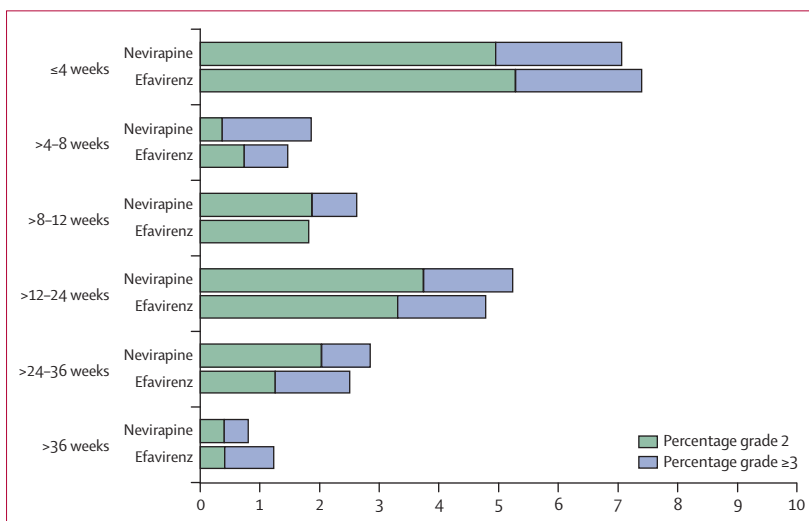


Figure 4: Patients presenting with an increase of alanine aminotransferase of grade 2 or grade 3 intensity during follow-up in the safety population

immune reconstitution, death, and incident AIDS events did not differ between the two groups. Our switch-equals-failure analysis in the intention-to-treat population favoured the efavirenz regimen, which resulted in six treatment substitutions compared with 15 for patients randomly allocated to receive the nevirapine regimen. All substitutions were made because of safety reasons or pregnancy and none was attributed to loss of efficacy.

Several reasons might explain why nevirapine did not show non-inferiority. One possibility is that the two tested regimens have the same efficacy, and that the rifampicin interaction drives the difference in virological response. Indeed, the large non-inferiority randomised clinical 2NN trial²³ comparing nevirapine-based and efavirenz-based regimens in patients with HIV but not tuberculosis reported no significant differences in virological efficacy between groups at 48 weeks (HIV-1 RNA threshold of 50 copies per mL). A Cochrane meta-analysis²⁵ of seven randomised clinical trials (60% of participants were from the 2NN study²³) also failed to show a significant difference between the two regimens. The 2NN study²³ thus could not show the non-inferiority of the nevirapine-based regimen. However, several findings from our study suggest that the significant difference in virological response between the two groups could have been attributable to nevirapine's lower intrinsic potency rather than to the interaction with rifampicin. First, the difference remained the same during and after tuberculosis treatment (which was discontinued at week 24) and seemed more pronounced at week 48. Second, although not representative of all patients, the nevirapine trough concentrations from the first 20 patients enrolled in the trial showed a median minimum concentration of 4.9 mg/L, which is higher than the minimum therapeutic concentration of 3 mg/L.¹⁹ Finally, the 48 week efficacy of the nevirapine regimen in our study (64.6%)

was in the range (61–69%) reported from randomised trials that used the same regimen in patients with HIV without tuberculosis co-infection.^{23,26–28} The hypothesis that nevirapine has a lower intrinsic antiviral potency than does efavirenz is also supported by recent results of the HIV-CAUSAL prospective cohort²⁹ which reported 54% more virological failures in patients after 12 months on an nevirapine regimen than on an efavirenz regimen, and by a review³⁰ of studies comparing nevirapine and efavirenz in tenofovir-based regimens, which concluded that nevirapine regimens also show increased rates of virological failure.

Our results differ from those obtained in the two previous randomised trials comparing nevirapine-based and efavirenz-based regimens in patients co-infected with HIV and tuberculosis (panel). The N₂R study¹³ from Thailand did not report differences in 48 week efficacy between the nevirapine (71·8%) and efavirenz (73·2%) regimens in their intention-to-treat population. However, the trial was not sufficiently powered (140 patients) to show non-inferiority of the nevirapine regimen. The second study, a non-inferiority trial from India,¹¹ was halted by the IDMC because of a lower efficacy noted in the nevirapine group (65%; once-daily nevirapine) than in the efavirenz group (85%) at week 24 with an HIV-1 RNA threshold of 400 copies per mL. A post-hoc analysis with the same cutoff in our trial did not show a significant difference: 219 (77%) of 285 patients in the nevirapine group versus 230 (81%) of 285 in the efavirenz group

($p=0\cdot2599$). These conflicting results might be explained by differences in nevirapine administration (once-daily vs twice-daily or whether escalating dosage was used), methodological differences, differences in treatment adherence, and genetic differences in NNRTI disposition that lead to variability between individuals in plasma clearance, effect, and tolerance.³¹

Although introduced at full dose, nevirapine was well tolerated in our study, with a low rate of severe biological hepatic toxicity (7%) compared with the 10% average reported in previous trials of patients with HIV without tuberculosis co-infection, and the proportion of severe rash was very low (1%).³² This low incidence of rash was probably attributable to the low baseline CD4 cell counts in patients starting treatment in this trial but might be also explained by a genetic variation of nevirapine metabolism, resulting in diminished plasma concentration of the metabolite 12 hydroxy-nevirapine, which is associated with a lower risk of nevirapine-induced rash.³³

Our trial has several limitations. First, despite appropriate randomisation (baseline characteristics did not differ between the two groups), slightly fewer patients with smear-positive pulmonary tuberculosis were enrolled in the nevirapine group than in the efavirenz group. Second, the proportion of patients who had pulmonary tuberculosis confirmed with *M tuberculosis* culture was low in comparison with microscopy results. In Mozambique, such culturing is not part of routine tuberculosis diagnosis. However, in this trial it was done once patients were referred to the trial sites, on average, 2 weeks after the start of tuberculosis treatment, whereas microscopy tests were done before tuberculosis treatment was started at the clinic. Because of this delay, some cultures might have tested negative. Moreover, the challenges of shipping sputum samples abroad for this test resulted in a high rate of specimen contamination (7%). Third, several patients withdrew from the trial after migrating to South Africa during follow-up and were no longer able to access the study sites. Most of these patients left the trial after 24 weeks of follow-up and slightly more voluntary withdrawals occurred in the efavirenz arm, which could not be explained. Nonetheless, such a pattern of withdrawal is unlikely to be related to a poor efavirenz tolerability because most withdrawals occurred after 24 weeks after the start of antiretroviral therapy. Fourth, the risk of bias in investigators' management of an open-label design should not be ignored. However, the efficacy outcome and hepatitis, one of the main safety outcomes, were established principally from laboratory results. Finally, the choice of a predefined 10% non-inferiority margin merits discussion. Some investigators suggest adoption of a larger non-inferiority efficacy margin of 12% with 95% power on the basis of HIV trials in previously untreated patients that suggest such trials are often overpowered because of an underestimation of the success rates and that a loss of efficacy could be accepted

Panel: Research in context

Systematic review

We searched PubMed for randomised controlled trials published in English between Jan 1, 1970, and Nov 31, 2012, with the following search string: ("tuberculosis"[Text Word]) AND "nevirapine"[Text Word] OR ("tuberculosis"[Text Word] AND "non-nucleoside reverse transcriptase inhibitor"[Text Word]) OR ("antiretroviral therapy"[Text Word] AND "tuberculosis"[Text Word]). We identified only two randomised controlled trials that compared nevirapine-based and efavirenz-based antiretroviral therapies in patients co-infected with HIV and tuberculosis treated with rifampicin.^{11,13} One of these trials¹¹ assessed once-daily nevirapine and was prematurely halted because of the reduced efficacy (65%) in the nevirapine group compared with the efavirenz group (85%) at week 24. The other trial¹³ did not show a significant difference in the 48 week virological efficacy between the nevirapine and efavirenz groups but was not powered to show non-inferiority of the nevirapine regimen. In both trials, the nevirapine-escalating dose was used, which could result in subtherapeutic nevirapine concentrations at antiretroviral therapy initiation in patients on rifampicin.

Interpretation

To our knowledge, our trial is the first to compare a nevirapine regimen with an efavirenz regimen in patients co-infected with HIV and tuberculosis without use of a nevirapine escalating dose and the first to have sufficient power for a non-inferiority analysis. Although non-inferiority of the nevirapine regimen was not shown in our study, efficacy results at 48 weeks were comparable with those reported for patients with HIV but not tuberculosis and the co-administration of nevirapine and rifampicin was well tolerated. Nevirapine might therefore be regarded as an acceptable alternative in patients unable to tolerate efavirenz or who have a contraindication to efavirenz.

if the new treatment has some other advantage.³⁴ In our trial, the estimated success rate was not underestimated but the choice of higher non-inferiority margin (12%) might have slightly changed the results of the trial but not the conclusion.

Few alternatives to efavirenz exist for patients co-infected with HIV and tuberculosis. Use of a triple nucleoside reverse transcriptase inhibitor regimen is not ideal because of its reduced efficacy (especially in patients with a high HIV-RNA at treatment initiation) compared with the efavirenz regimen in patients with HIV without tuberculosis.^{1,23,35} Replacement of rifampicin by rifabutin, a weaker enzyme inducer, would preclude use of a fixed-dose combination-based tuberculosis therapy (a cornerstone of the WHO tuberculosis control strategy), thereby making treatment much more expensive.³⁶ The use of a 600 mg maintenance dose of nevirapine has been also suggested but was associated with an increased rate of hypersensitivity reactions and premature termination of a randomised trial from Thailand.³⁷

Overall, non-inferiority of the nevirapine regimen in terms of efficacy for patients co-infected with HIV and tuberculosis was not shown in this trial. This outcome might be attributed to a slightly reduced intrinsic potency of nevirapine compared with efavirenz rather than to co-administration with rifampicin. However, we also noted that initiation of nevirapine at full dose showed 48 week efficacy results comparable with those reported for patients with HIV but not tuberculosis, and was well tolerated. Nevirapine could therefore be regarded as an acceptable alternative in patients unable to tolerate efavirenz or who have a contraindication to efavirenz.

Contributors

MB and AC conceived and designed the study. MB and NB implemented and led the study. EB designed and did the statistical analysis. EB and CS were in charge of the data management of the trial. AS, CM, A-MT, LC, RB, EN, CR, IJ, and AC critically revised the study design, contributed to the interpretation of results, and were members of the trial scientific advisory board. IJ coordinated the laboratory analysis, CR coordinated the virological analyses, and A-MT coordinated the pharmacological analyses. MB wrote and prepared the report. All authors reviewed and approved the final version of the report.

CARINEMO study group

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Conflicts of interest

We declare that we have no conflicts of interest.

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