Efficacy and Safety of Once-Daily Nevirapine- or Efavirenz-Based Antiretroviral Therapy in HIV-Associated Tuberculosis: A Randomized Clinical Trial

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Background. Nevirapine (NVP) can be safely and effectively administered once-daily but has not been assessed in human immunodeficiency virus (HIV)–infected patients with tuberculosis (TB). We studied the safety and efficacy of once-daily NVP, compared with efavirenz (EFV; standard therapy); both drugs were administered in combination with 2 nucleoside reverse-transcriptase inhibitors.

Methods. An open-label, noninferiority, randomized controlled clinical trial was conducted at 3 sites in southern India. HIV-infected patients with TB were treated with a standard short-course anti-TB regimen ($2EHRZ_3/4RH_3$; [2 months of Ethambutol, Isoniazid, Rifampicin, Pyrazinamide / 4 months of Isoniazid and Rifampicin] thrice weekly) and randomized to receive once-daily EFV at a dose of 600 mg or NVP at a dose of 400 mg (after 14 days of 200 mg administered once daily) with didanosine 250/400 mg and lamivudine 300 mg after 2 months. Sputum smears and mycobacterial cultures were performed every month. CD4+ cell count, viral load, and liver function test results were monitored periodically. Primary outcome was a composite of death, virological failure, default, or serious adverse event (SAE) at 24 weeks. Both intent-to-treat and per protocol analyses were done, and planned interim analyses were performed.

Results. A total of 116 patients (75% [87 patients] of whom had pulmonary TB), with a mean age of 36 years, a median CD4+ cell count of 84 cells/mm^3, and a median viral load of 310 000 copies/mL, were randomized. At 24 weeks, 50 of 59 patients in the EFV group and 37 of 57 patients in the NVP group had virological suppression ($P = .024$). There were no deaths, 1 SAE, and 5 treatment failures in the EFV arm, compared with 5 deaths, 2 SAEs, and 10 treatment failures in the NVP arm. The trial was halted by the data and safety monitoring board at the second interim analysis. Favorable TB treatment outcomes were observed in 93% of the patients in the EFV arm and 84% of the patients in the NVP arm ($P = .058$).

Conclusions. Compared with a regimen of didanosine, lamivudine, and EFV, a regimen of once-daily didanosine, lamivudine, and NVP was inferior and was associated with more frequent virologic failure and death.

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Tuberculosis (TB) is often the first manifestation of human immunodeficiency virus (HIV) infection in countries with a high prevalence of TB [1]. Coinfected patients presenting with TB are often immunosuppressed and in need of antiretroviral treatment (ART). In 2009, it was estimated that, of the 9.4 million new TB cases worldwide, approximately 1.1 million were in individuals coinfected with HIV, and these cases accounted for 27% of TB-related deaths. Because of rapid scale-up of testing worldwide, an increasing number

of coinfected patients are being identified [2]. The World Health Organization now recommends ART for all patients with TB and HIV coinfection regardless of CD4+ cell count, to be initiated within a few weeks of TB treatment [3–8]. Proposed regimens include combinations of 2 nucleoside reverse-transcriptase inhibitors (NRTIs) and a nonnucleoside reverse-transcriptase inhibitor (NNRTI), with costs and toxicity varying depending on the choice of drugs [8].

For treatment of TB in patients with HIV infection, regimens that contain rifampicin throughout the treatment period have better outcomes (lower treatment failure and recurrence rates) than do nonrifampicin regimens [9–11]. However, simultaneous treatment of both infections is complicated by the fact that rifampicin, a potent inducer of the hepatic cytochrome P450 enzymes, leads to a reduction in levels of NNRTIs in blood [12, 13]. Of the 2 widely available NNRTIs, efavirenz (EFV) is the preferred drug for coadministration with rifampicin because it is associated with less drug interaction and is administered with once-daily dosing [14, 15]. However, nevirapine is the most widely used NNRTI worldwide, because it is inexpensive, nonteratogenic, and available in fixed-drug combinations. Although nevirapine (NVP) can be administered once daily with efficacy and safety equivalent to that associated with twice-daily treatment in HIV-infected patients, no studies of once-daily treatment have been conducted among patients receiving anti-TB treatment (ATT) [16, 17]. Retrospective cohort analyses of patients initiating ART (twice-daily nevirapine) while receiving ATT have had conflicting results with respect to virologic outcomes [18, 19].

We performed a randomized controlled clinical trial to compare the efficacy and safety of a once-daily ART regimen of didanosine, lamivudine, and NVP with a standard regimen of didanosine, lamivudine, and EFV among patients with HIV-1 infection and TB. If NVP used once-daily in combination with rifampicin were found to be safe and noninferior to EFV, such a regimen would be practical, affordable, and lend itself to directly observed treatment. Drugs that had evidence for once-daily use and were available in India in 2003 were selected for this trial.

METHODS

Study Design and Setting

This was an open label, parallel arm, randomized controlled clinical trial. The study was conducted at 3 sites of the Tuberculosis Research Centre (TRC) in Chennai, Vellore, and Madurai, located in southern India, during the period May 2006–June 2008.

Inclusion and Exclusion Criteria

HIV-infected patients who were at least 18 years of age with newly diagnosed TB, were nonpregnant, and had CD4+ cell counts <250 cells/mm^3 were eligible. Exclusion criteria included previous ATT or ART for >1 month, HIV-2 infection, major psychiatric illness, aspartate aminotransferase and alanine aminotransferase levels >2.5 times the upper limit of normal and having a severe non–HIV-related disease. The protocol was approved by the institutional and national ethics committees, and written informed consent was obtained from all patients. The trial was registered in the National Institutes of Health Clinical Trials Registry, NCT 00332306, and the full protocol is available upon request.

Recruitment and Randomization

At study entry, patients had a complete history and physical examination, chest radiograph posterior-anterior view, and laboratory investigations that included hematological analysis (ABX Pentra60; Horiba ABX Diagnostics), CD4+ cell counts (Beckman Coulter Epics XL), HIV-1 RNA level (Roche Amplicor, version 1.5), blood glucose levels, and liver and renal function tests (Olympus AU400). Three sputum specimens (1 spot and 2 overnight samples) were collected for acid-fast bacillus smear and culture, and relevant investigations were performed for diagnosis of extra-pulmonary TB. Smears were stained with auramine-rhodamine and examined by fluorescent microscopy; sputum was processed by modified Petroff's method and cultured on Lowenstein-Jensen medium [20, 21]. Extra-pulmonary TB was diagnosed based on cyto- and histopathological (for lymph node specimens) or radiographic and biochemical (for pleural effusion specimens) parameters. All microbiological and laboratory investigations were done by technicians blinded to the treatment given.

Permuted block randomization (blocks of 8) was done centrally using a computer-generated list of random numbers, stratified by site and 2 levels of CD4+ cell count ($\leq$150 vs $>$150 cells/mm^3) and viral load ($\leq$50 000 vs $>$50 000 copies/mL) each. Allocation codes concealed in sealed, opaque, sequentially numbered envelopes were prepared by statisticians and provided to each site for patient enrollment by study physicians.

Study Intervention

All patients received the standard national anti-tuberculosis regimen with isoniazid, rifampicin, ethambutol, and pyrazinamide for the first 2 months followed by isoniazid and rifampicin for the subsequent 4 months, thrice-weekly throughout. Dosages of drugs were as follows: isoniazid, 600 mg; rifampicin, 450/600 mg for body weight $<$ or $\geq$60 kg; ethambutol, 1200 mg; and pyrazinamide, 1500 mg. After the intensive phase, patients were randomized to one of the anti-retroviral regimens, along with the continuation phase of ATT. The study regimen was didanosine, lamivudine, and nevirapine, whereas the control regimen was didanosine, lamivudine, and efavirenz. Dosages used were as follows: didanosine, 250/400 mg for body weight $<$ or $\geq$60 kg; lamivudine, 300 mg; efavirenz,

600 mg; and nevirapine, 400 mg (after 14 days of 200 mg) once-daily. Every batch of drugs was assayed to ensure quality [22]. All drugs were administered under direct observation in the clinic 3 days a week and supplied to the patient for the remaining days. In addition to ATT and ART, patients received 1 tablet of trimethoprim-sulfamethoxazole at double strength, pyridoxine 10 mg, and multivitamins daily, in combination with psychosocial and adherence counseling.

Clinical and Laboratory Follow-up

Patients were followed up every month with a review of adherence, new symptoms, and possible toxicity. Complete blood counts, CD4+ cell counts, and HIV-1 RNA levels were measured at 4, 16, and 24 weeks after ART initiation. Liver function was assessed every 2 weeks until the eighth week and then once every 12 weeks. Three specimens of sputum were collected each month for smear and culture for *Mycobacterium tuberculosis*. A chest radiograph was taken at the end of the intensive phase, at the end of ATT, and in the event of clinical deterioration. Additional investigations were done as per clinical indication.

Study Endpoints

The primary composite study endpoint was related to the efficacy of the ART regimen at 24 weeks: death, HIV-1 RNA level >400 copies/mL, default, or termination of study drug as a result of toxicity were considered unfavorable. With respect to pulmonary TB, the response was considered favorable if all sputum cultures were negative in the last 2 months of treatment. Unfavorable responses to ATT included failure (clinical or bacteriological), default, or death due to TB. For extra pulmonary TB, favorable response was defined as improvement of symptoms, regression of lymph nodes, and/or radiographic improvement.

Statistical Analysis

We assumed a favorable virologic response rate of 90% at 24 weeks with the control (EFV) regimen and a noninferiority margin of 15% for the NVP regimen. With a power of 80% and a significance level of 5%, the sample size per group was 90, allowing for a 20% loss due to death or loss to follow-up.

Both the intent-to-treat (ITT) and per-protocol analysis were performed using SPSS software, version 11.3 (SPSS). For per-protocol analysis, only patients with >90% adherence (estimated by pill counts during surprise home visits and directly observed treatment) were considered. The χ^2 test was used to compare the proportion of patients who had a favorable response and relative risk was calculated. Interim analyses were planned after 25%, 50%, and 75% of enrolled patients completed 24 weeks of ART, to be reviewed by the data safety monitoring board (DSMB). Prespecified stopping rules were based on the O'Brien–Fleming boundary for significance, which maintained an overall P value of .05 [23].

RESULTS

Baseline Characteristics

Five hundred and sixty-four patients with suspected TB and HIV coinfection were screened; 122 met the initial inclusion criteria and were enrolled. A total of 116 (93 men and 23 women) were randomized to an antiretroviral regimen at 2 months: 59 were randomized to the EFV regimen, and 57 were randomized to the NVP regimen (Figure 1). The DSMB halted enrollment to the study after the second interim analysis, because the difference in response between the regimens had crossed the O'Brien–Fleming significance boundary.

At baseline, the 2 groups had similar demographic and clinical characteristics (Table 1). Two-thirds of patients had intrathoracic TB; radiographic lesions included parenchymal opacities, pleural effusion, hilar adenopathy, and miliary TB. Baseline cultures were positive for *M. tuberculosis* in 46 patients in the EFV arm and 40 patients in the NVP arm. A total of 105 patients completed 24 weeks of follow-up after ART initiation, whereas 6 were lost to follow up and 5 died.

Treatment Outcomes

Primary Study Outcome (ITT). The proportion of patients alive, on the same regimen, and with HIV RNA levels <400 copies/mL was significantly higher with the EFV regimen (50 [85%] of 59 patients) than with the NVP regimen (37 [65%] of 57) ($P = .024$). The point estimate of the difference in efficacy between the regimens was 20% (95% confidence interval [CI], 11.2%–28.8%). Figure 2*A* shows the absolute number of patients with detectable viral load > 400 copies/mL at various time points. The proportion with viral load <400 copies/mL was 70% and 63% at 4 weeks, 96% and 76% at 16 weeks, and 85% (95% CI, 76%–94%) and 65% (95% CI, 53%–77%) at 24 weeks in the EFV and NVP arms, respectively. The relative risk of treatment failure in the NVP arm was 1.28 (95% CI, 1.03–1.6). There were 5 virological failures and no deaths in the EFV arm versus 10 virological failures and 5 deaths in the NVP arm. One patient terminated EFV treatment because of psychosis, and 2 patients in the NVP arm switched therapy to EFV because of Stevens–Johnson syndrome. Three patients defaulted in each group.

Ninety-two percent of the EFV group and 93% of the NVP group had >90% adherence to study drugs (P = not significant) and were included in the per-protocol analysis. Fifty (91%) of 55 patients in the EFV group (95% CI, 83%–99%) and Thirty-six (70%) of 52 patients in the NVP group (95% CI, 58%–82%) had an undetectable viral load at week 24 ($P = .006$).

Response to ATT. Baseline drug susceptibility results were available for 78 patients: 3 isolates were resistant to isoniazid alone, 3 isolates were resistant to streptomycin alone, and 1 patient had multidrug-resistant TB. At the end of intensive

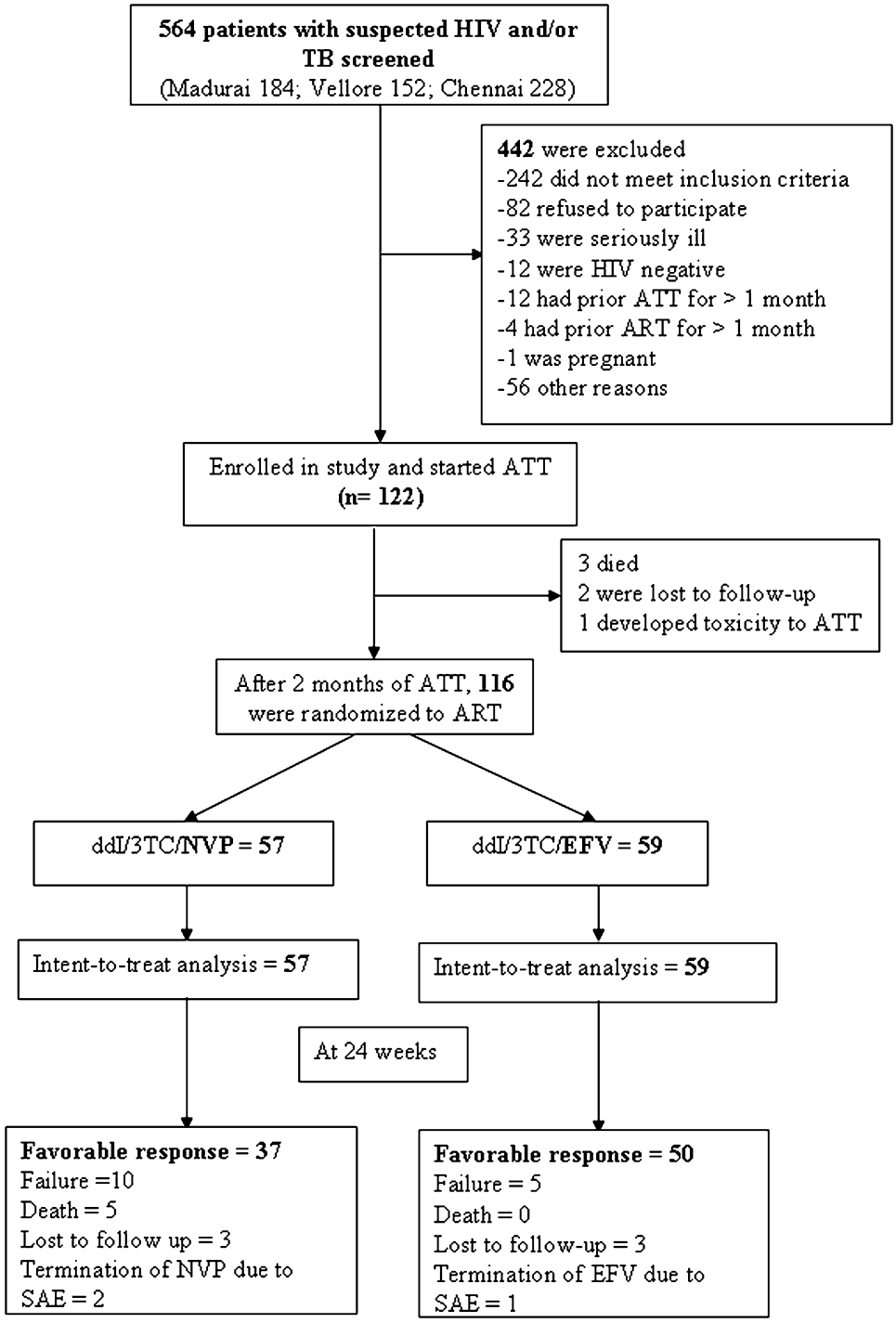

Figure 1. Trial profile.

phase, sputum smears were negative in 82% of the patients, whereas culture results were negative in 88% of the patients. At the end of ATT, 55 patients (93%) in the EFV arm and 48 patients (84%) in the NVP arm had a favorable response ($P = .058$). One patient experienced treatment failure and 3 patients defaulted in the EFV arm, whereas there were 3 deaths (including in the patient with multidrug-resistant TB), 3 treatment failures (2 clinical failures and 1 bacteriological failure), and 3 defaulters in the NVP arm.

Change in Clinical and Laboratory Parameters. With ATT and ART, patients in both regimens demonstrated significant increases in weight (with mean weight [± standard deviation {SD}] increasing from 42.6 ± 8.5 kg to 49.2 ± 8.4 kg and from 41.6 ± 7.6 kg to 48.1 ± 7.7 kg]); body mass index (BMI),

Table 1. Pretreatment Characteristics of Patients in Intent-to-Treat Analysis

Characteristic of study subjects	Efavirenz regimen (n = 59)	Nevirapine regimen (n = 57)
Age, mean years (±SD)	34.4 ± 7.5	37.8 ± 7.7
Male sex, no. (%) of subjects	49 (83)	44 (77)
BMI, mean value (±SD)	16.3 ± 2.6	16.4 ± 2.4
CD4+ cell count, median cells/mm^3 (IQR)	85 (47–85)	83 (33–135)
Viral load, median copies/mL (IQR)	362 000 (41 575–750 000)	282 000 (128 500–649 500)
Pulmonary TB		
Sputum culture positive, no. (%) of subjects	43 (73)	37 (65)
Sputum culture negative, no. of subjects	2	5
Extra-pulmonary TB, no. of subjects		
Overall	14	15
Culture positive (lymph node/pleural effusion)	3	3
Culture negative	11	12

Abbreviations: BMI, body mass index defined as the weight in kilograms divided by the square of height in meters; IQR, interquartile range; SD, standard deviation; TB, tuberculosis.

defined as the weight in kilograms divided by the square of height in meters (with mean BMI [± SD] increasing from 16.3 ± 2.6 to 18.6 ± 2.3 and from 16.3 ± 2.3 to 18.9 ± 2.4), and hemoglobin level (with mean hemoglobin level [± SD] increasing from 11.4 ± 1.8 g/dL to 12. 9 ± 2.2 g/dL and from 9.5 ± 2.0 g/dL to 12.7 ± 2.7 g/dL) in the EFV and NVP groups, respectively ($P < .05$ for all). There were no significant changes in mean liver or renal function parameters or serum amylase levels in either arm (results not shown). Figure 2*B* shows the change in CD4+ cell count; the mean increase (±SD) at 24 weeks was 215 ± 101 cells/mm^{3}and 201 ± 101 cells/mm^3 in the EFV and NVP groups, respectively (P = not significant).

Adverse Drug Reactions. There were a total of 57 adverse drug reactions in the EFV arm: 44 cases of grade I or grade II dizziness, 6 cases of rash, 5 cases of gastrointestinal symptoms (including 2 of jaundice that required temporary withholding of drugs), and 1 case each of psychosis and peripheral neuropathy (requiring substitution of the offending drug). In the NVP arm, there were 33 adverse drug reactions, including 16 neurological, 3 gastrointestinal, and 14 cutaneous events (including 2 cases that required substitution with a different drug) (Table 2). Serious adverse events included 2 cases of severe peripheral neuropathy, secondary to receipt of didanosine, which required switching treatment to tenofovir (1 case in each study arm), 1 case of EFV-induced psychosis, and 2 cases of Stevens–Johnson syndrome associated with receipt of NVP (Table 3). There were no deaths attributable to adverse drug reactions.

Immune Reconstitution Inflammatory Syndrome. Twenty-five (21%) of 116 patients had symptoms suggestive of immune reconstitution inflammatory syndrome (IRIS). There was radiographic deterioration in 10 patients and extrapulmonary manifestations in 15 (8 patients had lymph node enlargement, 1 patient had tuberculoma, and 6 patients had pleural effusion).

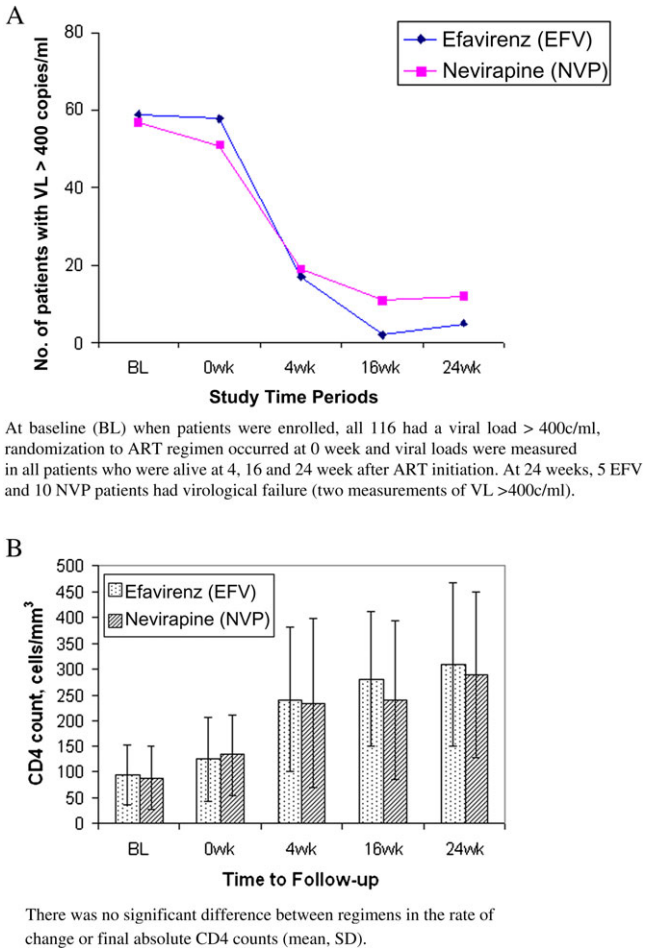

Figure 2. *A*, Virological response to treatment for patients available for evaluation over time (no. of patients with viral load >400 copies/mL). *B*, Immunological response to treatment (mean CD4+ cell count) over time for all evaluable patients.

Table 2. Incidence and Severity of Adverse Events in the Study Population, by Regimen

	Efavirenz regimen, by grade					Nevirapine regimen, by grade				
Adverse event	Total	I	II	III	IV	Total	I	II	III	IV
Neurological	46	35	9	1	1	16	9	6	1	
Paraesthesia		11	4	1 (D)[a]			9	2	1 (D)[a]	
Vivid dreams		3						1		
Dizziness		21	5					3		
Major depression					1 (D)[b]					
Gastrointestinal	5	1	2		2	3	1	1		1
Abdominal pain		1					1			1 (T)
Vomiting			2					1		
Hepatitis/jaundice					2 (T)					
Cutaneous	6	5	1			14	9	2	1	2
Stevens Johnson syndrome										2 (D)[c]
Itching		3	1				8	2		
Rash		2					1		1	
Total	57	41	12	1	3	33	19	9	2	3

Abbreviations: D, terminated and replaced with different drug; ddI, didanosine; EFV, efavirenz; NVP, nevirapine, T, temporarily withheld.

[a] ddI replaced with tenofovir.

[b] EFV replaced with NVP.

[c] NVP replaced with EFV.

Six patients became asymptomatic without any intervention, 10 patients received anti-inflammatory drugs, and 9 patients received a course of corticosteroids.

Deaths. All 5 deaths in our study were related to neurological complications of HIV infection: 2 were due to neuroencephalopathy, 1 was due to cerebellar syndrome, 1 was due to toxoplasmosis with disseminated *M. kansassi* infection, and 1 was due to possible TB meningitis. Although 3 patients died during the first month of ART, 2 died in the fifth month. None of the deaths were considered to be due to IRIS, although this could not be definitively ruled out.

DISCUSSION

This open-label, randomized clinical trial demonstrated that didanosine, lamivudine, and NVP administered once daily was inferior (65% efficacy) to didanosine, lamivudine, and EFV (85% efficacy) among HIV-infected patients receiving concomitant anti-TB therapy. Per-protocol analysis among patients with >90% treatment adherence confirmed the results, with efficacy of 70% and 91%, respectively. No previous randomized trial has compared once-daily NVP and EFV among patients with HIV infection and TB, although most programs and clinicians prefer the use of EFV because of pharmacokinetic and safety reasons [8, 24–26].

Two retrospective cohort studies in South Africa and Thailand among patients starting ART with concurrent TB reported lower rates of virologic suppression with NVP, compared with EFV [18, 19]. Furthermore, a regimen of didanosine, lamivudine, and EFV has excellent results in terms of both virological efficacy and safety when used with and without ATT [27–29]. Although clinical trials have demonstrated that once-daily NVP is as effective as twice-daily administration, none have tested its use among patients with concomitant TB [14, 15].

Table 3. Drug-Induced Serious Adverse Events (SAEs), by Regimen

Patient	Trial regimen	Offending drug	Diagnosis	Action taken	Month of SAE	Outcome
1	NVP	NVP	Steven-Johnson syndrome	Switched to EFV	3	Resolved
2	NVP	NVP	Steven-Johnson syndrome	Switched to EFV	1	Resolved
3	NVP	Possibly ddI	Possible pancreatitis; possible gastritis	ART withheld	2	Improved
4	NVP	ddI	Sensory/motor peripheral neuropathy	Switched to tenofovir	3	Improved
5	EFV	ddI	Sensory/motor peripheral neuropathy	Switched to tenofovir	3	Improved
6	EFV	EFV	Psychosis	Switched to NVP	1	Resolved

Abbreviations: ART, antiretroviral therapy; ddI, didanosine; EFV, efavirenz; NVP, nevirapine.

Response to TB treatment was marginally better in the EFV arm than in the NVP arm. Concomitant ART improves TB outcomes; we had earlier demonstrated a favorable response of 83% in ART-naive patients using the same TB regimen [30]. Recent studies have demonstrated lower mortality among coinfected patients (CD4+ cell count, <500 cells/mm^3) who initiated ART early, compared with those for whom ART was deferred [4, 5]. The Cambodian Early versus Late Introduction of Antiretroviral drugs (CAMELIA) and ACTG522I trials have demonstrated the benefit of earlier initiation of ART therapy in patients with TB and HIV coinfection with very low CD4+ cell counts (<50 cells/mm^3) [31, 32]. In our study, we had 37 patients with a baseline CD4+ cell count <50 cells/mm^3 (15 in the EFV arm and 22 in the NVP arm). There was no mortality among patients in the EFV group despite low CD4+ cell counts, whereas the outcome in the NVP arm was probably related to the performance of the regimen (which resulted in subtherapeutic NVP levels during the lead-in phase) and not the timing of ART initiation. Therefore, although earlier ART initiation might have improved outcomes, it is unlikely to have altered the difference in response between the 2 regimens, which was the primary question addressed by this study.

The overall incidence of adverse events in our trial was low, and most were easily managed. The most common adverse effects were dizziness and sleep disturbances associated with receipt of EFV; the majority of adverse effects were mild and subsided within the first few days of treatment. There were 2 cases of grade III/IV hepatotoxicity in the EFV arm, which improved after temporary withdrawal of drugs. In previous cohorts, reported rates of hepatotoxicity have been low and comparable between EFV and NVP when those drugs are administered in combination with rifampicin, although rates have been higher than among patients without TB [26, 33]. However, peripheral neuropathy was of concern and may have been aggravated by the concomitant use of didanosine and isoniazid among patients with advanced HIV disease. Although most patients responded to symptomatic treatment, which included analgesics, nonsteroidal anti-inflammatory drugs, high-dose pyridoxine, and carbamezapine, 2 patients required the substitution of didanosine with tenofovir. Although cutaneous reactions have been reported to be more common in patients who receive once-daily NVP, these were mostly mild in our study; 2 patients with NVP-induced Stevens–Johnson syndrome recovered with symptomatic treatment and tolerated EFV well later, which was the only treatment option available [34].

Primary drug resistance to antiretroviral drugs was negligible among this population. At the time of treatment failure, V106M and Y181C were the major NNRTI mutations, whereas M184V and L741/V were the common NRTI mutations [35].

The strengths of our study include the generalizability of the study findings, given the degree of immunosuppression at baseline, which is typical for TB and HIV coinfection cohorts in resource-limited settings. The comparability of the randomized groups, the close clinical and laboratory monitoring, oversight by DSMB and ethics committees, the observation of treatment thrice weekly, the high rates of adherence to treatment, and the extensive follow-up are other strengths. Limitations include the early stopping of the trial by the DSMB, which limits the conclusions that can be drawn; however, the halting of the trial was based on prespecified stopping rules. The use of tenofovir instead of didanosine may have improved tolerability, but cost considerations and the availability of generics determined the choice of drugs. Furthermore, ART was not used during the intensive phase of ATT. Now evidence suggests that patients with CD4+ cell counts <50 cells/mm^3 should initiate ART during the first weeks of ATT [31]. Furthermore, NVP could have been initiated without the lead-in phase, because liver enzymes were in an induced state because of rifampicin; however, safety concerns and a lack of pilot data dissuaded us from following this option. A recent report on rifampicin-treated patients from Thailand showed that, although a 200-mg NVP lead-in dose led to significant short-term suboptimal NVP concentrations, a higher lead-in of dose of 400 mg followed by 600 mg per day was associated with a high rate of NVP hypersensitivity [36]. Future research should explore the possibilities of using rifabutin instead of rifampicin for TB treatment in these patients. We used thrice-weekly therapy because this is the standard TB treatment regimen in India, although recent evidence suggests that this regimen may be suboptimal for patients infected with HIV [37].

Our study contributes to the growing body of literature on optimal treatment of HIV-infected patients with TB [37, 38]. Although the once-daily treatment concept is attractive because of convenience, greater adherence among patients, and the possibility of directly observed therapy, our results indicate that NVP cannot be used once daily in combination with rifampicin-containing ATT. The once-daily regimen of didanosine, lamivudine, and EFV was safe, efficacious, and well-tolerated and had a favorable resistance profile, with low emergence of thymidine-associated mutations among patients with virologic failure.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

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