Outcomes of Nevirapine- and Efavirenz-Based Antiretroviral Therapy When Coadministered With Rifampicin-Based Antitubercular Therapy

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Context Rifampicin-based antitubercular therapy reduces the plasma concentrations of nevirapine and efavirenz. The virological consequences of these interactions are not well described.

Objective To assess the effectiveness and tolerability of concomitant efavirenz- or nevirapine-based combination antiretroviral therapy and rifampicin-based antitubercular therapy.

Design, Setting, and Participants Cohort analysis of prospectively collected routine clinical data in a community–based South African antiretroviral treatment program. Antiretroviral treatment-naive adults enrolled between May 2001 and June 2006 were included in the analysis, and were followed up until the end of 2006.

Interventions Patients starting antiretroviral therapy with or without concurrent antitubercular therapy received either efavirenz or nevirapine at standard doses. Patients developing tuberculosis while taking antiretroviral therapy that included nevirapine were either changed to efavirenz or continued taking nevirapine.

Main Outcome Measures Viral load of 400 copies/mL or more after 6, 12, and 18 months of antiretroviral therapy; time to the first viral load of 400 copies/mL or more; time to confirmed virological failure (2 consecutive values ≥5000 copies/mL); time to death; and time to treatment-limiting toxicity were assessed.

Results The analysis included 2035 individuals who started antiretroviral therapy with efavirenz (1074 with concurrent tuberculosis) and 1935 with nevirapine (209 with concurrent tuberculosis). There were no differences in time to death or substitution of either antiretroviral drug for toxicity with and without concurrent tuberculosis. Patients starting nevirapine with concurrent tuberculosis were at a higher risk of elevated viral load most notably at 6 months (16.3%; 95% confidence interval [CI], 10.6%-23.5%) than those without tuberculosis (8.3%; 95% CI, 6.7%-10.0%; adjusted odds ratio [OR], 2.1; 95% CI, 1.2-3.4; and in the combined estimate, adjusted OR, 1.7; 95% CI, 1.2-2.6). In the time-to-event analysis of confirmed virological failure (2 consecutive values of ≥5000 copies/mL), patients starting nevirapine with concurrent tuberculosis developed virological failure sooner (adjusted hazard ratio [HR] 2.2; 95% CI, 1.3-3.7). There were no differences between patients starting efavirenz with and without concurrent tuberculosis (adjusted OR, 1.1; 95% CI, 0.8-1.5 [combined estimate] and adjusted HR, 1.1; 95% CI, 0.6-2.0, respectively). There was no difference in time to virological rebound in patients free of tuberculosis and those developing tuberculosis during follow-up while taking nevirapine (adjusted HR, 1.0; 95% CI, 0.5-2.0) or efavirenz (adjusted HR, 0.8; 95% CI, 0.4-1.7).

Conclusion In this cohort study, virological outcomes were inferior when nevirapine-based antiretroviral therapy was commenced while taking antitubercular treatment (vs without concurrent tuberculosis) but comparable when starting efavirenz-based antiretroviral therapy (vs without concurrent tuberculosis) or when tuberculosis developed while taking established nevirapine- or efavirenz-based therapies.

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Antiretroviral therapy (ART) programs are rapidly being scaled up in resource-limited countries, where tuberculosis is the most common opportunistic infection.[1] Combination ART is frequently initiated when patients are being treated for tuberculosis.[2,3] Although ART reduces tuberculosis incidence, tuberculosis continues to occur at considerably higher rates than in individuals who are not infected with human immunodeficiency virus (HIV).[1-4] Coadministration of ART and antitubercular therapy may be complicated by shared toxicity, notably hepatotoxicity,[5] or by adverse drug interactions. Rifampicin is a potent inducer of cytochrome P450 enzymes, which metabolize many drugs including nonnucleoside reverse transcriptase inhibitor (NNRTI) antiretroviral agents. The NNRTIs are recommended as components of initial combination ART regimens in the public health approach advocated by the World Health Organization (WHO).[6]

Of the 2 available NNRTIs, efavirenz is preferred for coadministration with rifampicin[6,7] because the reduction in the concentration of efavirenz is more modest, efavirenz has a lower risk of hepato-

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toxicity, and there are several studies showing good ART outcomes with efavirenz.[8,9] Some experts recommend increasing the dose of efavirenz when coadministered with rifampicin,[6] but evidence, including data from a randomized controlled trial,[10] suggests that standard doses are adequate (although there are concerns that there are insufficient data on patients weighing more than 60 kg).[7]

Nevirapine (often in fixed-dose combination formulations) is the most widely used NNRTI in resource-limited countries because it is much cheaper than efavirenz and, unlike efavirenz, is suitable for women of childbearing potential because it is not a known teratogen. In many countries, it is the only available NNRTI. Pharmacokinetic studies show a more significant reduction in plasma nevirapine concentrations (20%-55% reduction in serum concentrations or the area under the curve) compared with efavirenz when coadministered at standard doses with rifampicin.[9,11-16] Nevirapine has a higher risk of hepatotoxicity than efavirenz, although only a small proportion of patients develop clinical hepatitis.[17-19] There are 3 small published studies (32 patients from Spain[20] and 70 patients[21] and 111 patients from Thailand[22]) that suggest that nevirapine can be safely and effectively coadministered with rifampicin. However, the findings from the Thai studies may not be generalizable to other populations due to ethnic differences in drug effects and the low body weight of the patients, and the Spanish study was retrospective without a comparison group.

Thus a need for more studies exists, particularly from Africa where approximately 85% of HIV-associated cases of tuberculosis occur.[4] Our primary objective was therefore to assess the virological outcomes of concomitant efavirenz- or nevirapine-based combination ART and rifampicin-based antitubercular therapy in a cohort of South African patients from a public sector ART program established in 2001.[23]

METHODS

Setting

This study was conducted at 3 community health centers in the Cape Town township of Khayelitsha, where ART has been available since May 2001, with the number of patients starting ART increasing dramatically in recent years. ART-naive individuals enrolled between May 2001 and June 2006 were included in the analysis and were followed up until the end of 2006. The community of 400 000 inhabitants has an extremely high burden of both HIV and tuberculosis, with antenatal HIV seroprevalence of more than 30%,[23,24] and tuberculosis case-finding exceeding 1500 per 100 000 annually.[2] This government program has been supported by Médecins Sans Frontières since inception.

The cohort received approval in 2005 from the University of Cape Town ethics committee for analyses (including those with a view to scientific publication) based on anonymized routine clinical data without requiring informed consent. All data in this analysis were anonymized and had been collected as part of the routine standard of care intervention.

Antiretroviral Therapy Program

Patients were referred to the dedicated HIV services within these community health centers from local clinics and hospitals, as well as from the tuberculosis services and the prevention of mother-to-child transmission program. Once referred, patients accessed treatment based on clinical eligibility, treatment readiness, and clinical severity. Race is not routinely measured as part of clinical or administrative data, but the study site is located in a township in which residents are of black African or mixed ancestry, which describes the patients represented in analyses herein. Women who had been exposed through a regimen intended to prevent mother-to-child transmission to short-course zidovudine or peripartum nevirapine[25] were offered the same first-line ART as other women with and without concurrent tuberculosis.

Antiretroviral drugs were provided weekly or fortnightly for the first 2 months of ART, then monthly until the first suppressed viral load, and thereafter either monthly or bimonthly. Patients were seen by a nurse or physician at each follow-up visit and either received the drugs during the consultation or from a dedicated dispensing room immediately after the consultation. Patients were all provided with weekly pillboxes.

There is a structured adherence promotion program at the antiretroviral clinics, which has previously been described.[26] Adherence is assessed during consultations by pill counts and self-report, especially shortly after initiation of ART and if patients default or experience virological failure. Quantitatively, adherence is indirectly reflected by viral load outcomes and retention in care.

The first-line ART regimen has always consisted of an NNRTI (either efavirenz or nevirapine) together with 2 nucleoside reverse transcriptase inhibitors. Guidelines in use strongly recommended prescribing efavirenz with rifampicin-based antitubercular therapy until 2004 when provincial guidelines changed to allow clinicians to select either nevirapine or efavirenz.[27] Thereafter, clinical practice in the choice of NNRTI with antitubercular therapy varied, with some clinicians continuing to prescribe efavirenz while others prescribed nevirapine.

Standard doses of both efavirenz (600 mg daily) and nevirapine (lead-in dose of 200 mg daily for 2 weeks followed by 200 mg every 12 hours) were used with concurrent tuberculosis treatment in keeping with provincial, national, and international guidelines.[6,27,28] The clinical protocols provide for monitoring of viral load and CD4 cell count every 6 months. Baseline viral loads are no longer universally drawn in treatment-naive adults. Patients are deemed eligible for ART when their CD4 cell count approaches or falls below 200 cells/μL or when they have a WHO clinical stage IV illness other than extrapulmonary tuberculosis. The local definition of virological failure is 2 consecutive viral load measurements of 5000 copies/mL or higher. Viral load tests were performed by the National Health Laboratory Service, initially using the NucliSens HIV-1 QT assay and later the NucliSens EasyQ HIV-1 assay (bioMérieux, Boxtel, the Netherlands).

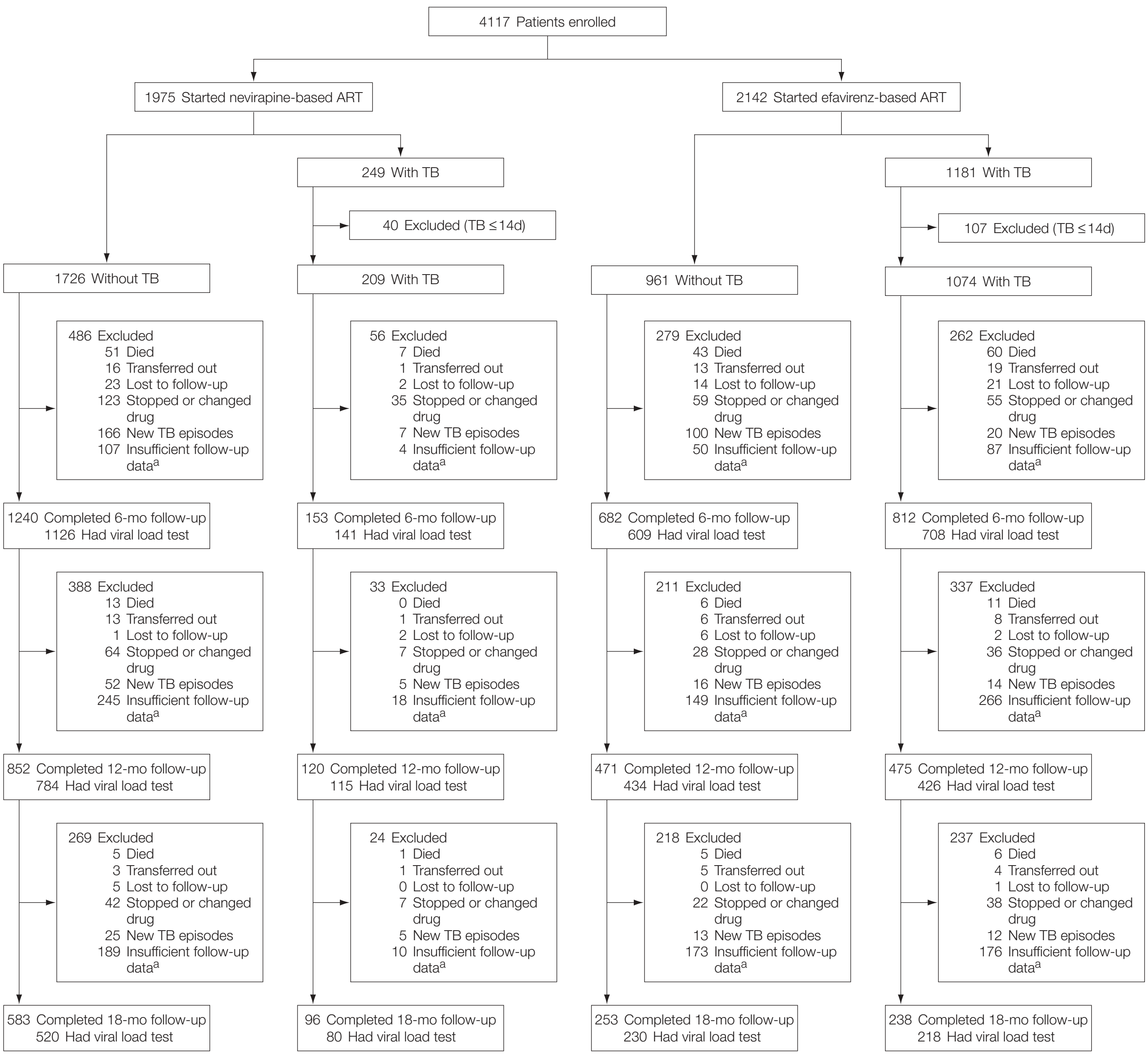
Tuberculosis Services

Tuberculosis medication was provided daily (5 days a week) at 8 dedicated tuberculosis clinics in the community and was directly observed either by clinic staff or by trained community-based tuberculosis treatment supporters. Fixed-dose combinations are used to promote adherence (for new tuberculosis cases, these comprise rifampicin, pyrazinamide, isoniazid, and ethambutol for 2 months, followed by rifampicin and isoniazid for 4 months). Tuberculosis was diagnosed according to standard guidelines, with either positive microscopy for acid-fast bacilli, a positive culture of *Mycobacterium tuberculosis*, or after the application of an algorithm for identifying smear-negative tuberculosis.[29]

Data Management and Analysis

Routine clinical data have been prospectively entered into an electronic patient information system, which is regularly validated for accuracy and complete-

Figure 1. Inclusion of Patients in the Analysis



ART indicates antiretroviral therapy; TB, tuberculosis.
[a]Additional censoring at each duration of follow-up was due to the patients not being in care for long enough at the close of the study.

ness. In this analysis, all treatment-naive individuals 14 years or older, with a CD4 cell count lower than 250 cells/µL, who started receiving NNRTI-based ART by June 30, 2006, were included. Patients were excluded if they had concurrent tuberculosis at the time that they started ART, but subsequently discontinued tuberculosis therapy within 14 days of starting ART. The remaining patients were classified into 4 groups based on whether ART initiation overlapped with concurrent treatment for tuberculosis and based on which NNRTI was part of their starting ART regimen (FIGURE 1). Patients were followed up until the earliest of the following possibilities: loss to the program (death, lost to follow-up, transferred out); interruption of ART therapy for any reason; substitution of the initial NNRTI due to toxicity or contraindications (eg, efavirenz changed to nevirapine in pregnancy); starting tuberculosis treatment due to a subsequent diagnosis; or the last visit prior to December 31, 2006. Patients were classified as lost to follow-up after 6 months without a visit to the service. Viral loads were classified as 6-, 12-, or 18-month values based on the duration closest to the actual dates of the test, provided the test was performed within 3 months of the designated duration.

The analysis was conducted between October 2007 and February 2008. Baseline characteristics were described as medians with interquartile ranges for continuous variables and as proportions with

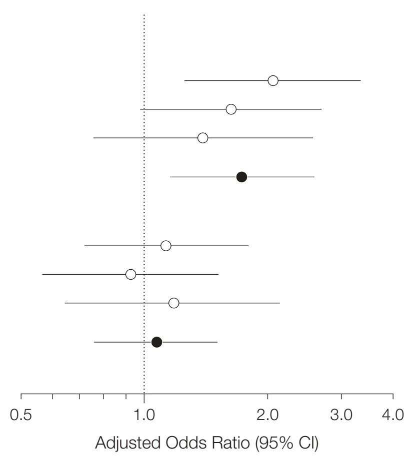
Table 1. Baseline Characteristics of Patients Starting Antiretroviral Therapy Relative to the Nonnucleoside Reverse Transcriptase Inhibitor Used and Concurrent Tuberculosis

	Tuberculosis			No Tuberculosis		
	Nevirapine (n = 209)[a]	Efavirenz (n = 1074)[b]	*P* Value[c]	Nevirapine (n = 1726)[d]	Efavirenz (n = 961)[e]	*P* Value
Age, median (IQR), y	32 (28-37)	32 (28-38)	.47	31 (27-37)	34 (29-40)	<.001
CD4 cell count, median (IQR), cells/µL	80 (42-137)	61 (27-117)	.002	116 (58-167)	93 (37-155)	<.001
Viral load, median (IQR), $\log_{10}$ copies/mL	5.3 (4.6-5.7)	5.3 (4.8-5.7)	.28	5.0 (4.4-5.5)	5.1 (4.6-5.5)	.04
Weight, median (IQR), kg	56 (51-65)	56 (49-63)	.45	60 (53-69)	59 (52-68)	.009
ALT, median (IQR), UL	24 (18-33.5)	27 (19-40)	.07	23 (18-33)	32 (21-53)	<.001
Duration of TB treatment, median (IQR), d	87 (60-135)	73 (44-115)	<.001			
Women, % (95% CI)	73.7 (67.2-79.5)	62.1 (59.1-65.0)	<.001	80.0 (78.0-81.9)	57.1 (53.9-60.3)	<.001
AIDS diagnosis, % (95% CI)	55.0 (48.0-61.9)	58.1 (55.1-61.1)	.002	27.3 (25.2-29.5)	37.9 (34.8-41.0)	<.001
Zidovudine in starting regimen, % (95% CI)	4.3 (1.5-7.1)	14.4 (12.3-16.5)	<.001	12.4 (10.8-14.0)	31.3 (28.4-34.3)	<.001
Extrapulmonary TB, % (95% CI)	37.3 (30.7-44.3)	37.2 (34.3-40.2)	.98			

Abbreviation: ALT, alanine aminotransferase; CI, confidence interval; IQR, interquartile range; TB, tuberculosis.
[a]The number of patients with ALT values was 128; weight, 203; and viral load, 181.
[b]The number of patients with ALT values was 688; weight, 1054; and viral load, 806.
[c]Rank-sum test for continuous variables, and χ^2 test for binary variables.
[d]The number of patients with ALT values was 1107; weight, 1668; and viral load, 1314.
[e]The number of patients with ALT values was 489; weight, 943; and viral load, 757.

Figure 2. Failure to Suppress Viral Load in Patients With Concurrent Tuberculosis at the Start of Antiretroviral Therapy vs Those Without Concurrent Tuberculosis

	Viral Load ≥400 Copies/mL		Adjusted Odds Ratio[a] (95% CI)
Nevirapine	No. (%[95% CI]) Without TB	No. (%[95 CI]) With TB	
6 mo	93 (8.3 [6.7-10.0])	23 (16.3 [10.6-23.5])	2.1 (1.2-3.4)
12 mo	96 (12.2 [10.0-14.7])	23 (20.0 [13.1-28.5])	1.6 (1.0-2.7)
18 mo	73 (14.0 [11.2-17.3])	16 (20.0 [11.9-30.4])	1.4 (0.7-2.6)
Combined[b]			1.7 (1.2-2.6)
Efavirenz			
6 mo	35 (5.7 [4.0-7.9])	45 (6.4 [4.7-8.4])	1.1 (0.7-1.8)
12 mo	35 (8.1 [5.7-11.0])	34 (8.0 [5.6-11.0])	0.9 (0.6-1.5)
18 mo	24 (10.4 [6.8-15.1])	25 (11.5 [7.6-16.5])	1.2 (0.6-2.2)
Combined[b]			1.1 (0.8-1.5)



CI indicates confidence interval; TB, tuberculosis.
[a]Adjusted for age, sex, and baseline CD4 cell count. The adjusted odds ratios and 95% CIs were rounded to 1 decimal.
[b]Combined odds ratios were calculated with generalized estimating equation and an exchangeable correlation matrix.

Table 2. Multivariate Model of Associations With Failure to Suppress Viral Load[a]

	OR (95% CI)	*P* Value
Women	1.0 (0.7-1.2)	.73
<30 y	1.4 (1.1-1.8)	.003
Baseline CD4 cell count, per 25 cells/µL increase	0.9 (0.9-1.0)	.004
NNRTI and TB at start of ART		
Efavirenz, no TB	1 [Reference]	<.001
Efavirenz and prevalent TB[b]	1.1 (0.8-1.6)	
Nevirapine, no TB	1.6 (1.1-2.2)	
Nevirapine and prevalent TB[b]	3.2 (2.0-5.2)	
Duration on ART, mo		
6	1 [Reference]	<.001
12	1.5 (1.2-1.7)	
18	1.8 (1.4-2.1)	
Weight at baseline, kg		
<60	1 [Reference]	.06
60-79.9	1.2 (0.9-1.5)	
≥80	1.6 (1.1-2.4)	
Year of ART initiation		
2001-2002	1 [Reference]	.08
2003	0.7 (0.4-1.2)	
2004	0.7 (0.5-1.1)	
2005	0.6 (0.4-0.8)	
2006	0.7 (0.4-1.2)	

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; NNRTI, nonnucleoside reverse transcriptase inhibitor; OR, odds ratio; TB, tuberculosis.
[a] Model included 5283 observations involving 2670 patients.
[b] Patients had received concurrent treatment for tuberculosis for at least 14 days at the time of starting ART.

exact binomial confidence intervals (CIs) for categorical variables, compared between groups, respectively, through rank sum and χ^2 statistics.

The proportions of patients with viral loads of 400 copies/mL or more were calculated at each duration in each of the 4 groups (Figure 1). The odds of a value at or higher than this threshold in patients who were receiving concurrent tuberculosis treatment when starting ART were compared with those who were not, in separate multivariate logistic regression models at each duration for each NNRTI. Pooled odds ratios (ORs) across all durations were additionally determined for each NNRTI and for all 4 groups together with generalized estimating equation repeated-measures analyses accounting for intraindividual correlation through an exchangeable correlation matrix.

For all multivariate models, variables were included based on a priori considerations, if they were themselves associated with the outcome or if they changed the other associations in the model.

Kaplan-Meier failure estimates were determined comparing the 2 tuberculosis exposure groups receiving each NNRTI for time to death, time to NNRTI substitution due to toxicity, time to the first viral load at the threshold of 400 copies/mL or more (restricted to values beyond 30 days of follow-up), time to loss to follow-up, and time to virological failure as defined above. In the analysis of time to death, patients were not censored with subsequent tuberculosis episodes or with changes or interruptions to the NNRTI. In the analysis of time to treatment-limiting toxicity, patients starting ART with TB were censored at the end of the initial tuberculosis episode. Log-rank statistics and adjusted hazard ratios (HRs) from Cox proportional hazard models were determined for each comparison. The proportional hazards assumptions were validated for the Cox models based on Schoenfeld residuals. The CD4 cell count changes relative to baseline were compared at 18 months in separate multivariate linear regression models for each NNRTI.

A second analysis was performed in patients who did not have tuberculosis at the start of ART, in which the time to virological rebound was determined from the time of the first viral load lower than 400 copies/mL. Concurrent tuberculosis treatment as a result of incident tuberculosis during follow-up was included as a time-varying exposure in both Kaplan-Meier estimates and multivariate Cox proportional hazard models. Patients developing tuberculosis remained in this exposure group even if they were followed up beyond the end of the tuberculosis treatment episode. Follow-up was censored in the same way as in the first analysis, except in the case of incident tuberculosis whereby patients were censored if a second episode of tuberculosis occurred during follow-up.

Using the 6-month follow-up duration, the 141 and 1126 patients assessed who started nevirapine-based ART with or without concurrent antitubercular therapy would ensure 88% power to detect a 10% decline in viral load suppression in the group receiving concurrent tuberculosis treatment, assuming a 90% suppression in the reference group ($\alpha = .05$)

The analysis was conducted using Stata statistical software, 10.0 (StataCorp Inc, College Station, Texas). In each analysis, only observations with complete data on the outcomes and covariates were used, while the completeness of both the main outcome and covariate data are reported (Figure 1 and TABLE 1, respectively). All statistical tests were 2-sided.

RESULTS

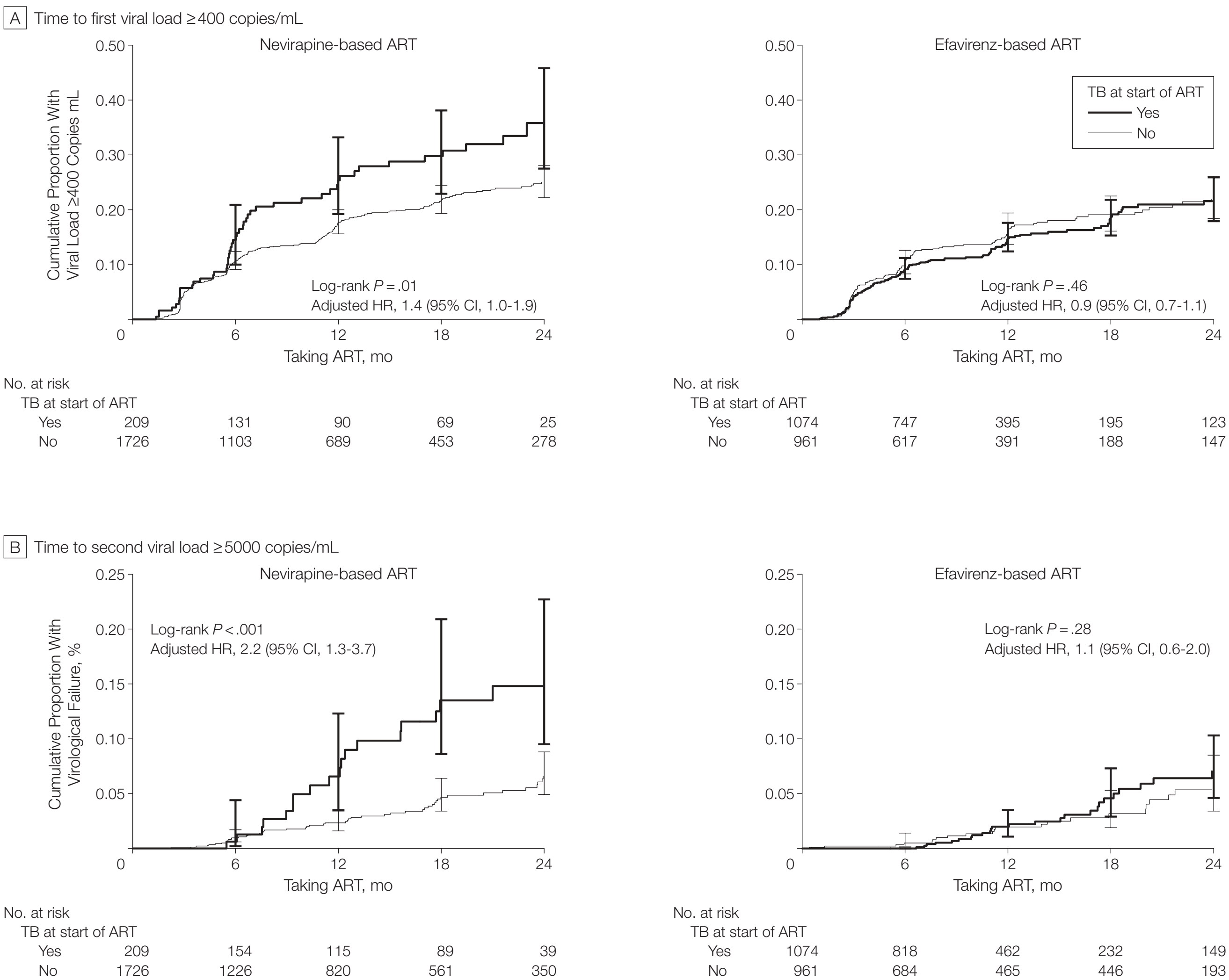
The proportion of patients starting ART while receiving concurrent tuberculosis therapy increased from 21% (17 of 80) in 2001 to 40% (439 of 1099) in 2006. Since 2004, the majority of patients initiated nevirapine-based ART, although in patients with concurrent tuberculosis, efavirenz use has still predominated.

Of 4117 individuals who met the initial inclusion criteria, 2687 were not receiving tuberculosis treatment at the start of therapy (Figure 1). Of the remaining 1430 who started ART while receiving concurrent tuberculosis therapy, 249 started taking nevirapine-based ART and 1181 started taking efavirenz-based ART. Of these, 209 and 1074 patients, respectively, had overlapping treatment for at least 14 days. Overall, in all groups at all durations of follow-up, between 83% and 96% of patients who were eligible for virological assessment and inclusion in the analysis were assessed.

Patients with concurrent tuberculosis were compared between NNRTI groups at the start of ART (Table 1) and were similar with respect to age, baseline viral load where available, weight (median of 56 kg in both groups with concurrent tuberculosis), alanine aminotransferase where available, and the proportion with extrapulmonary tuberculosis. Patients with tuberculosis initiating nevirapine had a slightly higher CD4 cell count (80 vs 61 cells/μL, $P=.002$) and had been receiving tuberculosis therapy for slightly longer than those initiating efavirenz (87 vs 73 days, $P<.001$). They were also more likely to be women (73.7% vs 62.1%, $P<.001$ [because efavirenz is teratogenic, it is often avoided in women of childbearing potential]), less likely to have started taking zidovudine (4.3% vs 14.4%, $P<.001$), and were less likely to have a stage IV–defining illness (55.0% vs 58.1%, $P=.002$). Findings in the same directions were observed comparing baseline characteristics between NNRTI groups without concurrent tuberculosis (Table 1), except that patients initiating efavirenz were older and had higher baseline aminotransferase values when available.

Overall, the proportion of patients with elevated viral loads was lowest at 6 months while taking ART in all 4 groups (**FIGURE 2**). There was no discernable dif-

Figure 3. Cumulative Estimates of Time to Elevated Viral Load and Virological Failure

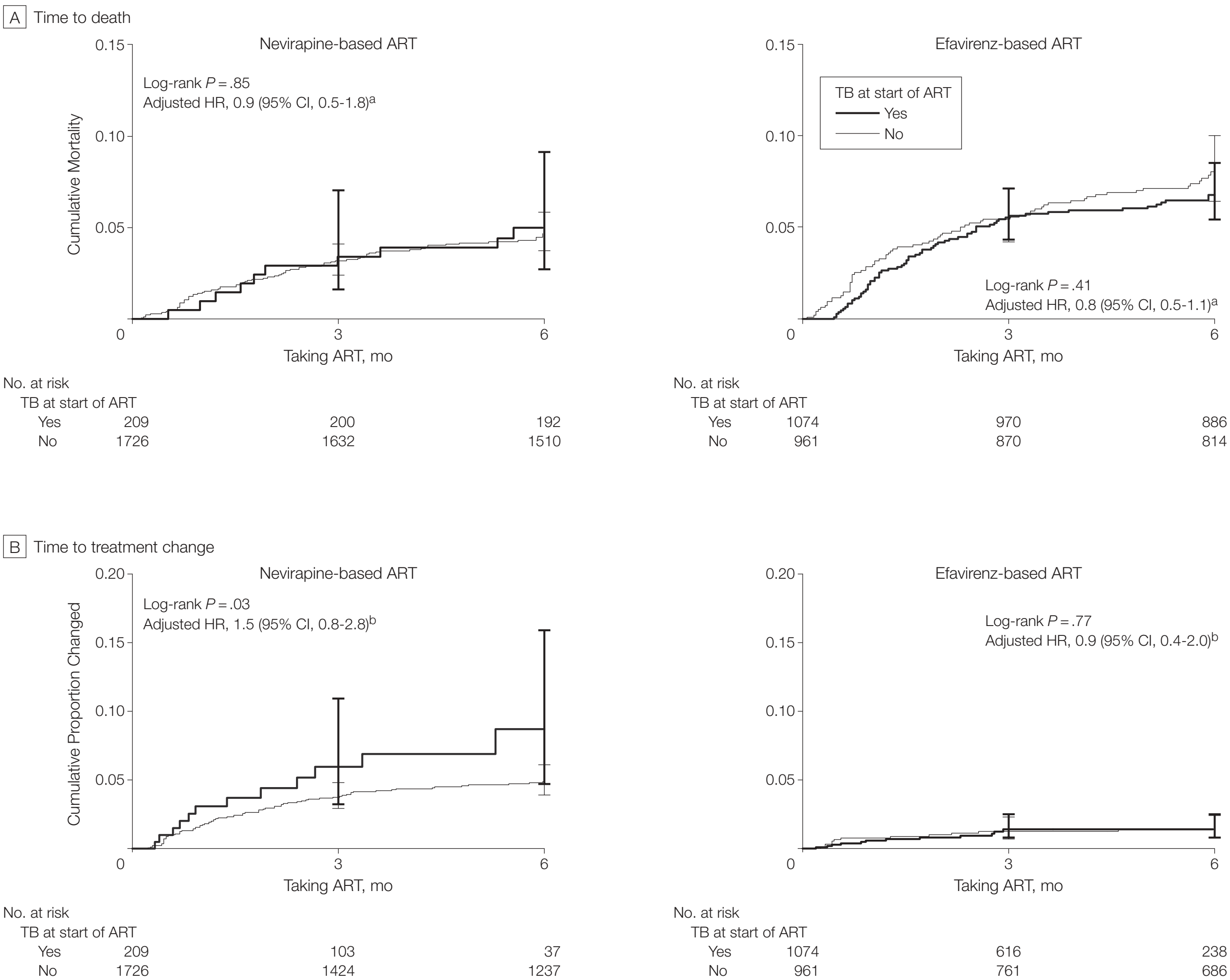


ART indicates antiretroviral therapy; CI, confidence interval; HR, hazard ratio; TB, tuberculosis. Error bars indicate 95% CIs. Adjusted for age, sex, and baseline CD4 cell count.

ference in this measure based on baseline tuberculosis therapy status in patients initiating efavirenz (combined adjusted OR, 1.1; 95% CI, 0.8-1.5). However, a higher proportion of patients initiating nevirapine with initial concurrent tuberculosis had elevated viral loads during follow-up than those without concurrent tuberculosis. This was most notable at 6 months (16.3%; 95% CI, 10.6%-23.5% vs 8.3%; 95% CI, 6.7%-10.0%; adjusted OR, 2.1; 95% CI, 1.2-3.4), and in the combined estimate (adjusted OR, 1.7; 95% CI, 1.2-2.6).

A model combining all the groups together demonstrated clearly the inferior virological outcomes (failure to suppress viral load) in the group starting to take both nevirapine and tuberculosis treatment relative to the efavirenz groups (eg, adjusted OR, 3.2; 95% CI, 2.0-5.2 for the group initiating nevirapine and tuberculosis treatment vs the group initiating efavirenz without concurrent tuberculosis at the start of ART, **TABLE 2**). The outcomes associated with receiving nevirapine were inferior even without concurrent tuberculosis (adjusted OR, 1.6; 95% CI, 1.1-2.2 for the group initiating nevirapine without concurrent tuberculosis vs the group initiating efavirenz without concurrent tuberculosis). Age younger than 30 years, a low baseline CD4 cell count, and increasing baseline weight were independently associated with failure to suppress viral load in this model. The use of zidovudine over stavudine in the starting regimen was not associated with the outcome; therefore, this was not included in the final model. We found little evidence for interactions between the NNRTI used or con-

Figure 4. Cumulative Estimates of Time to Death and Regimen Change Due to Toxicity



ART indicates antiretroviral therapy; CI, confidence interval; HR, hazard ratio; TB, tuberculosis. Error bars indicate 95% CIs.
[a] Adjusted for age, sex, baseline CD4 cell count, and year of ART initiation.
[b] Adjusted for age, sex, and baseline CD4 cell count.

current tuberculosis and any of the other exposure variables in the model (all *P* values >.05 [likelihood ratio test]). In alternate models that included available baseline viral load data, this was independently associated with failure to suppress subsequent viral loads (adjusted OR, 1.3 for each $\log_{10}$ increase in the baseline value, 95% CI, 1.1-1.6) and did not confound the associations between this outcome—choice of NNRTI—and concomitant tuberculosis.

The time-to-event analysis of failure to suppress viral load (FIGURE 3A) provided adjusted HR estimates consistent with the pooled adjusted OR estimate above (for nevirapine, adjusted HR, 1.4; 95% CI, 1.0-1.9; for efavirenz, adjusted HR, 0.9; 95% CI, 0.7-1.1). The difference in the case of receiving nevirapine with and without concurrent tuberculosis treatment was more marked when assessing time to confirmed virological failure (adjusted HR, 2.2; 95% CI, 1.3-3.7; Figure 3B). Concurrent tuberculosis treatment was not associated with time to confirmed virological failure in patients starting efavirenz-based ART (adjusted HR, 1.1; 95% CI, 0.6-2.0).

Other Outcome Measures

In comparing other outcomes, there was no difference after adjustment between the groups receiving tuberculosis treatment vs those without concurrent tuberculosis for each NNRTI in regard to mortality (adjusted HR for nevirapine, 0.9; 95% CI, 0.5-1.8; adjusted HR for efavirenz, 0.8; 95% CI, 0.5-1.1; FIGURE 4A), or in regard to time to toxicity-mediated NNRTI substitution (adjusted HR for nevirapine, 1.5; 95% CI, 0.8-2.8; adjusted HR for efavirenz, 0.9; 95% CI, 0.4-2.0; Figure 4B). In patients without concurrent tuberculosis, those patients receiving nevirapine were more likely to have their therapy substituted due to toxicity compared with those receiving efavirenz (cumulative proportion receiving nevirapine having treatment substitution by 6 months, 4.9%; 95% CI, 3.9%-6.1% vs 1.4%; 95% CI, 0.8%-2.4% in the case of efavirenz).

For both nevirapine and efavirenz, concurrent tuberculosis treatment at the start of ART was associated with an additional gain of 29 cells/μL in CD4 cell count at 18 months compared with baseline, adjusted for age, sex, and baseline CD4 cell count (95% CI, 1-56 for nevirapine; 95% CI, 6-51 for efavirenz), in comparison with patients taking nevirapine and efavirenz without tuberculosis.

In the 4 groups combined, viral load suppression to less than 400 copies/mL was 92.4% (95% CI, 91.3%-93.4%) at 6 months, 89.3% (95% CI, 87.8%-90.7%) at 12 months, and 86.8% (95% CI, 84.6%-88.8%) at 18 months of ART. Cumulative loss to follow-up was 5.6% (95% CI, 4.4%-7.5%) at 24 months of ART and was comparable between the 4 groups.

Incident Tuberculosis in Patients Already Receiving NNRTI-Based ART

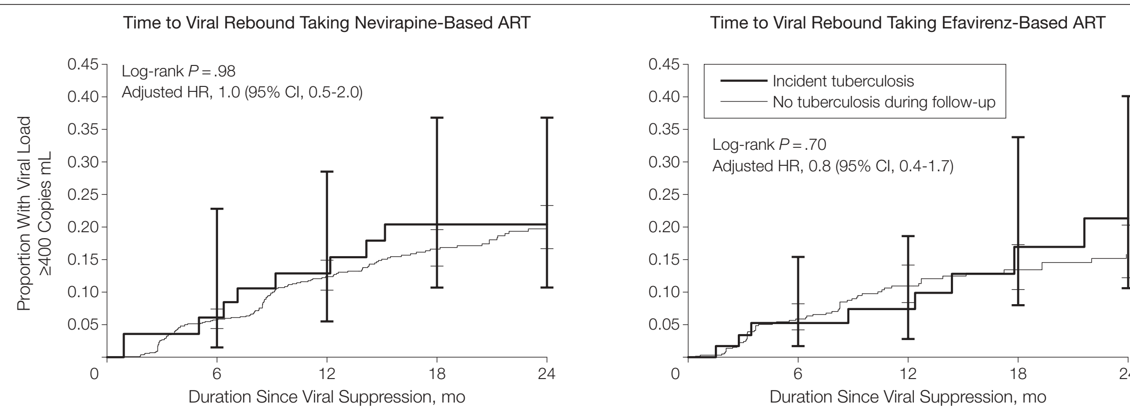
The final analysis compared the time to virological rebound between patients remaining free of tuberculosis during follow-up and those who were initially free of tuberculosis but subsequently started tuberculosis treatment due to a new tuberculosis episode (FIGURE 5). There was no difference in time to rebound between the groups among those who did and did not experience incident tuberculosis receiving either NNRTI (adjusted HR, 1.0; 95% CI, 0.5-2.0 for nevirapine; adjusted HR, 0.8; 95% CI, 0.4-1.7 for efavirenz).

COMMENT

Main Findings

Coadministered rifampicin-based antitubercular therapy at ART initiation resulted in higher probabilities of an elevated viral load or virological failure in the first 2 years of therapy in patients taking nevirapine-based ART but not in patients who started efavirenz-based ART. In spite of these differences, viro-

Figure 5. Cumulative Estimates of Time to Elevated Viral Load Since First Suppressing Viral Load (≥ 400 copies/mL) in Patients Without Tuberculosis at the Start of Antiretroviral Therapy, Stratified by Subsequent Incident Tuberculosis



No. at risk	0	6	12	18	24	0	6	12	18	24
Incident tuberculosis	27	40	35	28	17	56	49	38	20	15
No tuberculosis during follow-up	1136	771	534	336	184	634	428	262	167	133

ART indicates antiretroviral therapy; CI, confidence interval; HR, hazard ratio. Error bars indicate 95% CIs. Adjusted for age, sex, and baseline CD4 cell count.

logical outcomes were good, with 80% of patients in the initial nevirapine-rifampicin group being virologically suppressed at 18 months' duration of ART. For both NNRTIs, incident tuberculosis during follow-up did not result in an increased risk of virological rebound.

Underlying Mechanisms

The differential findings between the group starting nevirapine with prevalent tuberculosis and those developing tuberculosis once already established on ART could be the result of the limited power of the latter analysis to detect a difference due to the inclusion of fewer patients with incident tuberculosis. An alternative explanation, however, is a drug interaction mediated by rifampicin during the lead-in dosing phase of nevirapine. A 2-week lead-in period of once daily instead of twice daily dosing is recommended to allow for the autoinduction of the cytochrome P450 enzyme system by nevirapine. In patients taking rifampicin, the system is however already induced. A recent Malawian study[30] found that 59% of patients coinfected with HIV and tuberculosis had subtherapeutic nevirapine concentrations during the lead-in dosing phase. A Thai study that compared patients initiating efavirenz-based or nevirapine-based ART with concurrent tuberculosis reported an OR between these groups for achieving a viral load lower than 50 copies/mL at 48 weeks of 0.590 (95% CI, 0.302-1.153)[22] but was based on smaller numbers of patients.

Strengths and Limitations of This Study

The published literature on the virological efficacy of standard doses of NNRTI-based ART coadministered with rifampicin is sparse, but the data are generally encouraging. The existing studies have, however, been limited by small sample sizes[8,20,21,30,31] or by the failure to include a control group.[30,31]

Key strengths of our study include the large sample size of patients starting ART, a good follow-up rate, and the assessment of virological responses by failure to suppress, rebound, and confirmed failure. Adherence in this cohort, as best as can be measured, was generally good as reflected by virological suppression and comparably low rates of loss to follow-up between groups. Thus, it seems unlikely that differences in adherence account for the differences that we found in virological outcomes.

The study has a number of limitations. First, although we demonstrated inferior virological outcomes in patients starting ART with prevalent tuberculosis and nevirapine, we were unable to demonstrate differences in survival or CD4 cell count change. Interpretation is therefore based on the premise that virological failure would eventually result in clinical failure. Second, although we believe that the decision to use nevirapine with rifampicin in this study has been a systematic one rather than by clinical indication, as an observational study, there remains the possibility of residual confounding by indication. In comparing the clinical characteristics of patients with tuberculosis when starting ART, it would appear that if anything, the sicker coinfected patients with a higher risk of virological failure were more likely to start efavirenz-based ART as evidenced by a lower median baseline CD4 cell count, a higher probability of having AIDS, and a shorter duration of tuberculosis treatment. Third, the detection limit of the viral load assay in our study was 400 copies/mL, whereas virological suppression to values 10-fold lower than this are required for long-term suppression.[32] Finally, it was not possible with the available data to compare tuberculosis outcomes between the groups studied.

Additional Findings

The association with increased weight and failure to suppress viral load in the combined model underlines the importance of weight in assessing the adequacy of NNRTI dosing. In addition to concerns about subtherapeutic dosing, at the other end of the spectrum, a low baseline weight has been associated with NNRTI toxicity.[19] More detailed analyses of associations between weight and virological outcomes and toxicity in patients on NNRTIs are required in this setting.

For both NNRTIs, CD4 cell count increases were higher in patients who commenced ART with prevalent tuberculosis compared with patients without tuberculosis. The likely explanation for this is the additive effect of the CD4 cell count increase observed when tuberculosis is treated in the absence of ART.[33] This confounds any attempt to determine the effect of the observed differences in virological outcomes on CD4 cell count changes.

The association between nevirapine use and failure to suppress viral load in patients without concurrent tuberculosis is consistent with data from both randomized controlled trials[18] and a number of observational studies.[34-36] The more rapid development of treatment-limiting toxicity in patients receiving nevirapine compared with those receiving efavirenz, irrespective of tuberculosis treatment, has previously been described together with a characterization of the toxicities involved.[19]

CONCLUSION

Nonnucleoside reverse transcriptase inhibitor–based ART is tolerable and effective when coadministered with rifampicin-containing antitubercular therapy. Probabilities of elevated viral loads during follow-up and confirmed virological failure are higher in patients with prevalent tuberculosis starting nevirapine-based ART. Given the continued reliance on nevirapine-containing ART regimens in Africa, together with the important role tuberculosis services play as an entry point for ART, further prospective studies exploring this outcome are warranted. One of the most striking aspects of our study was the demonstration that 40% of patients starting ART in recent years have concurrent tuberculosis, underscoring the public health importance of improving affordable treatment options for patients infected with HIV and tuberculosis in this setting.

Author Contributions: Dr Boulle had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Boulle, Van Cutsem, Cohen, Hilderbrand, Goemaere, Coetzee, Maartens.
Acquisition of data: Boulle, Van Cutsem, Hilderbrand, Mathee, Abrahams, Goemaere, Coetzee.
Analysis and interpretation of data: Boulle, Van Cutsem, Cohen.
Drafting of the manuscript: Boulle, Van Cutsem, Abrahams, Maartens.
Critical revision of the manuscript for important intellectual content: Van Cutsem, Cohen, Hilderbrand, Mathee, Goemaere, Coetzee.
Statistical analysis: Boulle, Van Cutsem, Cohen.
Obtained funding: Hilderbrand, Goemaere, Coetzee.
Administrative, technical, or material support: Van Cutsem, Hilderbrand, Mathee, Abrahams, Goemaere.
Study supervision: Van Cutsem, Coetzee, Maartens.
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