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Early changes in hepatic function among HIV–tuberculosis patients treated with nevirapine or efavirenz along with rifampin-based anti-tuberculosis therapy

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SUMMARY

Objectives: To describe the longitudinal changes in hepatic function among HIV-infected tuberculosis (TB) patients receiving once-daily nevirapine (NVP)- or efavirenz (EFV)-based antiretroviral treatment (ART) along with rifampin-containing anti-TB treatment.

Methods: This was a nested study within a randomized clinical trial, taking place between May 2006 and June 2008 at the National Institute for Research in Tuberculosis, Chennai, India. Antiretroviral-naïve HIV-infected TB patients were initiated on an intermittent short-course regimen and randomized to receive didanosine and lamivudine with either NVP (400 mg) or EFV (600 mg) once-daily. Blood was analyzed for alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum alkaline phosphatase (SAP), and bilirubin at baseline, at ART initiation, fortnightly after ART initiation until 2 months, then monthly until 6 months and 6-monthly thereafter.

Results: Of the 168 patients included (79% men, median CD4 count 93 cells/mm^3, median viral load 242 000 copies/ml), 104 were on EFV-based ART and 64 on NVP-based ART. There was a small but statistically significant elevation in ALT and SAP at 2 weeks and AST at 6 weeks after ART initiation. The proportion of patients with rate-limiting toxicity of liver enzymes was small. None had treatment terminated because of hepatotoxicity.

Conclusion: Hepatotoxicity is not a major concern when HIV-infected TB patients, with normal baseline liver function initiate treatment for both infections simultaneously.

1. Introduction

It is estimated that there are approximately 1.1 million adults co-infected with HIV and tuberculosis (TB) globally.[1] The World Health Organization (WHO) recommends initiating antiretroviral treatment (ART) for all HIV–TB co-infected patients within a few weeks of TB treatment, regardless of CD4 cell count, to reduce all-cause mortality and improve TB treatment outcomes.[2,3] In a public health approach, recommended ART regimens include combinations of two nucleoside reverse transcriptase inhibitors (NRTIs) and a non-nucleoside reverse transcriptase inhibitor (NNRTI), with nevirapine (NVP) or efavirenz (EFV) being the preferred NNRTIs.[2] For the treatment of TB, regimens containing isoniazid and a rifamycin throughout are recommended, as they have better outcomes in terms of lower failure and recurrence rates.[4,5]

Although studies have reported clinical and virological efficacy with the concurrent use of NNRTI and rifamycin-based TB treatment,[6,7] few reports have been published on the safety of the concomitant use of these regimens. Isoniazid, rifampin, NVP, and EFV are all associated with hepatotoxicity, and little is known about the relative rates of hepatotoxicity with either NVP or EFV in the setting of rifampin-based TB treatment.[8] Further, there is no information on rates of hepatotoxicity among HIV–TB co-infected patients treated with an intermittent (three times weekly) regimen. Studies in HIV-uninfected populations suggest that toxicity rates tend to be lower in patients given intermittent compared to daily chemotherapy.[9]

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In India, standard TB treatment consists of 2 months of isoniazid (H), rifampin (R), pyrazinamide (Z), and ethambutol (E), followed by 4 months of H and R given three times weekly throughout ($2EHRZ_3/4RH_3$). ART is begun between 2 weeks and 2 months following the initiation of anti-TB therapy (ATT), based on CD4 cell counts, with a combination therapy of two NRTIs with one NNRTI, EFV being the preferred drug for co-administration with rifampin. However NVP is the most widely used NNRTI worldwide as it is inexpensive, non-teratogenic, is available in fixed drug combinations, and can also be administered once-daily. No detailed comparative data exist on the effects of these regimens on liver enzymes.

We studied the changes in liver function during and after treatment with rifampin-based ATT given along with once-daily NNRTI-based ART, in adults with HIV–TB co-infection who participated in a clinical trial in Tamilnadu, India (ClinicalTrials.gov; NCT00332306).

2. Methods

This study was part of a prospective randomized controlled clinical trial "Efficacy and safety of once-daily nevirapine- or efavirenz-based antiretroviral therapy when co-administered with rifampin-based antitubercular therapy", the details of which have been described elsewhere.[10] In brief, between May 2006 and June 2008, HIV-1-infected adults with active TB and a CD4 count $\leq$250 cells/mm^3 were enrolled in a study at the National Institute for Research in Tuberculosis (formerly the Tuberculosis Research Centre). Patients with prior ART or ATT, an HIV-2 infection, or serum aminotransferases >2.5 times the upper limit of normal (ULN) were excluded. The 'once-daily ART' controlled clinical trial collected detailed clinical and laboratory data to monitor the safety and efficacy of administering different ART regimens in combination with ATT. Therefore, it was possible to monitor the development of hepatotoxicity at various time points in the trial.

All patients enrolled in the 'once-daily ART' study initiated a standard TB treatment with four drugs: isoniazid (600 mg), rifampin (450/600 mg based on body weight <60 or >=60 kg), ethambutol (1200 mg), and pyrazinamide (1500 mg) for the first 2 months; two drugs, isoniazid and rifampin, were used for the subsequent 4 months. All drugs were administered three times weekly ($2EHRZ_3/4RH_3$) under direct observation, in accordance with national guidelines. After 2 months of TB treatment, participants were randomized to the once-daily ART regimen (month 0) with either NVP (400 mg, after a lead-in period of 200 mg once-daily) or EFV (600 mg per day), along with didanosine (250/400 mg for body weight <60 or $\geq$60 kg) and lamivudine (300 mg).

The time of ATT initiation was defined as 'baseline' and the time of ART initiation (i.e., 2 months after ATT initiation) as month 0. Subsequent weeks/months are chronological with reference to month 0 throughout this article. ART was administered under direct supervision 3 days per week and supplied to the patient for self-administration on the remaining days. ATT was stopped at 6 months and ART was continued (Figure 1).

Liver function tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum alkaline phosphatase (SAP), and bilirubin were measured using an automated analyzer (Olympus AU400, Japan) at baseline (month 2), month 0, then every 2 weeks until week 8 (month 2) and then once every 8 weeks until 6 months. Hepatotoxicity grades were defined in accordance with the AIDS Clinical Trials Group (ACTG) criteria: grade I, 1.25–2.5 times ULN; grade II, 2.5–5.0 times ULN; grade III, 5–10 times ULN; grade IV, >10 times ULN.[11] Mild hepatotoxicity was defined as ACTG grades I and II, and severe toxicity as grades III and IV.

2.1. Statistical analysis

The distribution of each variable was checked cross-sectionally at baseline and follow-up. All unusual values were verified. Mean values and standard deviations were tabulated for normally distributed variables; the median and 25th and 75th percentiles were tabulated for skewed variables. We compared baseline liver enzymes and various baseline demographic and clinical characteristics between treatment groups using the Student's *t*-test or the Wilcoxon rank-sum test, as appropriate. Changes in liver enzymes during both the early and late stage of treatment were compared with baseline levels using repeated measures analyses, with skewed variables transformed to attain normality. We also compared changes in liver enzymes between treatment groups using the Mann–Whitney *U*-test. We compared the proportion of patients with liver enzyme abnormalities at baseline vs. at 12 months using the McNemar test for correlated proportions and the Chi-square test to compare between the two treatment groups. All tests used $\alpha = 0.05$ as the cut-off for statistical significance. Analyses were performed using SPSS software version 14.0 (SPSS Inc., Chicago, IL, USA).

The study was approved by the ethics committee of the National Institute for Research in Tuberculosis, and informed written consent was obtained from all patients prior to study enrollment.

3. Results

Of the 179 patients enrolled into the once-daily ART study, 168 patients (132 men, 36 women) were found eligible for the current analysis (11 were not randomized – early drop-outs). Follow-up data were available for 157 patients at 4 months, 151 at 6 months, and 140 patients at 12 months (15 patients died, 11 were lost to follow-up, and two missed study visits) (Figure 1).

3.1. Patient characteristics

At baseline, the 168 HIV-infected patients with TB (79% men) had a mean age of 36 years, mean body weight of 42 kg, a median CD4 count of 93 cells/mm^3, and HIV viral load of 242 000 copies/ml. One hundred and four patients were randomized to the EFV arm and 64 to the NVP arm (the data safety monitoring board stopped the intake of patients into the NVP arm after the first interim analysis, which explains the unequal numbers). At baseline, patients did not differ significantly between the two treatment arms with respect to body weight, CD4 cell count, or viral load (Table 1). Forty-four percent of patients consumed alcohol (often or habitually) and 2.4% had a hepatitis co-infection (hepatitis B in three patients, hepatitis C in one patient). None of the patients in our study population had a hepatitis B and C co-infection. Drug intake was directly observed 3 days a week and overall adherence was >90%. The majority of subjects had an undetectable HIV load after 12 months of ART.

3.2. Baseline liver enzymes

Baseline liver enzymes were comparable in the two treatment groups. AST and ALT were significantly higher among patients with CD4 counts <90 cells/mm^3 (54 vs. 41 mg/dl, $p < 0.002$, and 35 vs. 27 mg/dl, $p = 0.01$, respectively), while SAP was higher among patients with a viral load >300 000 (249 vs. 171 mg/dl, $p = 0.04$). These cut-offs were based on the median levels at baseline.

At baseline, ALT was >100 mg/dl in three patients (2%), AST was >100 mg/dl in seven patients (6%), and SAP was >350 mg/dl in 18 patients (12%); these patients were excluded from the analysis.