Outcomes from treating tuberculosis with rifampicin or rifabutin in HIV-infected persons also receiving antiretroviral therapy

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To the Editors:

Treatment of tuberculosis and HIV co-infection poses a number of important challenges for clinicians, including drug-drug interactions between components of antiretroviral therapy (ART) and anti-tuberculosis treatment.[1] This is especially important between ritonavir-boosted protease inhibitor (PI) therapy and rifampicin, a key component of quadruple short-course tuberculosis treatment.

Current United Kingdom and United States guidelines recommend that HIV-tuberculosis co-infected patients should be treated for both tuberculosis and HIV contemporaneously, in order to achieve optimal outcomes. [2,3] Where the use of first-line ART with a non-nucleoside reverse transcriptase inhibitor (NNRTI) is contraindicated, for example acquired or transmitted resistance, intolerance, or toxicity of NNRTI, a ritonavir-boosted PI ART regimen is recommended. However, there are significant interactions between ritonavir-boosted PIs and rifampicin. [1,4] Rifampicin is a potent inducer of several cytochrome P450 isoenzymes, including CYP3A4, as well as P-glycoprotein, and phase-2 enzyme activity, which have important actions on the metabolism of PIs and NNRTI. [1,4,5] These effects may lead to sub-therapeutic PI levels even when PI pharmacokinetics are boosted by ritonavir and, as a result ritonavir-boosted PI regimes are contraindicated in co-administration with rifampicin. [2,3,4,5]

Rifabutin, a rifamycin family member, is effective in treatment of tuberculosis in HIV-negative subjects. [6,7,8] Based on pharmacokinetic studies rifabutin has less of an effect than rifampicin on inducing hepatic enzymes, [9] and can be used in combination with PI-based ART regimens. [10] Several studies have reported good outcomes from rifabutin-based regimens for treatment of tuberculosis in HIV-infected individuals, but there is a paucity of data describing outcomes in HIV-infected patients with tuberculosis treated with rifabutin, while also receiving ART. [11,12,13] We undertook a retrospective, observational study of outcomes among HIV/tuberculosis co-infected patients who received either rifampicin or rifabutin for the treatment of tuberculosis as well as ART, in order to identify if outcomes differed according to type of rifamycin used.

Adult, HIV-infected individuals treated for tuberculosis with either rifampicin or rifabutin, and who received ART (containing either a ritonavir-boosted PI or an NNRTI) at two inner city HIV treatment centres (Chelsea and Westminster Hospital and University College London Hospitals, London, UK), between April 1999 and August 2011 were identified. Data were extracted from case note and electronic patient records, including patient demographics (age, gender, ethnicity, risk factor for HIV acquisition), prior history of tuberculosis, site of tuberculosis (pulmonary, lymph node, or disseminated), interval between diagnosis of tuberculosis and HIV, details of anti-tuberculosis and ART regimens, occurrence of adverse drug reactions (ADR) (Grade III/IV) requiring tuberculosis treatment interruption, [14] occurrence of immune reconstitution inflammatory syndrome (IRIS), and outcomes (completed treatment, died). End of treatment plasma HIV viral load, and change in CD4 count between the start and end of tuberculosis treatment were noted. Each patient was followed up for 24 months: outcomes during follow up, including death or recurrence, were recorded. [15] Patients with known rifamycin and, or isoniazid resistance were excluded.

Patients were categorised as having either definite or presumptive tuberculosis, as previously described. [16] ART was defined as the use of at least three antiretroviral drugs including either a ritonavir-boosted PI (lopinavir or darunavir*),* or an NNRTI. Prescription of anti-tuberculosis medication and ART was based British HIV Association Guidelines, [2] and was at the discretion of individual physicians: treatment was self-administered in the majority of patients. All patients started standard four-drug tuberculosis therapy with isoniazid, pyrazinamide, ethambutol, and either rifabutin or rifampicin, except for two rifabutin-treated patients who started a quinolone in place of pyrazinamide (both had indeterminate pyrazinamide sensitivities and were fully sensitive to the other first-line medications). Rifampicin dosing was weight-based (450 or 600 mg once daily) and was given with a NNRTI. Rifabutin 450 mg once daily was used with efavirenz, 300 mg once daily with nevirapine, and 150 mg three times weekly was given with a ritonavir-boosted PI. All other anti-tuberculosis drugs were taken daily.

Data were analysed using STATA SE12 (Statacorp LP, College Station, Texas, USA). The χ^2, Mann Whitney U, and Fisher's exact tests were used to compare rifabutin and rifampicin-treated

groups. A p value of < 0.05 was considered significant. Ethics committee approval was not required as this was an observational evaluation of clinical outcomes.

A total of 171 HIV-infected patients were treated for tuberculosis with rifabutin (n=41) or rifampicin (n=130) and also received ART, including either an NNRTI or a ritonavir-boosted PI (Table 1). Patients treated with rifabutin and rifampicin were similar in age, gender, site of tuberculosis, and duration of treatment, but differed in ethnicity, HIV transmission category, and the interval between diagnosis of HIV and tuberculosis; p = 0.003, p = 0.051, and p = 0.001, respectively (Table 1). At the end of tuberculosis treatment median CD4 increase, the proportion with an undetectable plasma HIV viral load (<50 copies/mL), and mortality were similar in rifabutin- and rifampicin-treated individuals. Overall, rifampicin-treated patients were more likely to have completed treatment (96.9%), than those who received rifabutin (87.8%); p = 0.037. By contrast, rifabutin-treated patients were slightly more likely to have a tuberculosis treatment interruption due to an ADR (p = 0.307), and much more likely to develop IRIS (p = 0.012). All patients who interrupted tuberculosis treatment because of an ADR completed the full course of treatment following reintroduction of medication. By 24 months of follow up two (5%) rifabutin-treated and five (4%) rifampicin-treated individuals had recurrent tuberculosis; two rifabutin-treated patients had died (one death was tuberculosis-related), and five rifampicin-treated patients had died (two deaths were tuberculosis-related).

In this two-centre, retrospective study of the treatment of tuberculosis in HIV infected adults, the major findings were that end of tuberculosis treatment median CD4 increases, the proportion with an undetectable plasma HIV viral load, and mortality were similar in rifabutin- and rifampicin-treated individuals; by 24 months of follow up similar numbers of rifabutin- and rifampicin-treated individuals had recurrent tuberculosis, and had died. Overall, rifampicin-treated patients were more likely to have completed treatment than those who received rifabutin, and rifabutin-treated patients were more likely to develop IRIS.

Comparison of the present data with previous studies of rifabutin-based treatment of tuberculosis in HIV infected individuals is hampered by their inconsistent use of ART and lack of 24 months outcome data. [13,17,18,19] Singh *et al*, reported a retrospective observational study of outcomes from treatment of tuberculosis, using either rifabutin or rifampicin, in 141 HIV positive patients attending a single University-affiliated hospital in London, UK, over an 11 year period. [13] Patients who did not receive ART, those who received antiretroviral therapy regimens that did not include either a ritonavir-boosted PI or a NNRTI, and those who received ART (including either a ritonavir-boosted PI or a NNRTI) during treatment of tuberculosis were included. No differences in rates of adverse drug reaction, completion of tuberculosis treatment, or relapse of tuberculosis following completion of treatment were reported. [13] By contrast, the present study only included individuals who received ART containing either a ritonavir-boosted PI or an NNRTI during tuberculosis treatment, and all were treated using UK national guidelines for treatment of tuberculosis in HIV co-infection. [2]

The present study has several limitations. Firstly, it is retrospective in design and there were only a relatively small number of rifabutin-treated individuals. Secondly, therapeutic drug monitoring data was not available for the majority of patients so optimal therapeutic doses could not be assessed. Thirdly, many rifabutin-treated individuals were already receiving ART before anti-tuberculosis treatment was started, whereas rifampicin-treated patients were often ART-naive at the time of initiating anti-tuberculosis treatment. Finally, treatment was provided in a “developed world” setting and the observed outcomes may not be reproducible in a “developing world” setting where the majority of HIV/TB co-infection occurs**.**

In conclusion, the present study shows good outcomes from co-treatment of tuberculosis and HIV with either rifabutin or rifampicin and either NNRTI- or ritonavir-boosted PI-containing ART, however there is a clear need for prospective randomised clinical trials to identify effective, safe, evidence-based regimens for co-treatment of HIV and tuberculosis in patients needing ritonavir-boosted PI-based ART, [20] as well as the optimal dosing schedule for rifabutin when co-administered with a ritonavir-boosted PI. [21]

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