Administration of efavirenz (600 mg/day) with rifampicin results in highly variable levels but excellent clinical outcomes in patients treated for tuberculosis and HIV

Gerald Friedland¹,²,³*, Saye Khoo², Christopher Jack³ and Umesh Laloo³

¹Yale University, New Haven, CT, USA; ²University of Liverpool, Liverpool, UK; ³Nelson R Mandela School of Medicine, University of KwaZulu Natal, Durban, South Africa

Received 22 June 2006; returned 10 August 2006; revised 7 September 2006; accepted 10 September 2006

Objectives: Pharmacokinetic interactions between rifampicin and antiretroviral therapy (ART), including efavirenz, are problematic and need to be better defined to determine proper dose and to be correlated with short-term and long-term clinical outcomes.

Patients and methods: Consenting patients with smear-positive pulmonary TB and HIV received once daily didanosine + lamivudine + efavirenz (600 mg), with rifampicin-containing TB regimen by directly observed therapy and self-administration at TB therapy completion. Trough efavirenz levels were measured by HPLC at 1, 2, 4 and 6 months while on rifampicin and after discontinuation. HIV and TB outcomes were monitored.

Results: Twenty African patients were enrolled [15 female, mean age 31 years, baseline weight 59.4 kg (range 45–97), viral load 5.75 log₁₀ copies/mL and CD4 230 cells/mm³]. Seventy-two efavirenz concentrations were available from 19 patients (58 on, 14 after rifampicin). The geometric mean efavirenz concentration was 1730 ng/mL (range 354–27 179) on and 1377 ng/mL (range 572–3975) off rifampicin (P = 0.55). Inter-subject variability in efavirenz concentrations was greater on rifampicin (CV 157% versus 58% off) with relatively consistent intra-subject variation over time (median CV 24%). Over half of patients had efavirenz concentrations above or below the expected therapeutic range (1000–4000 ng/mL). Efavirenz levels were not predicted by weight or gender and were not associated with HIV clinical outcomes. Overall 80% of patients had non-detectable viral loads at 6 months and 65% at 21 months with a cumulative CD4 cell increase of 196 cells/mm³.

Conclusions: In this longitudinal study, despite wide variability in plasma efavirenz concentrations during rifampicin administration, excellent clinical outcomes were obtained. In African patients treated for HIV and TB, our data support the routine use of efavirenz at 600 mg/day when receiving rifampicin.

Keywords: antiretroviral therapy, drug interactions, TB

Introduction

Tuberculosis (TB) is the leading cause of morbidity and mortality in persons with HIV/AIDS in sub-Saharan Africa and worldwide. Administration of anti-TB and antiretroviral therapy (ART) to co-infected patients is advocated to improve outcomes of both diseases. However, the optimal use and dosing of ART agents in the presence of potent induction of drug metabolizing (cytochrome P450) enzymes by rifampicin-containing TB regimens remains controversial. Specifically, conflicting or lack of data has resulted in uncertainty over whether dose increment of efavirenz is required with concomitant rifampicin (e.g. from 600 to 800 mg/day in adults). Drug interaction data derive mainly from studies performed outside Africa, in some cases from healthy volunteers. Further, longitudinal data measuring efavirenz concentrations during and after rifampicin administration and pharmacodynamic correlations are lacking. Dosing concerns are relevant to both efavirenz toxicity in the presence of elevated levels and ART failure were levels to be subtherapeutic. To address these pharmacokinetic and therapeutic issues, we report the results of efavirenz levels during and after rifampicin administration among previously reported TB and HIV co-infected patients and describe the relationship of these concentrations to short-and long-term clinical outcomes.

*Corresponding author. Yale University School of Medicine AIDS Program, 135 College Street, Suite 323, New Haven, CT 06510-2483, USA. Tel: +1-203-688-6959; Fax: +1-203-737-4051; E-mail: Gerald.friedland@yale.edu
Patients and methods

Patients

Patients who provided written informed consent with newly diagnosed smear-positive pulmonary TB and HIV were enrolled at a municipal TB clinic in Durban, South Africa. Exclusion criteria included present or previous ART, current pregnancy and aspartate transaminase/alanine transaminase >5x normal value.

Treatment

TB therapy comprised daily rifampicin, isoniazid, pyrazinamide and ethambutol for 2 months followed by daily rifampicin and isoniazid for 4–6 months. ART comprised once daily didanosine (weight-adjusted: ≥60 kg, 400 mg; <60 kg, 250 mg), lamivudine and efavirenz (600 mg). Both medications were administered from 8 to 9 am by directly observed therapy (DOT) Monday–Friday. On weekends, ART was self-administered at the same time. Efavirenz levels were not adjusted by weight at baseline or during the study duration. Adherence was assessed using a validated questionnaire on Monday morning after self-administration. At the conclusion of TB therapy, ART was continued by self-administration. Baseline and serial measurement of weight, viral load, CD4 cell count, liver function, medication adherence and clinical examinations were carried out. Adverse events were assessed for severity using the AIDS Clinical Trials Group (ACTG) grading scheme (http://www.nih.gov). The study received approval from the Ethics Committee of the Nelson Mandela School of Medicine and the Human Investigations Committee of Yale School of Medicine.

Pharmacokinetic sampling

A trough plasma efavirenz sample was collected from each patient on a Monday morning at months 1, 2, 4 and 6 on TB treatment and after cessation of TB therapy. Samples were centrifuged and plasma stored at −70°C prior to shipment to Liverpool for analysis upon completion of the study. Efavirenz was measured using validated high performance liquid chromatography with UV detection (HPLC-UV) as previously described. The lower limit of quantification of efavirenz was taken as the lowest point on the standard curves (100 ng/mL). Intra-assay and inter-assay coefficients of variation at 5 ng/mL were 10.8% and 14.9%, respectively. The therapeutic range was defined as 1000–4000 ng/mL (www.hivpharmacology.com).

Statistical analysis

Inter-subject variability was expressed as coefficient of variation (CV%). Intra-subject variability was measured in patients with at least four samples taken over the first 6 months. Summary statistics were recorded for clinical outcomes. Concentration data were log-transformed and compared with selected variables using the Mann–Whitney test. Correlation with body weight was assessed using simple linear regression.

Results

Enrolment and follow-up

Twenty patients were enrolled; all were black Africans, 15 female, mean age 31 years (range 18–52) and weight 59.4 kg (range 45–97). Baseline viral load was 5.75 log_{10} copies/mL (range 3.81–7.53), and mean CD4 count was 230 cells/mm^3 (range 24–499).

Therapeutic outcomes

Seventeen patients completed TB/HIV therapy and 16 had undetectable viral load and a mean CD4 cell rise of 148 cells/mm^3. Nineteen were cured of TB. Three patients remained vireamic, 2 with lamivudine and efavirenz resistance mutations. Fourteen patients completed >15 months of self-administration; 13 had non-detectable viral loads and 1 had a viral load of 140 copies/mL. Cumulative CD4 cell increase was 196 cells/mm^3 (Figure 1 and Table 1). There was no recurrence of TB. Seven patients reported dizziness and poor concentration (35%), during the first few weeks after initiation of efavirenz therapy which did not warrant discontinuation of ART. In addition to DOT, high levels of self-reported adherence were recorded by standardized monthly questionnaires and overall 88% of scheduled clinic visits were kept. Two patients were lost to follow-up and one stopped ART secondary to hepatic toxicity and alcohol intake.

Efavirenz concentrations

Seventy-two efavirenz concentrations were available from 19 patients (58 taken during rifampicin and 14 after rifampicin). There was substantial inter-subject variation in plasma efavirenz concentrations on rifampicin (CV 157%) with less variability following rifampicin discontinuation (CV 58%). Results were relatively consistent for each subject with modest intra-individual variation (CV 24%) (Table 1). The geometric mean efavirenz concentration on rifampicin varied over time (Figure 1) and overall was 1730 ng/mL (range 354–27 179) and off rifampicin was 1377 ng/mL (range 572–3975) (P = 0.55). Four patients had repeatedly high efavirenz concentrations during rifampicin therapy. These normalized in three after the intensive phase or cessation of rifampicin therapy. Four out of six patients with repeatedly low efavirenz levels during rifampicin therapy normalized these by the end of treatment or following rifampicin discontinuation. Six other patients had efavirenz concentrations which varied between low and normal during rifampicin administration, four of whom had normal efavirenz concentrations after rifampicin discontinuation. Of note, over half of the patients had efavirenz concentrations above or below the expected therapeutic range and only two had plasma efavirenz concentrations consistently in this range throughout anti-TB therapy.

Of the two patients with virological failure, one had subtherapeutic efavirenz concentrations and one had concentrations in the normal range. No clear association was observed between neuropsychiatric symptoms and plasma efavirenz levels. However, both patients with plasma efavirenz levels consistently ~10 000 ng/mL developed neuropsychiatric toxicity. Body weight did not correlate with efavirenz concentrations either on (r^2 = 0.07; P = 0.27) or off (r^2 = 0.02; P = 0.65) rifampicin and efavirenz exposure was not associated with gender (P = 0.39) or liver function.

Discussion

This study is the first to report on serial efavirenz trough concentrations on and off rifampicin among patients receiving concomitant TB and HIV therapy. In addition, the study is among only a few to relate these findings to short- and long-term therapeutic outcomes. Several important observations arise from this study. Firstly, substantially greater inter-subject variation in
Efavirenz and rifampicin in the treatment of TB and HIV disease

Table 1. HIV therapeutic outcomes and efavirenz concentrations (ng/mL) during and after directly observed therapy with rifampicin-containing TB regimen

<table>
<thead>
<tr>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 4</th>
<th>Month 6</th>
<th>Post-rifampicin</th>
<th>Toxicity</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>518</td>
<td>883</td>
<td>1380</td>
<td>1097</td>
<td>1137</td>
<td></td>
</tr>
<tr>
<td>S2</td>
<td>594</td>
<td>396</td>
<td>416</td>
<td></td>
<td>932</td>
<td></td>
</tr>
<tr>
<td>S4</td>
<td>456</td>
<td>790</td>
<td>511</td>
<td>1270</td>
<td></td>
<td>fail</td>
</tr>
<tr>
<td>S5</td>
<td>599</td>
<td>518</td>
<td>354</td>
<td>632</td>
<td>CNS</td>
<td></td>
</tr>
<tr>
<td>S6</td>
<td>737</td>
<td>551</td>
<td>581</td>
<td>1275</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S7</td>
<td></td>
<td>938</td>
<td>1505</td>
<td>1536</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S9</td>
<td>6490</td>
<td>10 311</td>
<td>2225</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S10</td>
<td>2101</td>
<td>2307</td>
<td>2728</td>
<td>3536</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S11</td>
<td>3144</td>
<td>2177</td>
<td>2231</td>
<td>1783</td>
<td>CNS</td>
<td>fail</td>
</tr>
<tr>
<td>S14</td>
<td>3210</td>
<td></td>
<td>5437</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S15</td>
<td>609</td>
<td>1516</td>
<td>1813</td>
<td>2082</td>
<td>CNS</td>
<td></td>
</tr>
<tr>
<td>S17</td>
<td>445</td>
<td>732</td>
<td>882</td>
<td>1166</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S20</td>
<td>23 695</td>
<td>27 179</td>
<td>24 696</td>
<td>3975</td>
<td>CNS</td>
<td></td>
</tr>
<tr>
<td>S21</td>
<td>1910</td>
<td>1907</td>
<td>428</td>
<td>1479</td>
<td>CNS</td>
<td></td>
</tr>
<tr>
<td>S22</td>
<td>1339</td>
<td></td>
<td></td>
<td>667</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S23</td>
<td>3312</td>
<td>2729</td>
<td>892</td>
<td>572</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S24</td>
<td>5998</td>
<td>5771</td>
<td>6706</td>
<td>6841</td>
<td>787</td>
<td></td>
</tr>
<tr>
<td>S25</td>
<td>1089</td>
<td>553</td>
<td></td>
<td>2586</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S26</td>
<td>11 731</td>
<td>14 394</td>
<td>16 189</td>
<td>11 535</td>
<td>CNS</td>
<td></td>
</tr>
</tbody>
</table>

Fail, detectable viral load with resistance; CNS, neuropsychiatric symptoms.
Efavirenz concentrations at months 1, 2, 4 and 6 of rifampicin and efavirenz concomitant administration and at month 21 after 15 months without rifampicin (therapeutic range 1000–4000 ng/mL; bold formatting, low; italic formatting, high; no formatting, normal). Most patients had efavirenz concentrations above or below the expected therapeutic range and only two had concentrations in the therapeutic range throughout TB therapy.
EFV concentrations occurred during concomitant rifampicin administration (CV 157% versus 58% off rifampicin), although intra-subject levels were relatively consistent over time (CV 24%). Second, EFV concentrations on rifampicin were not associated with body weight, gender or liver function. Third, short- and long-term HIV treatment outcomes were excellent and not associated with EFV concentrations when administered with rifampicin at a dose of 600 mg/kg.

The optimal dose of EFV when administered with rifampicin has not been established. Clinical guidelines in co-infected adults vary from 600 to 800 mg/day.2–4 These recommendations have been made in the context of considerable inter-individual variability in EFV levels and often without supporting pharmacodynamic information.7–9

The potential clinical sequelae of excessively high or low EFV concentrations are important and include treatment failure with subtherapeutic concentrations and neurotoxicity with excessively high levels.7 The clinical significance in terms of both efficacy and toxicity of the complex pharmacokinetic interaction between EFV and rifampicin is unclear since most studies have been cross-sectional in design. Here, we have shown large inter-individual variability and modest intra-individual variability in plasma EFV concentrations over time, with normalization in a significant proportion of patients after rifampicin discontinuation. In our study, although a daily dose of 600 mg EFV was associated with wide inter-individual variability and persistently abnormal EFV concentrations (both high and low) in over half of African patients during anti-TB therapy, both short- and long-term treatment efficacy and toxicity outcomes were excellent. Similar findings have been reported from Thailand10 and other studies have also suggested that standard dosing of EFV during TB treatment is associated with good HIV therapeutic outcomes.

Several limitations of this study must be noted. Although multiple determinations were made over time, the sample size was small. Secondly, although sampling was at trough (~24 h post-dose) self-reported timings may not have been completely accurate. However, most doses were by DOT and a validated adherence measure was employed and revealed few missed weekend doses. Further, since EFV has a long half-life (>30 h) and a relatively flat pharmacokinetic curve, any inaccuracies in timing of weekend doses would not be expected to exert a major effect, and would certainly not account for the observed wide variability.

Our results indicate that optimal dosing of EFV should be determined primarily through trials assessing clinical outcome, with pharmacokinetic data informing the design of those trials. This study and other available data suggest that a dose of 600 mg of EFV per day is sufficient when administered with rifampicin in the treatment of African adults with both TB and HIV disease.

Acknowledgements

We wish to acknowledge the contributions of Coleen Zinyani, study nurse, Vikesh Naidoo, study coordinator, the staffs of the Prince Cyril Zulu Communicable Diseases Clinic and Philani Clinic at King Edward VIII Hospital and the patients who participated in the study. Presented in preliminary form at the Twelfth Conference on Retroviruses and Opportunistic Infections, Boston, MA, USA, February 2005 (Abstract 154) and the Fifteenth International AIDS Conference, Bangkok, Thailand, July 2004 (Abstract MoPeB3355). The study was supported by grants from the Irene Diamond Fund, the Doris Duke Charitable Foundation and the Wellcome Trust. Drug analysis was funded by the Liverpool School of Tropical Medicine DfID HIV/AIDS and STI Knowledge Programme.

Transparency declarations

Dr G. F. received grant support form Bristol-Myers Squibb Company and Boehringer Ingelheim Pharmaceuticals, Inc. Dr S. H. K. has been a consultant to Bristol-Myers Squibb, Gilead, GlaxoSmithKline and Johnson & Johnson, and has received research grants from Abbott, Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb Company, Gilead, Pfizer, Johnson & Johnson, Drs C. J. and U. L. have no conflicts to declare during the course of this study.

References