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Once-daily directly observed therapy lopinavir/ritonavir plus indinavir as a protease inhibitor-only salvage therapy in heavily pretreated HIV-1-infected patients: a pilot study

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Lopinavir/ritonavir plus indinavir was administered once daily as directly observed protease inhibitor-only therapy in 12 heavily pretreated HIV-1-infected patients with multiple virological failures and advanced immunosuppression (CD4 cell count 95×10^6 cells/ μ l). The treatment was well tolerated. At weeks 12, 24 and 48, most patients on treatment achieved viral suppression of less than 400 copies/ml and a corresponding median CD4 T-cell count increase. Pharmacokinetic data indicated therapeutic concentrations for both protease inhibitors in most patients.

Potent antiretroviral therapy (ART) significantly decreases the morbidity and mortality of HIV infection [1]. Psychiatric co-morbidity or low social support are risk factors for poor adherence and virological failure. Once-daily regimens and directly observed therapy (DOT) may counter treatment failure, but options are often limited because of drug resistance.

Between October 2002 and October 2004 we conducted a pilot study to evaluate a once-daily boosted dual protease inhibitor (PI)-only regimen. Lopinavir/ritonavir (LPV/r) plus indinavir was given in heavily pretreated HIV-1-infected patients with a history of poor adherence and virological failure to nucleoside reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI). Therapeutic drug monitoring (TDM) of both PI was performed after 2 weeks of treatment.

Patients ($n = 12$) were mostly men (8/12, 67%), median age 41 years (range 27–63), weight 56 kg (range 44–91) and body mass index 21 kg/m^2 (range 16–29). Previous AIDS was found in eight out of 12 (67%) and hepatitis C virus (HCV) in 10 out of 12 (83%) patients. Of the latter

10 patients, eight had detectable HCV viraemia and four elevation of alanine aminotransferase. All patients had severe psychiatric co-morbidity (major depression or psychotic disorder), and seven were active intravenous drug users. All patients had a history of poor adherence, with a median of six therapy changes (range 3–11) containing one or more PI. Resistance testing at baseline detected M184V, K103N, and a median of four (range 3–6) thymidine analogue mutations in nine patients, and moderate genotypic resistance to lopinavir (M36I, M46I, A71LPT and L90M) in one patient. Median baseline HIV-1-RNA was $4.4 \log_{10}$ copies/ml (range 3.3–5.9) and CD4 T-cell count was 95×10^6 cells/ml (range 10–244). Boosted dual PI consisted of LPV/r with five to six pills (133.3/33.3 mg) and indinavir with two to three pills (400 mg), given as DOT once a day. The dose was adjusted according to TDM in five out of 12 patients to achieve trough levels of more than 150 ng/ml for indinavir and 4000–6000 ng/ml for lopinavir [2].

ART was generally well tolerated. Four patients reported mild diarrhoea, but no kidney or liver toxicity was observed. In five patients, lipid parameters (triglycerides and cholesterol) were increased by 20% above baseline after 12 weeks. No AIDS-defining event occurred, but one patient died from a relapsing non-Hodgkin lymphoma after 16 weeks.

TDM was performed in 10 patients after 2 weeks of treatment. The PI plasma concentration of lopinavir and/or indinavir were above the 90th percentile in five patients and between the 50th and 75th percentile in two patients. The LPV/r and indinavir dose was lowered in three and two patients, respectively. All five patients with higher concentrations of lopinavir or indinavir showed full viral suppression at week 24. In two patients, whose PI plasma levels were below the 25th percentile for either indinavir or lopinavir, viral suppression was achieved after 12 weeks and maintained over 24 and 48 weeks, respectively, without dose adjustment. In one patient experiencing virological failure (week 5), TDM indicated insufficient PI levels (< 10th percentile). Suboptimal adherence was suggested in this patient, as drug interactions were excluded.

At week 12, eight out of nine patients (89%) on treatment and 67% in the intention-to-treat (ITT) analysis achieved viral suppression of less than 400 copies/ml, of whom five showed a viral load of less than 50 copies/ml (55% on treatment and 42% ITT). At weeks 24 and 48, six out of seven (86% on treatment and 50% ITT) and all four patients on treatment (44% ITT) still maintained viral suppression of less than 400 copies/ml, respectively (Table 1). A median CD4 T-cell count increase of 79, 50 and 93×10^6 cells/ml was observed after 12, 24 and 48 weeks, respectively. Seven out of 12 patients discontinued treatment, five within 12 weeks, mostly as a result of the patient's wish (non-adherence). One

Table 1. Efficacy of a once-daily boosted protease inhibitor therapy with lopinavir/ritonavir plus indinavir in 12 patients: on-treatment and intention-to-treat analysis.

	Baseline	Week 12	Week 24	Week 48
Median HIV-1 RNA (log ₁₀ copies/ml)	4.4 (3.5–5.9)	1.7 (0.7–3.8)	1.3 (0.7–4.0)	1.4 (1.1–2.3)
Responders: OT (n, %)				
< 400 copies/ml		8/9 (89)	6/7 (86)	4/4 (100)
< 50 copies/ml		5/9 (55)	4/7 (57)	3/4 (75)
Responders: ITT (n, %)				
< 400 copies/ml		8/12 (67)	6/12 (50)	4/9 (44)
< 50 copies/ml		5/12 (42)	4/12 (33)	3/9 (33)
Median CD4 T-cell count (×10 ⁶ cells/ml)	95 (10–244)	160 (99–345)	160 (106–484)	211 (204–506)
Median ΔCD4 T-cell count (×10 ⁶ cells/ml)		79 (41–201)	50 (15–327)	93 (27–295)

ITT, Intention-to-treat; OT, on-treatment.

patient, who showed moderate PI resistance (M36I, M46I, A71LPT, L90M) at baseline, experienced virological failure at week 5 with the emergence of four new mutations (L10I, K20I, I54V, L63P). Two patients with a viral load greater than 400 copies/ml at weeks 12 and 24, respectively, demonstrated no resistance to both PI as measured by genotypic and phenotypic testing.

This pilot study provides evidence that directly observed once-daily combination therapy of LPV/r and indinavir is well tolerated and effective in patients with poor adherence and limited NRTI and NNRTI options. The efficacy of this boosted dual PI combination was previously demonstrated in drug-experienced patients treated with LPV/r and indinavir twice a day [3,4]. In our study, severe psychiatric co-morbidity and the high risk of non-adherence required a DOT once-daily regimen. The once-daily administration of LPV/r recently proved efficient in drug-naïve patients [5]. The combination of LPV/r plus indinavir may be particularly valuable as ritonavir has a double boosting effect on lopinavir and indinavir, resulting in the pharmacokinetic enhancement of both PI without increasing the pill count [6–8]. Indinavir penetrates into the central nervous system and the genital tract [9], which may reduce the risk of emerging drug resistance in viral reservoirs [10]. Finally, LPV/r is particularly advantageous in the salvage setting.

Our preliminary pharmacokinetic data demonstrate that both PI were within therapeutic ranges to allow a once-daily administration in most patients. Previously, a concentration trough greater than 150 ng/ml for indinavir proved necessary for viral suppression [11], whereas a concentration trough greater than 5700 ng/ml for lopinavir was an independent predictor of virological response in a salvage setting [12]. In our study, no correlation between weight, body mass index and PI plasma level was observed. In five patients, four co-infected with HCV, PI levels greater than the 90th percentile were derived from random drug concentrations and the timepoint of the last drug intake. As only one of these patients showed mild elevation of alanine aminotransferase levels (45 U/l), a boosting effect of liver

inflammation caused by HCV on drug concentrations was unlikely [13]. In three out of five patients, for whom PI dosing was lowered for either LPV/r or indinavir, drug levels measured after 2 weeks were within the therapeutic range. In two patients, the lopinavir concentration remained above the 90th percentile and no additional dose adjustment was performed, because ART was well tolerated. In two other patients, full viral suppression was noted after 12 weeks despite a low concentration trough for indinavir or lopinavir.

In conclusion, our results suggest that this boosted dual PI-only regimen, given once a day, may be a valuable salvage therapy for patients with poor adherence and limited NRTI/NNRTI options.

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Efavirenz 600 mg/day versus efavirenz 800 mg/day in HIV-infected patients with tuberculosis receiving rifampicin: 48 weeks results

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The potential of drug–drug interaction between efavirenz and rifampicin is a major concern in the treatment of HIV and tuberculosis. The optimal efavirenz dosage is still unclear. Our randomized control trial study recently reported the similar efavirenz level between efavirenz 600 and 800 mg/day in HIV-infected patients receiving rifampicin. We report the similar virological and immunological outcomes at 48 weeks between the two groups. Efavirenz 600 mg/day should be sufficient for concurrent use with rifampicin.

The concomitant use of efavirenz and rifampicin is common in the treatment of HIV and tuberculosis. The

potential of drug–drug interaction is one of the major concerns because both efavirenz and rifampicin induce cytochrome P450 isoenzyme, and plasma efavirenz levels can be reduced by rifampicin [1–4]. The appropriate daily dosage of efavirenz is still unclear. The current guideline for the use of antiretroviral agents has recommended efavirenz 800 mg/day as an optional regimen of antiretroviral therapy (ART) in an HIV-infected patient who is concurrently receiving rifampicin [5].

To compare the plasma efavirenz level between efavirenz 600 mg/day-based ART and efavirenz 800 mg/day-based ART in HIV-infected patients who have active tuberculosis and were receiving a rifampicin-containing antituberculous regimen, we conducted a randomized controlled trial and found that the median plasma efavirenz levels were comparable between the two groups [6]. The study was continued to determine the long-term virological and immunological outcomes. An open-labelled randomized controlled trial enrolled Thai HIV-infected patients from two centres: Ramathibodi Hospital, Mahidol University, Bangkok and the Bamrasnaradura Institute, Ministry of Public Health, Nonthaburi, Thailand. The inclusion and exclusion criteria were described in the previous report [6]. The institutional ethics committees of both hospitals approved the study.

Block randomization, using STATA version 8.0 (Stata Corp., College Station, Texas, USA), was applied to allocate patients to two groups, one receiving efavirenz 600 mg at bedtime and the other receiving efavirenz 800 mg at bedtime. Both groups also took stavudine 30/40 mg and lamivudine 150 mg twice a day and rifampicin 450/600 mg daily. The dosage of stavudine was adjusted by body weight (i.e. stavudine 30 and 40 mg for body weights < 60 and > 60 kg, respectively). The dosage of rifampicin was 450 mg for body weights less than 50 kg and 600 mg for body weights greater than 50 kg. Power and Sample Size version 1.01 was used to calculate the sample size [7]. A *P* value of less than 0.05 was considered as statistically significant. All analyses were performed using STATA version 8.0 (Stata Corp.).

In the present report, we report the virological and immunological outcomes at 48 weeks after initiating ART. Thirty-four patients (81.0%) in the efavirenz 600 mg group and 31 patients (73.81%) in the efavirenz 800 mg group had continued efavirenz-based ART until 48 weeks. The reasons for the discontinuation of ART in the efavirenz 600 mg group were as follows: six (14.3%) were lost to follow-up; one (2.4%) died; and one (2.4%) suffered severe headache. For the efavirenz 800 mg group, six (14.2%) were lost to follow-up; three (7.1%) died; one (2.4%) had hepatitis; and one (2.4%) had skin rash. The causes of death in both groups included two lymphomas, one cryptococcal meningitis, and one tuberculous meningitis. Thirty-one out of 34 patients (91.2%) in the efavirenz 600 mg group and 27 out of 31 patients

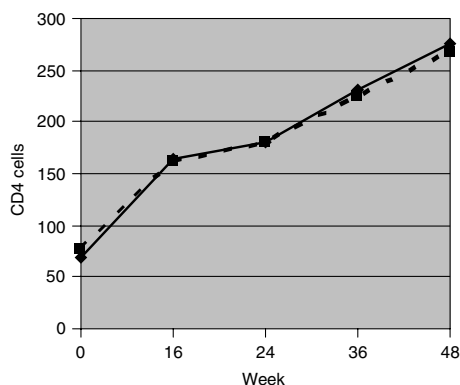


Fig. 1. Immunological outcomes at 48 weeks of antiretroviral therapy between the two treatment groups. —◆— Efavirenz 600 mg/day; —■— efavirenz 800 mg/day.

(87.1%) in the efavirenz 800 mg group achieved undetectable plasma HIV RNA ($P = 0.326$). By repeated measurement analysis of variance analysis, there was no significant difference in terms of mean CD4 cell change at 16, 24, 36, and 48 weeks after initiating efavirenz-based ART between the two groups, as shown in Fig. 1 ($P = 0.932$).

The results from our study indicate that efavirenz 600 mg/day should be adequate among Thai patients with an average body weight of 50 kg and receiving rifampicin. These findings suggest that the pharmacokinetic interaction between efavirenz and rifampicin observed in populations in developed countries does not significantly impact the antiviral response of efavirenz-based therapy in resource-limited settings. The long-term follow-up of this study may confirm these findings.

In a resource-limited setting in which access to ART is highly challenging and generic efavirenz is not available, the increased cost of efavirenz 800 mg/day compared with 600 mg/day may increase the barrier to good adherence and successful ART. A recent report showed that using efavirenz 800 mg/day increased toxicity, and most of the patients were unable to tolerate this high dosage [8]. The results from our study support the use of efavirenz 600 mg/day in patients with tuberculosis who are also receiving rifampicin. The results of virological and immunological outcomes also demonstrate that ART is effective and practical in resource-limited settings, even in patients with low CD4 cell counts and active opportunistic infections.

We conclude that immunological and virological outcomes at 48 weeks after initiating ART between efavirenz 600 mg/day and efavirenz 800 mg/day were comparable. Efavirenz 600 mg/day should be sufficient for HIV-infected patients receiving rifampicin. These results may not be applicable to other ethnic populations who have greater body weights.

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