Original article

A randomized comparison of second-line lopinavir/ritonavir monotherapy versus tenofovir/lamivudine/lopinavir/ritonavir in patients failing NNRTI regimens: the HIV STAR study

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Background: Data informing the use of boosted protease inhibitor (PI) monotherapy as second-line treatment are limited. There are also no randomized trials addressing treatment options after failing first-line non-nucleoside reverse transcriptase inhibitor (NNRTI)-regimens.

Methods: HIV-infected subjects ≥18 years, with HIV RNA≥1,000 copies/ml while using NNRTI plus 2 NRTIs, and naive to PIs were randomized to lopinavir/ritonavir (LPV/r) 400/100 mg twice daily monotherapy (mono-LPV/r) or tenofovir disoproxil fumarate (TDF) once daily plus lamivudine (3TC) twice daily plus LPV/r 400/100 mg twice daily (TDF/3TC/LPV/r) at nine sites in Thailand. The primary outcome was time-weighted area under curve (TWAUC) change in HIV RNA over 48 weeks. The a priori hypothesis was that the mono-LPV/r arm would be considered non-inferior if the upper 95% confidence limit in TWAUC mean difference was ≤0.5 log10 copies/ml.

Results: The intention-to-treat (ITT) population comprised 195 patients (mono-LPV/r n=98 and TDF/3TC/LPV/r n=97): male 58%, baseline mean (so) age of 38 (7) years, CD4+ T-cell count of 204 (135) cells/mm3 and HIV RNA of 4.1 (0.6) log10 copies/ml. The majority had HIV-1 recombinant CRF01_AE infection, and thymidine analogue mutation (TAM)-2 was 3× more common than TAM-1. At 48 weeks, the difference in TWAUC HIV RNA between arms was 0.15 (95% CI -0.04, 0.33) log10 copies/ml, consistent with our definition of non-inferiority. However, the proportion with HIV RNA<50 copies/ml was significantly lower in the mono-LPV/r arm: 61% versus 83% (ITT, P<0.01). Baseline HIV RNA≥5 log10 copies/ml (P<0.001) and mono-LPV/r use (P=0.003) were predictors of virological failure. Baseline genotypic sensitivity scores ≥2 and TAM-2 were associated with better virological control in subjects treated with the TDF-containing regimen.

Conclusions: In PI-naive patients failing NNRTI-based first-line HAART, mono-LPV/r had a significantly lower proportion of patients with HIV RNA<50 copies/ml compared to the TDF/3TC/LPV/r treatment. Thus, mono-LPV/r should not be recommended as a second-line option.
Introduction

Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based HAART is recommended as first-line therapy for HIV-infection [1,2]. The rate of virological failure of NNRTI-based HAART ranges from 38–44% [3]. In patients with treatment failure, a ritonavir-boosted protease inhibitor (PI) in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) selected on the basis of a drug-resistance test is recommended as second-line therapy [1,2]. However, HIV RNA testing is not routinely accessible in resource-limited settings, and by the time clinical or immunological failure is identified, patients generally have extensive NNRTI and NRTI mutations [4,5]. In these settings, it is unknown whether using NRTIs plus a boosted PI is beneficial, compared to treating with boosted PI alone. Moreover, the long-term mitochondrial and organ-specific toxicities of NNRTI and NRTI mutations [4,5]. In these settings, it is unknown whether using NRTIs plus a boosted PI is beneficial, compared to treating with boosted PI alone. Moreover, the long-term mitochondrial and organ-specific toxicities of NNRTI and NRTI mutations [4,5]. In these settings, it is unknown whether using NRTIs plus a boosted PI is beneficial, compared to treating with boosted PI alone. Moreover, the long-term mitochondrial and organ-specific toxicities of NNRTI and NRTI mutations [4,5]. In these settings, it is unknown whether using NRTIs plus a boosted PI is beneficial, compared to treating with boosted PI alone. Moreover, the long-term mitochondrial and organ-specific toxicities of NNRTI and NRTI mutations [4,5]. In these settings, it is unknown whether using NRTIs plus a boosted PI is beneficial, compared to treating with boosted PI alone. Moreover, the long-term mitochondrial and organ-specific toxicities of NNRTI and NRTI mutations [4,5]. In these settings, it is unknown whether using NRTIs plus a boosted PI is beneficial, compared to treating with boosted PI alone. Moreover, the long-term mitochondrial and organ-specific toxicities of NNRTI and NRTI mutations [4,5].

Boosted PI monotherapy has been studied in treatment-naive patients or adults who are virologically well suppressed [7–9]. Lopinavir/ritonavir (LPV/r) monotherapy (mono-LPV/r) has been the most investigated boosted PI because of its coformulation with ritonavir, and its high genetic barrier to resistance [10]. Six randomized controlled trials of mono-LPV/r versus LPV/r-based HAART have been conducted, including five in virologically suppressed patients, where mono-LPV/r was used as maintenance therapy, and one that was conducted in antiretroviral-therapy-naive patients with HIV RNA <100,000 copies/ml. These studies showed that the risk of virological failure was greater with mono-LPV/r compared to LPV/r-based HAART; 33.2% versus 22.9% (pooled OR 1.48 [95% CI 1.02, 2.13]; P = 0.037) [10]. Episodes of low-level HIV viraemia defined as HIV RNA 50–500 copies/ml were more common in patients receiving mono-LPV/r compared to those on LPV/r-based HAART, but low level viraemia could be controlled after intensification with two NRTIs [7,10,11].

There are limited data describing mono-PI as a second-line therapy in HIV-infected adults failing first-line NNRTI-based HAART. If mono-LPV/r can be used as second-line therapy, it could reduce pill burden, NRTI side effects, drug interactions, medication cost, and the need for genotyping, while preserving future treatment options. Bartlett et al. [12] reported a single-arm pilot study of mono-LPV/r following virological failure of first-line NNRTI-based regimens (ACTG5230), which showed promising preliminary activity of second-line mono-LPV/r with a CD4+ T-cell increase and HIV RNA <400 copies/ml at week 24 in 87% of the 122 enrolled subjects. However, ACTG5230 was an uncontrolled study with a short-term follow-up period, and the success rate at a lower cutoff of 50 copies/ml has not been reported. Here, we report an open-labelled randomized multicentre non-inferiority study of mono-LPV/r versus tenofovir (TDF)/lamivudine (3TC)/LPV/r as second-line therapy in HIV-infected adults failing NNRTI-based HAART.

Methods

Participants and randomization

From May 2008 to November 2009, Thai adults failing first-line NNRTI-based regimens from nine hospitals were enrolled in an open-labelled multicentre randomized trial, the HIV Second-line Therapy Anti-Retroviral study (the HIV STAR study; including patients who failed NNRTI-based regimens [clinicaltrial.gov identification number NCT00627055]). Subjects were eligible if they were HIV-infected adults aged ≥18 years, who had been treated with NNRTI-based HAART for ≥6 months, had HIV RNA ≥1,000 copies/ml, and had never used PIs. Exclusion criteria were active opportunistic infection at screening, pregnancy, positive hepatitis B surface antigen, alanine aminotransferase (ALT) ≥200 U/l and creatinine clearance <60 ml/min by the Cockcroft-Gault equation. Study subjects were also not allowed to take oral medication that interferes with the pharmacokinetics of LPV/r, including rifampicin, rifabutin, phenobarbital, phenytoin, carbamazepine, dexamethasone, ketoconazole and clarithromycin.

At enrolment, subjects were randomized to mono-LPV/r versus TDF/3TC/LPV/r. The randomizations were managed centrally by an independent biostatistician using a minimization scheme with a programme written in SAS Version 9.1 (SAS Corporation, Cary, NC, USA), and were stratified by site, baseline HIV RNA <5 or ≥5 log10 copies/ml and baseline CD4+ T-cell count <100 or ≥100 cells/mm3. The dosages were LPV/r 400/100 mg orally every 12 h, TDF 300 mg orally every 24 h and 3TC 150 mg orally every 12 h or 3TC 300 mg orally every 24 h. The formulations of LPV/r were soft gel capsules LPV/r (Kaletra®; 133/33 mg) and/or LPV/r tablets (Matrix®; 200/50 mg).

Clinical assessment

Weight (kg), height (cm), CD4%, CD4+ T-cell count, HIV RNA and ALT were assessed at week 0 then every 12 weeks until 48 weeks. HIV RNA analysis was performed centrally at the HIV-NAT laboratory in Bangkok, Thailand by the Cobas Ampliprep/TaqMan HIV-1 Viral load assay (Roche Molecular Systems, Inc., Branchburg, NJ, USA). Genotypic resistance tests using an in-house method validated for HIV clade A/E were performed centrally at the Vaccine and Cellular Immunology Laboratory (Chulalongkorn University, Bangkok, Thailand) [13], which has participated in...
the TreatAsia Quality Assurance Scheme (TAQAS) since 2006 [14]. Resistance testing was performed in subjects with HIV RNA≥1,000 copies/ml. Mutations were defined according to the Stanford Interpretation system. Multi-NRTI mutations were defined per IAS–USA list of mutations as having ≥4 thymidine analogue mutations (TAMs) or Q151M complex or 69 insertion [15]. The TAMs were M41L, D67N, K70R, L210W, T215F/Y, and K219E/Q. Two exclusive pathways of TAMs have been well described: TAM-1 profile, which includes M41L, L210W and T215F/Y, and TAM-2, including D67N, K70R and K219E/Q. The patterns of TAMs and their effects on virological control when TDF was included in the regimen were analysed [16]. The genotypic sensitivity score (GSS) is based on the Stanford resistance algorithm analytical results. For TDF, potential low-level resistance and low-level resistance were considered as susceptible to TDF, whereas other levels were considered as resistant. Clinical and laboratory adverse events were graded by the Division of AIDS grading table (December 2004) [17]. Adherence was evaluated at every visit by self-reported visual analogue scale [18].

Every 24 weeks, measures of fasting lipids, glucose and creatinine were performed. Estimated creatinine clearance was calculated by the Cockroft-Gault equation [19]. An independent Data Safety and Monitoring Board (DSMB) reviewed the overall quality of the trial and data from two interim analyses. The first analysis occurred when 60 participants had reached week 24. Stopping criteria were based on virological failure, resistance and safety data. The DSMB recommended a second interim analysis to occur when 100 subjects (50 in each arm) had reached week 24. At both reviews, the DSMB recommended continuing the study. The protocol was approved by the Thai Ministry of Public Health and local ethics committees. All subjects gave informed consent.

Primary endpoint, definitions and patient management
The primary endpoint was time-weighted area under the curve (TWAUC) mean change of log_{10} HIV RNA from baseline to week 48 by treatment arm. The secondary end points were in proportion with undetectable HIV RNA at levels <50 and <400 copies/ml, at weeks 24 and 48. At ≥24 weeks, if HIV RNA was ≥400 copies/ml, the patients returned within 4 weeks to receive adherence counselling and a repeat HIV RNA quantification. At this visit, the patients in the mono-LPV/r arm had TDF/3TC added while waiting for the result of repeated HIV RNA testing. If the repeated HIV RNA was <50 copies/ml, patients stopped TDF/3TC and continued mono-LPV/r. If the repeated HIV RNA was ≥50 copies/ml, the mono-LPV/r patients were instructed to continue TDF/3TC/LPV/r. The failing patients in the TDF/3TC/LPV/r arm had treatment modifications based on standard of care. Resistance assay was performed for samples with HIV RNA≥1,000 copies/ml.

Statistical procedures
Sample size calculations were based on the TWAUC mean change in log_{10} HIV RNA [20]. A priori we defined non-inferiority as the upper 95% confidence limit in TWAUC mean difference ≤0.5 log_{10} copies/ml. Assuming the between-patient variability corresponded to a standard deviation of 1.0 log_{10} and no difference between treatment arms, a sample size of 85 patients per arm would give a 90% chance that the two-sided 95% CI had an upper limit below 0.5 log_{10}. An additional 15 patients per arm were recruited to compensate for losses to follow-up. The TWAUC mean change from baseline HIV RNA to week 48 was calculated for each patient as the area under curve change from baseline to each follow-up HIV RNA measure, averaged over the patient’s total duration of follow-up. Comparison of time-weighted change between treatment arms was made by calculating difference between means, the corresponding 95% CI, and Student’s t-test-derived P-values. The intention-to-treat (ITT) population was defined as randomly assigned participants who received ≥1 study medication dose and attended ≥1 follow-up visit. There was no extrapolation of data for the primary endpoint. For continuous safety end points in ITT analysis, a last observation carried forward approach was adopted. In ITT analyses comparing the proportion of patients with undetectable HIV RNA, those with missing data, and those who had changes to their randomized regimen because of virological failure, were imputed as failures. Per protocol (PP) analyses were conducted for primary and secondary end points, and in these analyses participants were censored when the randomized therapy was ceased. Absolute differences in proportions were assessed using 95% CI, and χ²-derived P-values. Predictors of virological failure were assessed with logistic regression. A stepwise backwards approach was used to develop a multivariate model, starting with covariates with P<0.2 in univariate models and retaining those with P<0.05 in the final model. All analyses were undertaken using STATA 11 (StataCorp, College Station, TX, USA).

Results
A total of 200 HIV-infected adults were randomized, 100 to each of the two arms. Five were excluded from the ITT analysis because they did not return at week 0 (Figure 1). The demographic characteristics were similar between arms as shown in Table 1, but the...
mono-LPV/r included a higher proportion of males. At screening, 180 (92%) participants used 3TC, 123 (63%) used stavudine, 45 (23%) used zidovudine and 9 (5%) used TDF. Nevirapine and efavirenz were used in 167 (86%) and 28 (14%) participants, respectively.

Primary outcome
For 195 patients in the ITT population, the mean ± SD reductions in TWAUC were 1.74 ± 0.64 log_{10} for the mono-LPV/r arm and 1.89 ± 0.65 log_{10} for the TDF/3TC/LPV/r arm, which is an absolute difference of 0.15 log_{10} (95% CI -0.04, 0.33). Thus the mean difference in TWAUC in HIV RNA between the arms was consistent with our definition of non-inferiority in both the ITT and PP populations (Table 2). Because of gender imbalance in the treatment arms and a slight imbalance in the proportion of patients with baseline multidrug resistance, we conducted further adjusted analyses which did not change the interpretation of the primary end point (Table 2).

Secondary outcomes
The proportion of patients with HIV RNA <400 copies/ml in the mono-LPV/r arm was 74.5% versus 85.6% in the TDF/3TC/LPV/r arm (absolute difference -11.1%, 95% CI -22.2, 0.0; P = 0.053). However, significantly lower proportions of patients in the mono-LPV/r arm compared to the TDF/3TC/LPV/r arm had HIV RNA <200 (69.4% versus 85.6%; absolute difference -16.2%, 95% CI -27.7, -4.7; P = 0.01) and <50 copies/ml (61.2% versus 82.5%; absolute difference -22.2%, 95% CI -33.5, -9.0; P < 0.01). The proportion of patients in different HIV RNA strata over 48 weeks is presented in Figure 2.

Analyses by pre-specified subgroups
Randomization was stratified by baseline CD4+ T-cell count at a cutoff point of 100 cells/mm³, and by baseline HIV RNA at a cutoff point of 5 log copies/ml. The proportion with HIV RNA <50 copies/ml in the LPV/r arm versus the TDF/3TC/LPV/r arm in the ≥5 log strata were 1/9 (11%) and 6/10 (60%)
respectively (OR 12.0 [95% CI 1.1, 136.8]), and in the <5 log strata were 63/89 (71%) and 74/87 (85%), respectively (OR 2.3 [95% CI 1.1, 4.9]). The proportions of patients with HIV RNA<50 copies/ml in the mono-LPV/r arm versus the TDF/3TC/LPV/r arm in the CD4+ T-cell count <100 cells/mm³ strata were 11/20 (55%) and 24/24 (22%), respectively (OR 1.64 [95% CI 0.5, 5.6]) and in the CD4+ T-cell count ≥100 cells/mm³ strata were 53/78 (68%) and 64/73 (88%), respectively (OR 3.4 [95% CI 1.4, 7.8]). All were based on ITT analysis.

Analyses by patterns of baseline resistance: TAM-1, TAM-2 and genotypic sensitivity score

Based on the pol sequences, the majority (96%) of patients had recombinant CRF01_AE infection and 4% were CRF01_B. Almost all had 3TC-resistance-associated mutations (M184V/I), and approximately one-third had multi-NRTI resistance (Table 1). None had a 69 insertion. In total, 45 (23%) had TDF-resistance (including patients with K65R, any TAM-1 and/or three TAM-1).

Baseline NRTI-associated mutations, baseline GSS and the proportion with HIV RNA<50 copies/ml at week 48 are shown in Figure 3A and 3B. Approximately one-half (51%) of patients were found carrying any TAM, but TAM-2 profiles were more common than TAM-1 (47.7% versus 16.4%; 3:1 ratio). Similarly, a higher proportion of patients (approximately three-fold) carried all three mutations of TAM-2 compared with three TAM-1 mutations (16.9% versus 5.1%, respectively).

As shown in Figure 3B, in the TDF/3TC/LPV/r-treated group, patients with baseline GSS of ≥2 had a higher percentage of undetectable HIV RNA (<50 copies/ml) than those with GSS=1 (83.3% versus 79%, respectively).
This within-arm difference was not statistically different, but it was significant when compared to the mono-LPV/r arm (an undetectable rate of 65.3%; \( P < 0.05 \)). TAM-2 (either any mutation, or with all three mutants) were associated with better virological control in subjects treated with the TDF-containing regimen (Figure 3A).

Predictors of virological failure

By multivariate logistic regression analysis, HIV RNA \( \geq 5 \log_{10} \) copies/ml at time of NNRTI-based HAART failure (OR 7.87, 95% CI 2.73, 22.68; \( P < 0.001 \)) and mono-LPV/r treatment (OR 3.09, 95% CI 1.46, 6.55; \( P = 0.003 \)) were independently associated with virological failure. Gender, age, CDC clinical classification, duration of NNRTI-based HAART before enrolment, baseline haemoglobin, CD4\(^+\) T-cell count and adherence during the study evaluated by visual analogue scale were not significantly associated with virological failure.

None of the patients in the TDF/3TC/LPV/r arm had changed their HAART during the study period. A total of 17 patients in the mono-LPV/r arm with protocol-defined virological failure had TDF/3TC added. Overall, 9 (53%), 4 (23.5%) and 4 (23.5%) of these patients had HIV RNA \(< 50\), 50–1,000 and \(\geq 1,000\) copies/ml after 24 weeks of adding TDF/3TC. These patients continued TDF/3TC/LPV/r until their last visit in this study. Resistance tests were performed in 17 patients failing mono-LPV/r, and major PI mutations (M46I/L, 150V and V82A) were detected in 3 patients. The last HIV RNA results of these three patients after adding TDF/3TC were 40, 405 and 166,355 copies/ml, respectively. No major PI mutation was found in three patients in the TDF/3TC/LPV/r arm who had virological failure.

Clinical, immunological and metabolic treatment outcomes

One death was reported in each arm. A woman in the mono-LPV/r arm died at home from an unknown cause at week 24; her last CD4\(^+\) T-cell count was 105 cells/mm\(^3\) and HIV RNA was \(< 50\) copies/ml. A man in the TDF/3TC/LPV/r arm died from lymphoma at week 36; his last CD4\(^+\) T-cell count was 28 cells/mm\(^3\) and HIV RNA was \(< 50\) copies/ml. No other patients experienced CDC category C events. The treatment outcomes at week 48 are shown in Table 3. There were no differences except for subjects in the mono-LPV/r arm having significantly higher body weight, total cholesterol, triglycerides and creatinine clearance than those in TDF/3TC/LPV/r arm. Both arms had a median adherence of 100% over the duration of the study. CD4\(^+\) T-cell counts increased significantly from baseline in both arms.

There were 18 grade 3–4 adverse events in 10 patients that were at least possibly related to the study drugs (7 events in 7 patients in the mono-LPV/r arm...
and 11 events in 3 patients in TDF/3TC/LPV/r arm). They occurred at a median follow-up time of 23 weeks (IQR 6–47). Serious adverse events were reported in two patients in the mono-LPV/r arm (elevated triglycerides) and seven patients in the TDF/3TC/LPV/r arm (elevated triglycerides, gastrointestinal symptoms, elevated ALT and neutropenia).

**Discussion**

Among patients who had failed two NRTIs plus NNRTI but were PI-naive, by our predetermined primary end point and criteria, the mono-LPV/r arm was non-inferior to the TDF/3TC/LPV/r arm. However, mono-LPV/r was significantly poorer than the
The predictors of mono-LPV/r failure have been reported by other groups. In trials using mono-LPV/r as the maintenance therapy, lower baseline haemoglobin [28], CD4+ T-cell count [29] and adherence [28,29] were predictors of mono-LPV/r failure. However, these predictors could not be compared directly to our study because of the different scenarios of maintenance therapy in those studies versus salvage therapy in ours. Our study showed that higher baseline HIV RNA and mono-LPV/r treatment predicted virological failure. NNRTIs have a long terminal half-life and the enzymatic induction persists for a few weeks after cessation. Therefore, possible low levels of LPV/r within the first few weeks after switching from NNRTIs could occur from the drug interactions between LPV/r and NNRTI, a factor possibly contributing to treatment failure especially in the mono-LPV/r group. Patients in both arms

Table 3. Changes of parameters over 48 weeks

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Week 0</th>
<th>Change from week 0 to 48</th>
<th>Mean difference in week 48 change scores between arms (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mono-LPV/r</td>
<td>TDF/3TC/LPV/r</td>
<td>Mono-LPV/r</td>
<td>TDF/3TC/LPV/r</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>59.2 (10.6)</td>
<td>57.7 (10.4)</td>
<td>1.8 (4.3)</td>
<td>-0.5 (5.0)</td>
</tr>
<tr>
<td>CD4+ T-cell count, cells/mm²</td>
<td>194 (123)</td>
<td>211 (134)</td>
<td>137 (110)</td>
<td>114 (117)</td>
</tr>
<tr>
<td>ALT, IU/l</td>
<td>44.5 (27.8)</td>
<td>37.1 (21.9)</td>
<td>-10.2 (39.76)</td>
<td>-11.3 (29.1)</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>0.92 (0.19)</td>
<td>0.88 (0.18)</td>
<td>0.01 (0.14)</td>
<td>0.05 (0.19)</td>
</tr>
<tr>
<td>CrCl, ml/min²</td>
<td>93 (22)</td>
<td>88 (23)</td>
<td>1.2 (15.9)</td>
<td>-4.5 (16.8)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>188 (48)</td>
<td>196 (40)</td>
<td>36 (57)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Triglyceride, mg/dl</td>
<td>197 (129)</td>
<td>219 (164)</td>
<td>159 (272)</td>
<td>71 (176)</td>
</tr>
<tr>
<td>HDL, mg/dl</td>
<td>44.7 (13.4)</td>
<td>46.7 (16.1)</td>
<td>0.05 (22.9)</td>
<td>-3.7 (14.7)</td>
</tr>
<tr>
<td>Glucose, mg/dl</td>
<td>91 (22)</td>
<td>88 (17)</td>
<td>-0.06 (21)</td>
<td>-1.4 (19)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) unless otherwise indicated. *Creatinine clearance (CCr) was calculated by the Cockcroft-Gault equation. ALT, alanine aminotransferase; HDL, high-density lipoprotein; LPV/r, lopinavir/ritonavir; mono-LPV/r, lopinavir/ritonavir monotherapy; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine.

TDF/3TC/LPV/r arm by the secondary virological end point. Patients in the mono-LPV/r arm were more likely to have HIV viraemia between 50–200 copies/ml than when LPV/r was combined with two NRTIs. This observation is similar to results from previous mono-LPV/r studies [10]. When two NRTIs were added to mono-LPV/r in failing patients, a difference in proportions of patients achieving HIV RNA<50 copies/ml between the two arms remained. It is interesting that in the TDF/3TC/LPV/r arm, of which almost all patients had 3TC resistance, one-third had multi-NRTI resistance and one-fifth had TDF resistance (including patients with K65R, any TAM-1 and/or three TAM-1) and >80% achieved virological suppression <50 copies/ml, which was significantly higher than that in the mono-LPV/r arm (61% versus 83%, respectively; P<0.01). Our finding supports the use of TDF/3TC/LPV/r in patients who failed first-line NNRTI-based HAART and did not have significant TDF resistance.

Mono-LPV/r regimens may have some benefits. The improvement of CD4+ T-cell count and HIV RNA after switching to second-line mono-LPV/r had been reported from ACTG5230 [12]. However, the ACTG study reported a short follow-up period of 24 weeks and the HIV RNA cutoff was 400 copies/ml. Our study did not demonstrate a difference between arms using this HIV RNA cutoff threshold, but did show inferior virological suppression with the ultrasensitive assay (50 copies/ml threshold). In our study, improvement of CD4+ T-cell count and CDC progression during 48 weeks was comparable between arms. Moreover, our study found a small but statistically significant elevation in calculated creatinine clearance in patients treated with TDF. In some guidelines, mono-LPV/r is an option for patients who cannot tolerate NRTIs or who need treatment simplification [21,22]. However, this is not consistent among guidelines [23,24]. Our study demonstrates that mono-LPV/r as a second-line option should be used with caution, particularly in settings where close HIV RNA monitoring is not available. Approximately one-half of our patients who failed the mono-LPV/r regimen suppressed their HIV viraemia after TDF/3TC was added, similar to results from studies on previous HAART-naive patients [10]. This is likely due to the low proportion of our patients with TDF resistance. Of those who failed, 3/17 patients in the mono-LPV/r arm and none in the LPV/r-HAART arm developed major PI mutations.

Boosted PI can cause long-term metabolic side effects. Dyslipidaemia was common in both arms, but significant increases in triglycerides and total cholesterol were noted in patients in the mono-LPV/r arm compared to those in the TDF/3TC/LPV/r arm. It is possible that that persistent HIV RNA viraemia in the mono-LPV/r arm contributed to ongoing inflammation resulting in increased lipid levels [25], or TDF might have interacted with boosted PI regimens to influence lipid levels [26]. In addition, TDF has been reported to decrease lipid levels in healthy [27]. Long-term metabolic effects in this population should be monitored.
Our study found that TDF/3TC/LPV/r was superior to mono-LPV/r in patients who failed stavudine (d4T) or zidovudine/3TC/NRTI, although almost all subjects had 3TC resistance (M184V/I) and one-third had multidrug resistance NRTI mutations. Possible explanations are that TDF was active in suppressing HIV in most patients, the M184V mutation reduced the replicating capacity of HIV [31] and mono-LPV/r had insufficient potency in suppressing viraemia in patients with high HIV RNA. Baseline GSS analyses (Figure 3B) demonstrated that ≥2 active ARTs in the second-line regimen provided the better efficacy for virological control. Regarding TAMs, two pathways including TAM-1 (mutations 41L, 210W and 215Y) and TAM-2 (67N, 70R and 219E/Q) have been confirmed by a number of studies [16,32,33]. In HIV-1 subtype B, both zidovudine and d4T were associated with TAM-1 more commonly than the TAM-2 pathway [33,34]. However, non-B subtypes may show differences in this regard. A report from Thailand where HIV-1 subtype CRF01_AE is the most predominant subtype (like most South-East Asian countries) has found TAM-2 but not TAM-1 to be more common in patients, the majority of whom had failed d4T-containing NNRTI-based regimens [35]. More importantly, with regard to its susceptibility to TDF, TAM-1 (T215Y and L210W in particular) but not TAM-2 shows more cross-resistance to TDF [36]. In this study of which the majority of patients were infected with HIV-1 recombinant CRF01_AE and treated with d4T, TAM-2 (either any or all three) was approximately 3× more common than TAM-1 profile. Thus, patients carrying TAM-2 responded significantly better to TDF-containing second-line ART compared to those carrying TAM-1. This may not be applicable to other settings where subtype B predominates. Therefore resistance testing should be performed at the time of treatment failure whenever possible, and, if not, the active nucleosides might be prematurely discarded.

In terms of ethical considerations in conducting this study, we initiated this study because published data showing extensive NRTI resistance in Thai individuals failing first-line NRTI/NNRTI regimens cast doubt on the usefulness of available NRTIs in the next regimen [4,5,37]. In addition, the infrastructure for routine genotyping to guide NRTI selection for second-line regimens was not in place in the Thai public health system. This study reflects the reality in many resource-limited settings and tested the efficacy of LPV/r with or without two NRTIs, devoid of genotyping for NRTI selection. Our study illustrating TDF/3TC/LPV/r to be effective in most patients failing first-line regimens supports the scaling-up of such second-line regimens in settings without genotyping. More importantly, this study was monitored closely by a DSMB to ensure patients’ safety and protection.

Our study had some limitations. First, due to feasibility constraints our study was designed using a primary end point of TWAUC, not the more stringent design of ITT-time to loss of virological response algorithm at week 48 with a predefined non-inferiority margin (Δ) of 12%. Second, the high virological suppression rate we report in patients treated with TDF/3TC/LPV/r may not be applicable to those with a much more extensive duration of NNRTI-based failure. Third, this study is based on a population predominantly infected with HIV-1 recombinant CRF01_AE, which was found to preferentially use TAM-2 not TAM-1 as its thymidine-analogue resistance pathway, thus the results might not be directly applicable to subtype B settings. The strength of this study is that it is a randomized trial of mono-LPV/r as a second-line treatment in patients failing NRTI/NNRTI first-line. Another trial on second-line mono-LPV/r in Africa is ongoing [38].

In conclusion, LPV/r monotherapy should not be recommended as a second-line regimen, and if used, should be used with caution, particularly in settings where close HIV RNA monitoring is not available. This study supports the efficacy of second-line TDF/3TC/LPV/r-based regimens, particularly in patients whose viruses remained sensitive to TDF. In settings where more new classes are accessible, the second-line antiretroviral option is to switch to a fully-active antiretroviral triple combination guided by a genotypic HIV resistance test.

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The sponsors and investigators contributed to study concept and design, interpretation of data, preparation and review of the manuscript, and final approval of the paper for publication. KR and TB had full access to the data and took responsibility for the integrity of the data and the accuracy of the data analyses.

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The study results were presented in part as a late breaker poster presentation at the 18th Conference on Retroviruses and Opportunistic Infections, 28 February–2 March 2011, Boston, MA, USA (poster S84).

Disclosure statement

PC has received speaker honoraria or educational grants from Abbott, Bristol–Myers Squibb, Janssen–Cilag, GlaxoSmithKline, MSD, IDS and Roche. JA has received speakers’ fees or honoraria from Roche, Gilead, ViiV and Abbott. SS has received speakers’ fees or honoraria from Gilead, Pfizer, Tibotec and Abbott. BH has received travel grants, and speaker fees from Janssen, Gilead and MSD. KR has received speaker honoraria or educational grant support from Abbott, Gilead, Bristol–Myers Squibb, Merck, Roche, Janssen–Cilag, GlaxoSmithKline, Tibotec and the Governmental Pharmaceutical Organization. KR has also received a Professional Researcher Strengthening Grant from the National Science and Technology Development Agency, BIOTEC, Ministry of Science and Technology, and the National Research University Project of The Commission of High School Education in Thailand (CHE) and the Ratchaphiseksomphot Endowment Fund (HR1161A), and is the Thai Research fund (TRF) Senior Research Scholar. All other authors declare no competing interests.

Additional file

Additional file 1: A list of members of the HIV STAR Data Safety Monitoring Board, HIV STAR Study Group and consultants can be accessed via http://www.intmedpress.com/uploads/documents/AVT-12-OA-2554_Bunupuradah_Add_file_1.pdf

References


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