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ORIGINAL RESEARCH

Efficacy and tolerability of a double boosted protease inhibitor (lopinavir + saquinavir/ritonavir) regimen in HIV-infected patients who failed treatment with nonnucleoside reverse transcriptase inhibitors

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Objectives

Long-term nonnucleoside reverse transcriptase inhibitor (NNRTI)-based antiretroviral treatment failure in most developing countries has led to broad cross-resistance within NNRTI and nucleoside reverse transcriptase inhibitor (NRTI) classes. In this study, we investigated the efficacy and tolerability of a double boosted protease inhibitor (PI) regimen in this setting.

Methods

A total of 64 HIV-infected patients who had failed NNRTI-based regimens were randomized to receive either lopinavir/saquinavir/ritonavir [LPV/SQV/r; 400/1000/100 mg twice a day (bid)] alone or indinavir/ritonavir (IDV/r; 800/100 mg bid) plus two NRTIs optimized with genotypic drug resistance guidance. Patients who had no available optimized NRTI backbone were allocated to the LPV/SQV/r arm.

Results

At 48 weeks, the percentages of patients with plasma viral load < 50 HIV-1 RNA copies/mL were 60% (31 of 52 patients) in the LPV/SQV/r arm vs 50% (six of 12) in the IDV/r/2NRTIs arm in the intent-to-treat (ITT) analysis, and 61% (31 of 51) vs 71% (five of seven), respectively, in the as-treated analysis. The median (interquartile range) increases in absolute CD4 cell count from baseline were 177 (91–269) and 100 (52–225) cells/μL in the LPV/SQV/r and IDV/r/2NRTIs groups, respectively ($P = 0.32$). Four of 12 patients (33%) in the IDV/r/2NRTIs group experienced severe nausea and vomiting and four patients (8%) in the LPV/SQV/r group had significant hepatitis.

Conclusions

LPV/SQV/r and high-dose boosted IDV were not well tolerated and led to $<65\%$ ITT virological efficacy outcomes. A randomized larger scale study with new formulations and/or more tolerable boosted PIs in NNRTI-based failure is warranted.

Keywords: double boosted protease inhibitor, nonnucleoside reverse transcriptase inhibitor resistance, salvage therapy, Thailand

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Introduction

Since highly active antiretroviral therapy (HAART) for HIV infection became available, the rates of mortality and morbidity associated with HIV disease have declined [1,2]. The recommended first-line antiretroviral (ARV) combinations for HIV-infected persons are two nucleoside reverse transcriptase inhibitors (NRTIs) as a backbone plus either

nonnucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors (PIs) [3,4]. At present, an NNRTI-based regimen is the first-line antiretroviral therapy (ART) most commonly prescribed world-wide. In developing countries, the combination of stavudine (d4T), lamivudine (3TC) and nevirapine (NVP) has been widely used because of cost and resource constraints. In Thailand, the Government implemented an "Access to Care" programme in 2002, based on national treatment guidelines, to provide HAART to HIV-infected persons. The most common first-line treatment in Thailand is an NNRTI-based regimen, i.e. two NRTIs plus either nevirapine or efavirenz. With increasing use of HAART, treatment failure is inevitable. Most current guidelines for the treatment of patients with NNRTI-based regimen failure recommend boosted PIs plus two NRTIs based on genotypic sensitivity as a second-line option [3,4]. Of note, HIV-1 viral load testing is not accessible in most developing countries where resources are limited. Early detection of virological failure resulting from ARV resistance is therefore not possible in the majority of patients. Consequently, by the time clinical and/or immunological failure is recognized, many patients may have failed virologically for months or even years. Such long-term continuation of the failing regimen has led to a high level of cross-resistance within the NRTI drug class, so there are no effective NRTIs that can be recycled.

There have been no controlled studies whose results could be used to recommend a suitable and cost-effective option for second-line therapy in this setting. A number of options have been prescribed in clinical practice in Thailand, such as double boosted PIs [lopinavir/saquinavir/ritonavir (LPV/SQV/r) or lopinavir/indinavir/ritonavir (LPV/IDV/r)] alone, two recycled NRTIs + boosted PIs (bPIs), 3TC + bPIs, and single bPIs. Unfortunately, because of cost constraints, the most commonly prescribed bPI in developing countries is boosted indinavir/ritonavir (IDV/r), which is well known to be associated with kidney toxicity in a dose-dependent manner. It is not known whether there is an advantage of double bPI-based regimens over bPI-based regimens. We therefore evaluated the efficacy and tolerability of second-line ARV regimens in a study in which high-dose IDV/r [800/100 mg twice daily (bid)] in combination with an optimized background regimen (OBR) of NRTIs (optimized using genotypic guidance) was compared with a double bPI regimen (LPV/SQV/r; 400/1000/100 mg bid) in patients with NNRTI-based regimen failure in routine clinical care in seven hospitals in Thailand.

Methods

Subject selection

A total of 64 HIV-infected adult patients who had treatment failure after being treated with NNRTI-based regimens for at least 3 months were recruited between August 2003 and February 2004 from seven hospitals in Thailand: Srinagarind Hospital, Khon Kaen University ($n = 9$); King Chulalongkorn Memorial Hospital, Chulalongkorn University ($n = 10$) Siriraj Hospital, Mahidol University ($n = 11$); Ramathibodi Hospital, Mahidol University ($n = 9$); Bamrasnaradura Institute ($n = 9$); Chiang Mai University Hospital ($n = 10$) and Chonburi Hospital ($n = 6$). Treatment failure was defined as (1) virological failure (i.e. the patients had a viral load of > 1000 HIV-1 RNA copies/mL after 3 months of treatment); and/or (2) immunological failure (i.e. the absolute CD4 cell count decreased by $> 30\%$ of the maximum values); and/or (3) clinical failure [i.e. the patients developed one or more new or recurrent opportunistic infections (OIs) after 6 months of therapy]. Patients were excluded from the study if any of the following exclusion criteria were met: pregnancy; the presence of active OIs; any drugs being received that interact with the PIs; elevation of alanine aminotransferase/aspartate aminotransferase (ALT/AST) over 10 times the upper limit of normal; or allergy to the PIs being used in the study. The enrolled patients were also excluded if they became pregnant during the study, were intolerant to either of the PI regimens, developed active OIs after taking the study drugs for at least 3 months, or were lost to follow-up for a period of over 2 months. The institutional review board committees of the Thai Ministry of Public Health and of each university/hospital approved the study. All patients gave written informed consent to participate.

The following blood tests were performed at enrolment for each patient: (1) complete blood cell and CD4 cell counts; (2) a quantitative plasma HIV-1 RNA polymerase chain reaction with the Cobas Amplicor HIV-1 Monitor test, version 1.5 (Roche, Mannheim, Germany); and (3) an HIV-1 genotypic drug resistance assay using the Trugene HIV-1 genotyping kit (Visible Genetics, Toronto, Canada).

Study design

Patients were randomly assigned to either (1) the LPV/SQV/r group, receiving double boosted PIs alone, i.e. LPV/r (Kaletra®; Abbott Pharmaceuticals Cardinal Health, St. Petersburg, FL) 400/100 mg plus SQV soft gel capsules (Fortovase®; Hoffman-La Roche Inc., Nutley, NJ) 1000 mg, both taken bid; or (2) the IDV/r/2NRTIs group, receiving high-dose IDV (Crixivan®; Merck & Co., Inc., Elkton, VA) 800 mg plus ritonavir (Norvir®; Abbott Pharmaceuticals) 100 mg, both taken bid, in combination with two NRTIs chosen on the basis of a HIV-1 genotypic drug resistance assay. Of note, the only available NRTIs during the period of this study were zidovudine (ZDV), lamivudine (3TC), stavudine (d4T) and didanosine (ddI). Patients who did not

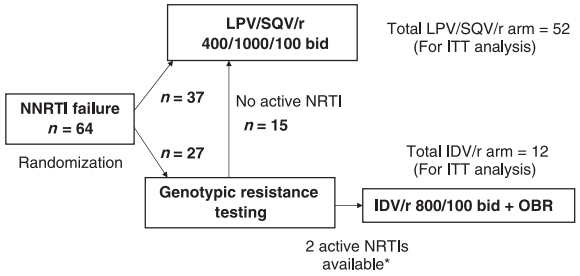
have genotypically active NRTIs available as an OBR were assigned to the double boosted PIs alone (LPV/SQV/r) arm. If patients could not tolerate their regimen, they were switched to the other regimen. Clinical status, CD4 cell count, HIV RNA viral load, and adverse events were monitored at weeks 12, 24, 36 and 48 of the study. The primary outcome was the proportion of patients with plasma HIV RNA < 50 copies/mL at 48 weeks. Secondary outcomes were the proportion of patients with HIV RNA < 400 copies/mL at 48 weeks and the proportion of patients who permanently discontinued the randomized treatment because of adverse events, changes in HIV RNA or changes in CD4 count.

Statistical analysis

The efficacy of treatments was determined according to both intent-to-treat (ITT) and as-treated analyses. In the ITT analysis, all patients who received LPV/SQV/r or IDV/r/2NRTIs on the basis of randomization and genotypic guidance were included in a missing equals failure analysis, and a noncompleter considered as failure (NC = F) analysis was used to evaluate the mean change in $\log_{10}$ viral load and immunological response. All statistical analyses were performed using SPSS (SPSS Inc., Chicago, IL), version 14.0. Pearson's χ^2 or Fisher's exact test was used to compare proportions, as appropriate. The Mann–Whitney *U*-test was used to analyse continuous variables that were not normally distributed. An independent-sample *t*-test was used to compare normally distributed variables. All *P*-values were two-tailed; $P < 0.05$ was considered to be statistically significant.

Results

Sixty-four patients were enrolled in the study, of whom 37 and 27 patients were randomly assigned to receive LPV/SQV/r alone and IDV/r/2NRTIs (selected on the basis of genotypic testing guidance), respectively. On the basis of the genotypic resistance testing results, 15 patients assigned to the IDV/r/2NRTIs group had no NRTI OBR available. Therefore, the final allocation was 12 patients in the IDV/r/2NRTIs group and 52 patients in the LPV/SQV/r group. The study design and patient characteristics are shown in Fig. 1. The mean age (standard deviation) of patients was 35.2 (6.5) and 34.5 (4.7) years in the LPV/SQV/r and IDV/r/2NRTIs groups, respectively. Approximately two-thirds of the patients in each group had HIV disease stage C and virological failure. The median CD4 cell count and mean HIV RNA viral load at enrolment in the IDV/r/2NRTIs group were slightly higher than those in the LPV/SQV/r group. Apart from the median duration of prior ART, which was significantly longer in the IDV/r/2NRTIs group (134 vs 198 weeks in the LPV/SQV/r and IDV/r/2NRTIs groups, respectively; $P = 0.02$), there were no statistically significant differences between the two treatment groups with respect to other baseline characteristics (Table 1).



Primary endpoint : Time of Loss of Virological Response (TLOVR) at 48 weeks
Secondary endpoints : Tolerability, changes of CD4+ count from baseline
* Available NRTIs during the period of study: ZDV, d4T, ddI and 3TC

Fig. 1 Study design and the overall patient disposition

Virological and immunological outcomes for the two treatment groups are presented in Figs 2 and 3. At 48 weeks, the percentages of patients with plasma HIV RNA < 50 copies/mL were 60% (31 of 52 patients) in the LPV/SQV/r arm vs 50% (six of 12) in the IDV/r/2NRTIs arm in the ITT analysis, and 61% (31 of 51) vs 71% (five of seven), respectively, in the as-treated analysis. At the same time-point, the percentages of patients with plasma HIV RNA

Table 1 Baseline demographic data for 64 HIV-infected patients who failed nonnucleoside reverse transcriptase inhibitor (NNRTI)-based antiretroviral therapy

Characteristic	Regimen		*P*-value
	LPV/SQV/r (*N* = 52)	IDV/r (*N* = 12)	
Age (years) [mean (SD)]	35.2 (6.5)	34.5 (4.7)	NS
Male [*n* (%)]	31 (59.6)	5 (41.7)	NS
HIV risk factor [*n* (%)]			NS
Heterosexual	48 (92.3)	12 (100)	
Injecting drug abuse	4 (7.7)	0 (0)	
HIV disease status (N = 63)* [*n* (%)]			NS
A	14 (26.9)	2 (16.7)	
B	6 (11.5)	1 (8.3)	
C	32 (61.5)	8 (66.7)	
Criteria for treatment failure [*n* (%)]			NS
Virological failure	33 (63.5)	8 (66.7)	
Immunological failure	18 (34.6)	2 (16.7)	
Clinical failure	1 (1.9)	2 (16.7)	
Duration of prior ARV treatment (weeks) [median (IQR)]	134 (84–172)	198 (133–301)	0.02
CD4 count (cells/mL) [median (IQR)]	95 (30–216)	127 (71–137)	NS
HIV RNA ($\log_{10}$ copies/mL) [mean (SD)]	4.44 (0.79)	4.47 (0.88)	NS

ARV, antiretroviral; SD, standard deviation; IQR, interquartile range; LPV, lopinavir; IDV, indinavir; r, ritonavir; SQV, saquinavir; NS, not significant.
*One patient in IDV/r/2 NRTIs regimen did not know his/her HIV disease status.

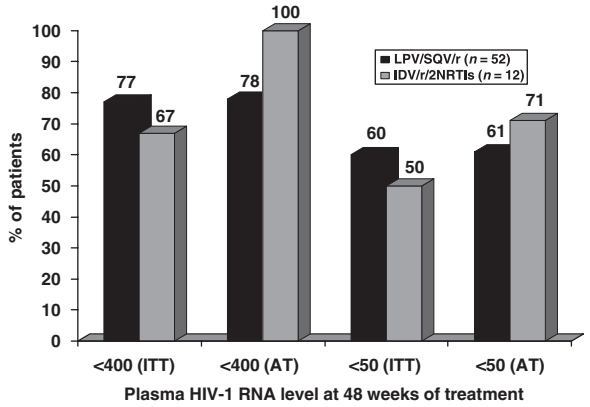


Fig. 2 At 48 weeks, the percentages of patients with plasma viral load < 50 HIV-1 RNA copies/mL were 60% for the lopinavir/saquinavir/ritonavir (LPV/SQV/r) regimen vs 50% for the regimen consisting of indinavir/ritonavir with an optimized nucleoside reverse transcriptase inhibitor (NRTI) background (IDV/r/2NRTIs) in the intent-to-treat (ITT) analysis, and 61 vs 71%, respectively, in the as-treated (AS) analysis.

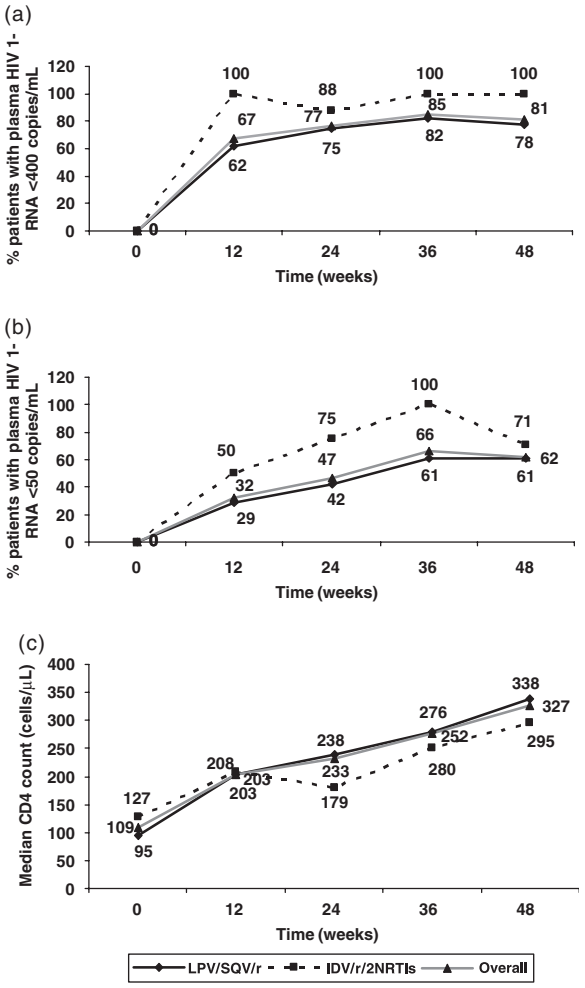


Fig. 3 Virological and immunological outcomes for the lopinavir/saquinavir/ritonavir (LPV/SQV/r) regimen vs the regimen consisting of indinavir/ritonavir with an optimized nucleoside reverse transcriptase inhibitor (NRTI) background (IDV/r/2NRTIs) in HIV-infected patients who failed nonnucleoside reverse transcriptase inhibitor (NNRTI)-based antiretroviral therapy. (a) The proportion of HIV-infected patients who had viral load < 400 HIV-1 RNA copies/mL. (b) The proportion of HIV-infected patients who had HIV-1 RNA < 50 copies/mL. (c) Median CD4 cell count response in HIV-infected patients.

< 400 copies/mL were 77% (40 of 52 patients) in the LPV/SQV/r arm vs 67% (eight of 12) in the IDV/r/2NRTIs arm in the ITT analysis, and 78% (40 of 51) vs 100% (seven of seven), respectively, in the as-treated analysis. There was a trend for higher rates of virological success in the IDV/r/2NRTIs group compared with the LPV/SQV/r group; however, this may be attributable to a lack of power, and the difference was not statistically significant. The mean decrease in HIV RNA from baseline was comparable between the two groups, being $-2.30\log_{10}$ copies/mL in the LPV/SQV/r group and $-2.51\log_{10}$ copies/mL in the IDV/r/2NRTIs group ($P = 0.60$). The patients treated with the LPV/SQV/r regimen had greater increases in absolute CD4 cell counts from baseline, but the difference between the two groups was not significant [median (interquartile range, IQR) increase 177 (91–269) vs 100 (52–225) cells/μL; $P = 0.32$].

The most common adverse events were nausea and vomiting. Four of the 12 patients (33%) assigned to the IDV/r/2NRTIs group developed severe nausea and vomiting which led to permanent discontinuation of the randomized treatment. Of these, one patient successfully continued treatment when switched to LPV/SQV/r and two patients were intolerant of treatment even when they were switched to LPV/SQV/r. The fourth patient refused to switch drugs and decided to withdraw consent. Four patients (8%) in the LPV/SQV/r group had elevation of ALT levels greater than five times the upper limit of normal.

During the 48-week study period, the proportion of patients who had a cholesterol level > 300 mg/dL was higher in the IDV/r/2NRTIs group than in the LPV/SQV/r group [38% (three of eight patients) and 17% (nine of 53 patients), respectively; $P = 0.18$]. The proportion of patients who had a triglyceride level > 500 mg/dL was 34% (18 of 53 patients) in the LPV/SQV/r group and 25% (two of eight patients) in the IDV/r/2NRTIs group ($P = 1.00$). At week 48, cholesterol levels were comparable between the two groups [median cholesterol (IQR) 210 (184–253) mg/dL in the LPV/SQV/r group vs 213 (171–305) mg/dL in the IDV/r/2NRTIs group; $P = 0.76$]. Triglyceride levels in the LPV/SQV/r group tended to be higher [median (IQR) 266 (177–400) mg/dL in the LPV/SQV/r group vs 158 (144–210) mg/dL in the IDV/r/2NRTIs group; $P = 0.12$].

One patient in the IDV/r/2NRTIs group was lost to follow-up at week 36 of the study. Two patients died during the study period. The causes of death were not associated with the study drugs: one patient died as a result of disseminated *Mycobacterium avium-intracellulare* infection and another as a result of underlying hepatocellular carcinoma in the IDV/r/2NRTIs and LPV/SQV/r groups, respectively.

Discussion

By the end of 2005, the World Health Organization (WHO) estimated that there were over 1.3 million HIV-infected people receiving ART in low-income and middle-income countries. This number has increased following the implementation of universal access to ART, with the WHO-recommended fixed-dose first-line combination of two NRTIs and one NNRTI, for all who need it [5]. As virological monitoring in these resource-limited settings is often not available, when treatment failure is identified, clinically or immunologically, many patients are inevitably harbouring significant levels of NRTI-resistant HIV at the time of switching. A recently published genotypic study on the same cohort of patients used here demonstrated that 42% of patients had multiple NRTI resistance, as indicated by more than three thymidine analogue mutations (TAMs) and/or Q151M [6]. The study also demonstrated that an independent factor associated with the presence of more than three TAMs was a duration of ARV medication exposure of >96 weeks [6]. These findings are similar to the results of a study by Sungkanuparph *et al*., [7] evaluating a second-line ARV regimen for HIV-1-infected Thai patients who failed an initial fixed-dose combination of d4T, 3TC and NVP. The study revealed that patients with a higher HIV RNA (>4 log copies/mL) at the time of treatment failure, as a result of delayed detection of virological failure, were more likely to have virus with TAMs and K65R and Q151M mutations, which limit future treatment options. The management of HIV treatment-experienced patients becomes much more complicated when there are few drug options available, in developing countries in particular. Most recent guidelines have recommended that the new HIV treatment in these patients should ideally include at least two (and preferably three) active agents, the selection of which should be guided by HIV resistance testing and by the patient's previous ART history [3,4]. New drug(s) from at least one new class should be selected to increase the likelihood of treatment success and to minimize the risk of cross-resistance. The PI class is thus suitable for salvage treatment, preferably combined with two optimized NRTIs.

In this exploratory study, we found that a second-line ARV regimen consisting of either double boosted PIs (LPV/SQV/r) or a boosted PI (IDV/r) in combination with an optimized NRTI backbone was less effective than one might have expected in PI-naïve patients. At 48 weeks of treatment, in an ITT analysis only 60 vs 50% of patients in the LPV/SQV/r arm vs the IDV/r/2NRTIs arm, respectively, had plasma HIV RNA <50 copies/mL, and these percentages were 61 vs 71%, respectively, in an as-treated analysis. In contrast, a study by Ananworanich *et al*. [8] assessing the efficacy of once-daily SQV/r (1600/100) with two NRTIs in 200 ARV-naïve HIV-infected Thai patients demonstrated that this regimen was well tolerated and had great clinical efficacy, with 96% of patients achieving a viral load <400 copies/mL and 89% of patients achieving a viral load <50 copies/mL after 24 weeks of treatment. In the present study, adverse effects occurred frequently in both study regimens, and included severe gastrointestinal irritation and hypercholesterolaemia, which were more common in the IDV/r/2NRTIs group, and significant elevation of liver enzymes and hypertriglyceridaemia, which were more frequently observed in the LPV/SQV/r group. Thus, low tolerability and high pill burden (particularly in the LPV/SQV/r arm) may be the main causes of the low virological success rates found in this study.

The WHO guidelines for ART in HIV-infected adults recommend using a ritonavir-boosted PI as the core of the treatment in HIV treatment-experienced patients [5]. However, there are insufficient data on the differences between ritonavir-boosted PIs to enable recommendations to be made concerning preferred PIs. IDV/r is effective and inexpensive but the incidence of adverse effects, such as nausea, vomiting and nephrolithiasis, makes this choice less attractive. The adverse effects of IDV/r (800/100 mg bid) are related to increased IDV peak concentration, and there is evidence that IDV/r at the lower dosage of 400/100 mg bid may offer the advantage of lower IDV peak concentrations, lower toxicity, and lower daily pill burden [9]. The trade-off at this dosage is that its trough concentrations may be lower than the optimal threshold in some patients [10]. The higher IDV/r dosage of 600/100 mg bid may be safe, well tolerated, and cost-effective in resource-limited settings. The clinical efficacy of the double boosted PI regimen consisting of LPV/SQV/r has been demonstrated in the LOPSAQ study, which determined the efficacy of LPV/SQV/r alone in 128 heavily pretreated patients who developed therapy failure as a result of NRTI and NNRTI resistance and/or systemic toxicities [11]. Seventy-eight of 128 patients (61%) had a viral load <400 copies/mL at week 48 of treatment, with a median viral load decrease of 3.5 $\log_{10}$ copies/mL and a median CD4 increase of 168 cells/μL. There was a significant

increase in triglyceride levels in these cases. Similar to our study, the proportion of patients who achieved an undetectable viral load was less impressive, and this could indicate the clinical significance of the NRTI backbone, which is likely to contribute to the control of viral replication [12]. In the setting of NRTI resistance, NRTI often preserve antiviral activity against the drug-resistant variant and result in selective maintenance of a less-fit viral population. It seems reasonable to suggest that the NRTI drug class should be incorporated in any salvage regimen, preferably OBR if available, to enhance efficacy. However, to date there have been no large randomized studies providing evidence to support this suggestion.

The preferred NRTI backbones recommended by the WHO in the setting of NNRTI-based treatment failure include tenofovir (TDF)/abacavir (ABC), ddI/ABC and TDF/3TC ± ZDV plus boosted PIs. However, TDF/ABC and ddI/ABC are not frequently used because ABC is very expensive and there is concern about drug hypersensitivity, leading to limitation of its use, especially in resource-poor settings. The regimen of TDF/3TC ± ZDV is very attractive as TDF is taken once daily and often retains activity against NRTI-resistant viral strains. In the setting of 3TC resistance, continuation of 3TC is now recommended by some experts because the M184V mutation may potentially decrease viral replication capacity as well as induce some degree of resensitization to ZDV or TDF [13]. ZDV may prevent or delay the emergence of the K65R mutation which confers resistance to TDF. We suggest that the combination of TDF/3TC ± ZDV plus affordable and less toxic boosted PIs should be evaluated in larger prospective randomized clinical trials to determine the best option for salvage therapy in treatment-experienced patients with NNRTI-based treatment failure. Of note, TDF has just recently become available in Asia.

Our study has several limitations that should be taken into consideration. Firstly, the number of patients was small, leading to low power to detect any significant difference. Secondly, the assigned randomization could not be maintained, and therefore there was potential for selection bias. Finally, information on metabolic complications was not complete, so we were unable to establish the rates of these complications accurately.

In summary, both the regimen consisting of double boosted PIs (LPV/SQV/r) alone and the regimen consisting of boosted PIs (IDV/r, 800/100 mg bid) in combination with an optimized NRTI background showed only moderate efficacy in ARV-experienced patients with treatment failure, because of tolerability issues. As a modest proportion of patients achieved an undetectable viral load after treatment and there was a high rate of adverse effects, neither regimen is an attractive option. Recently, more tolerable new formulations of currently available PIs (e.g. LPV/r as a Maltrex tablet and SQV as a 500 mg tablet), more tolerable PIs (e.g. atazanavir) and new ARV PIs (e.g. darunavir) have become available, and ARV combination therapy including these new options might be expected to offer much better efficacy and tolerability. Thus, large-scale, randomized, controlled trials to establish the best, most cost-effective second-line regimen options for patients who fail NNRTI-based HAART in both developing and developed countries are desperately needed.

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Appendix A: the study team

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