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Neurocognitive impairment in patients randomized to second-line lopinavir/ritonavir-based antiretroviral therapy vs. lopinavir/ritonavir monotherapy

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Abstract We compared rates of neurocognitive impairment (NCI) among 93 Thai adults failing non-nucleoside reverse transcriptase inhibitor (NNRTI)-based combination antiretroviral therapy (cART) before and after switching to

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lopinavir/ritonavir monotherapy (mLPV/r) vs. tenofovir/lamivudine/LPV/r (TDF/3TC/LPV/r). Participants completed the Color Trails 1 and 2, Digit Symbol, and Grooved Pegboard at weeks 0, 24, and 48. We calculated *z*-scores using normative data from 451 healthy HIV-negative Thais. We defined NCI as performance of <-1 SD on ≥2 tests. The Thai depression inventory was used to capture depressive symptoms. Lumbar puncture was optional at week 0 and 48. At baseline, median (IQR) age was 36.9 (32.8–40.5)years, and 46 % had primary school education or lower. The median CD4 count was 196 (107–292)cells/mm^3, and plasma HIV RNA was 4.1 (3.6–4.5)$\log_{10}$ copies/ml. Almost all (97 %) had circulating recombinant CRF01_AE. At baseline, 20 (47 %) of the mLPV/r vs. 22 (44 %) of TDF/3TC/LPV/r arms met NCI criteria (p=0.89). The frequency of NCI at week 48 was 30 vs. 32 % (p=0.85) with 6 vs. 7 % (p=0.85) developing NCI in the mLPV/r vs. TDF/3TC/LPV/r arms, respectively. Having NCI at baseline and lower education each predicted NCI at week 48. Depression scores at week 48 did not differ between arms (p=0.47). Cerebrospinal fluid HIV RNA of <50 copies/ml at 48 weeks was observed in five out of seven in mLPV/r vs. three out of four in TDF/3TC/LPV/r arm. The rates of NCI and depression did not differ among cases failing NNRTI-based cART who received mLPV/r compared to LPV/r triple therapy.

Keywords Lopinavir/ritonavir monotherapy · Neurocognitive impairment · Central nervous system penetration effectiveness score · Depression

Introduction

Several studies of boosted protease inhibitor monotherapy (mono-bPI) have recently been reported (Pulido et al. 2010; Bierman et al. 2009). Mono-bPI has the theoretical advantages of regimen simplification, improved adherence, and avoidance of long-term toxicity from nucleoside reverse transcriptase inhibitors. Risk for central nervous system (CNS) complications, including neurocognitive impairment (NCI), is a theoretical concern while using mono-bPI since there will be fewer antiretroviral medications to penetrate through to the CNS and thus, an inherent added risk for a lower CNS penetration effectiveness (Smurzynski et al. 2011; Letendre et al. 2010; Vernazza et al. 2007). There are limited data describing CNS outcomes on mono-bPI (Perez-Valero et al. 2011).

Most mono-bPI reports evaluated virologically suppressed patients who changed therapy and demonstrate efficacy in maintaining plasma viral suppression (Pulido et al. 2010; Bierman et al. 2009). Our team conducted an open-labeled multicenter randomized trial of lopinavir/ritonavir monotherapy (mLPV/r), in patients failing first-line non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens (HIV STAR study) (Bunupuradah et al. 2012). In the HIV STAR main study, we noted that patients randomized to mLPV/r had a higher frequency of low-level plasma viremia (between 50 and 200 copies/ml) than did the arm with triple therapy [tenofovir (TDF), lamivudine (3TC), and LPV/r] (Bunupuradah et al. 2012). We now report neurocognitive outcomes among HIV STAR participants who enrolled in this neurologic substudy.

Material and methods

Between May 2008 and November 2009, Thai adults failing NNRTI-based regimens from seven hospitals were enrolled into the open-labeled multicenter randomized HIV STAR study (The *H*IV *S*econd-line *T*herapy *A*nti-*R*etroviral study, clinical trial.gov identification number NCT00627055) (Bunupuradah et al. 2012). Subjects were included if they were HIV-infected and aged ≥18 years, who had been treated with NNRTI-based cART for at least 6 months, had HIV RNA ≥1,000 copies/mL, and no active opportunistic infection. Exclusion criteria were history of CNS infection (e.g., cryptococcal or tuberculous meningitis). The protocol was approved by the Thai Ministry of Public Health and local ethics committees. All subjects signed informed consent.

After completing a neurological examination performed by trained physicians, the participants underwent five cognitive tests at weeks 0, 24, and 48: Color trails 1 and 2, Escala de Inteligencia Wechsler para Adultos (EIWA) Digit Symbol, and the Grooved Pegboard test in the dominant and non-dominant hands. These tests have been used in Thai HIV-infected patients by our group (Valcour et al. 2007; Pumpradit et al. 2010; Valcour et al. 2009). The color trails 1 evaluates psychomotor speed, whereas the color trails 2 interrogates higher cognitive abilities and executive functioning through a series of "connect-the-dot" tests. The EIWA digit symbol test evaluates psychomotor speed, and the grooved pegboard test evaluates fine motor speed and dexterity. For all tests, *z*-scores were calculated using data from 451 age- and education-matched Thai HIV-negative healthy controls (Valcour et al. 2007). NCI was defined as having *z*-score of <-1 standard deviation (SD) compared to the age- and education-matched strata on≥two tests (Robertson et al. 2007). If *z*-score <-1 standard deviation of the two tests were both grooved pegboard tests, from dominant and non-dominant hands, they were counted as one abnormal test. A mean of all *z*-score for the five tests was calculated as the NPZ-5.

Depression questionnaire

To evaluate the presence of depressive symptoms, participants completed a self-rating Thai depression

inventory (TDI) questionnaire (Lotrakul and Sukanich 1999). This questionnaire is composed of 20 questions that examine the participant feelings over the previous 7 days. Based on published reports among Thais (Pumpradit et al. 2010), suggested interpretations fall into five categories: no depression (≤20), mild (21–25), moderate (26–34), major (35–40), or severe (≥40) depression.

Cerebrospinal fluid HIV RNA

Lumbar puncture was an optional evaluation to be completed at weeks 0 and 48 for participants in the neurologic substudy. Lumbar puncture was performed with an atraumatic Sprotte® needle. Cerebrospinal fluid HIV RNA measurement was performed with the Roche Amplicor v1.5 assay (Roche Molecular Systems, Inc., Branchburg, NJ 08876 USA) as done for plasma. The level of detection was 50 copies/ml.

Statistical procedures

All analyses were conducted using Stata version 11.0 (Stata Corp., College Station, TX). We performed descriptive analyses and comparisons to examine the demographic and clinical characteristics of patients. We used chi-square test for categorical variables and Wilcoxon rank sum test for continuous variables at baseline. The Wilcoxon signed-rank test was used to compare neuropsychological testing results between week 0 and week 48 in the two treatment arms. Linear regression was used for comparisons of changes in neuropsychological testing *z*-scores between randomized arms while adjusted for baseline NPZ-5. A multivariate analysis using a logistic regression model was employed to evaluate factors associated with NCI. Variables with a p value <0.20 in the univariate analysis were included in the full model. A stepwise selection procedure was used to assess the relative role of each risk factor. The level of significance was 0.05.

Results

Among the 200 adults enrolled into the main HIV STAR study, 93 enrolled in the neurological substudy with 43 (46 %) randomized to the mLPV/r arm and 50 (64 %) to the TDF/3TC/LPV/r arm (Fig. 1). The median (IQR) age was 36.9 (32.8–40.5)years, and 43 (46.2 %) had an educational level of primary school or lower. The proportions of participants with CDC clinical classifications A/B/C were 22:34:44 %. The median (IQR) T lymphocyte CD4 count was 196 (107–292)cells/mm^3, and plasma HIV RNA was 4.1 (3.6–4.5) $\log_{10}$ copies/ml (Table 1). Almost all (97 %) had circulating recombinant CRF01_AE and 3 % had subtype B. The median (IQR) duration of the first-line NNRTI-based cART was 3.9 (2.3–4.8)years, and all participants had been on lamivudine (3TC). Most (77 %) used stavudine or zidovudine (26 %) with tenofovir (TDF) and didanosine, being used in 5 and 2 %, respectively. Among NNRTIs, nevirapine and efavirenz were used in 93 and 7 %, respectively.

Prior to switching to PI, no differences were noted on the NPZ-5 between arms (p>0.05, Table 1). At baseline, 20 (47 %) in mLPV/r vs. 22 (44 %) in TDF/3TC/LPV/r arm met our NCI criteria (p=0.89; Fig. 2).

During the 48 weeks of follow-up, no death or loss to follow-up occurred. There was 1 neuropsychiatric event (dizziness) reported at week 1 after mLPV/r, while there were 16 neuropsychiatric events among 9 participants in the TDF/3TC/LPV/r arm (dizziness, paresthesia, peripheral neuropathy, insomnia, anxiety, and headache), occurring at a median (IQR) of 20 (8–37)weeks. All were felt to likely not be related to study medication except for one participant with recurrent dizziness and migraine.

At week 48, the median (IQR) CD4 T lymphocyte count was 318 cells/mm^3 in the mLPV/r arm and 350 cells/mm^3 in the TDF/3TC/LPV/r arm (p=0.33), representing a mean change from baseline of 119 cells/mm^3 in the mLPV/r arm vs. 123 cells/mm^3 in TDF/3TC/LPV/r arm (p=0.85). In contrast to the main study results (Bunupuradah et al. 2012), the proportion of patients in this substudy with plasma HIV RNA <50 copies/ml did not differ significantly at 77 % in mLPV/r

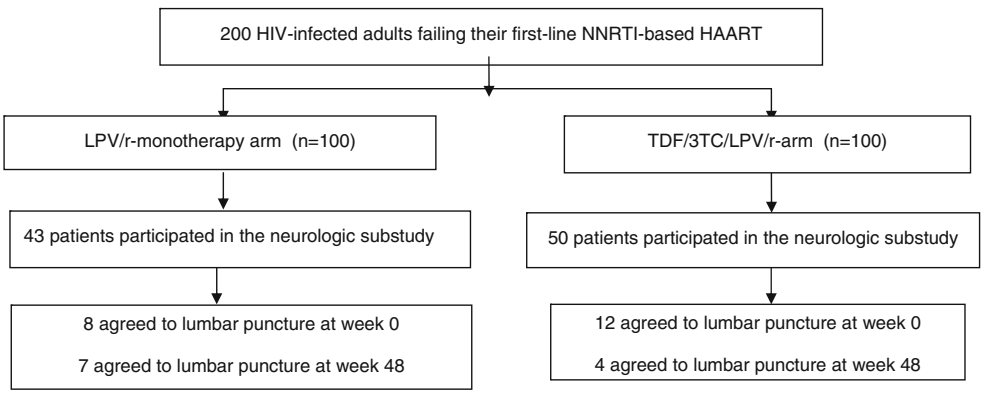

Fig. 1 Patient disposition diagram. TDF/3TC/LPV/r; tenefovir plus lamivudine plus lopinavir/ritonavir

Table 1 Baseline characteristics

Characteristics[a]	*N*	All, *N*=93	mLPV/r, *N*=43	TDF/3TC/LPV/r, *N*=50	*p*
Age (years)	93	36.9 (32.8–40.5)	35.4 (32.4–41.4)	36.9 (34.2–40.4)	0.81
Male, *n* (%)	93	56 (60.2)	32 (74.4)	24 (48)	0.01
Educational level, *n* (%)					
No certificate or primary school		43 (46.2)	17 (39.4)	26 (52.0)	0.57
Less than high school	90	26 (28.0)	15 (34.9)	11 (22.0)	
High school or higher		15 (16.1)	6 (14.0)	9 (18.0)	
Bachelor degree or higher		6 (6.5)	3 (7.0)	3 (6.0)	
Missing		3 (3.2)	2 (4.7)	1 (2.0)	
Monthly income (USD), *n* (%)					
≤150	93	36 (38.7)	13 (30.2)	23 (46.0)	0.11
151–450		46 (49.5)	24 (55.8)	22 (44.0)	
>451		5 (5.4)	4 (9.3)	1 (2.0)	
Missing		6 (6.4)	2 (4.7)	4 (8.0)	
Transmission route, *n* (%)	93				
Heterosexual		83 (89.3)	38 (88.4)	45 (90)	0.55
Homosexual		9 (9.6)	4 (9.3)	5 (10)	
Intravenous drug use		1 (1.1)	1 (2.3)	–	
Weight (kg)	93	60 (52–65.8)	59.1 (54–65.8)	60.1 (47.1–66)	0.27
Height (cm)	93	165 (158–168)	166 (161–170)	163 (156–165)	0.01
% CDC clinical classification A/B/C	93	22:34:44	21:33:46	22:26:42	0.91
% nevirapine/efavirenz	93	93:7	95:5	90:10	0.33
CD4 count nadir (cells/mm^3)	90	47 (10–106)	56 (11–117)	41 (9–95)	0.44
Hemoglobin median before switch to PI regimen (g/dL)	93	13.1 (12–14.2)	13.8 (12.3–14.8)	12.8 (11.5–13.9)	0.03
CD4 count before switch to PI regimen (cells/mm^3)	93	196 (107–292)	162 (113–286)	222 (101–301)	0.35
HIV-RNA log10copies/ml before switch to PI regimen	93	4.1 (3.6–4.5)	3.9 (3.6–4.5)	4.1 (3.7–4.5)	0.45
NPZ-5	93	0.08 (−0.53 to 0.42)	−0.04 (−0.54 to 0.30)	0.18 (−0.53 to 0.55)	0.18

PI protease inhibitor, *NCI* neurocognitive impairment, *mLPV/r* lopinavir/ritonavir monotherapy, *TDF/3TC/LPV/r* tenofovir/lamivudine/ lopinavir/ritonavir

[a] Data are presented as median (IQR)

and 86 % in TDF/3TC/LPV/r arm (p=0.25). Similar proportions of patients in the mLPV/r arm (90.7 %) had plasma HIV RNA <200 copies/ml compared to those in the triple drug arm (88 %) at week 48 (p=0.89).

In mLPV/r arm, NPZ-5 (SD) at week 0 was −0.26 (0.92), and NPZ-5 at week 48 was 0.08 (0.62; p<0.01). In TDF/3TC/LPV/r arm, NPZ-5 (SD) at week 0 was −0.01 (0.77), and NPZ-5 at week 48 was 0.16 (0.72; p=0.09). By linear regression analysis, the mean difference change of neuropsychological testing results between treatment groups over 48 weeks, adjusted for *Z*-score at baseline, was 0.06 [95 % confidence interval (CI), −0.16 to 0.27; p=0.60].

The frequency of NCI at week 48 was 30 % in mLPV/r vs. 32 % in TDF/3TC/LPV/r (p=0.85; Fig. 2). The mLPV/r arm had a significant improvement in the NPZ-5 (all p< 0.01), while the TDF/3TC/LPV/r arm demonstrated only marginal evidence of improvement in the NPZ-5 (p=0.09). Among patients who had NCI at baseline, 26 % in the mLPV/r and 22 % in the TDF/3TC/LPV/r arm did not reach NCI criteria at week 48. Among participants who did not have NCI at baseline, 6 % of mLPV/r vs. 7 % of TDF/3TC/LPV/r developed NCI (p=0.85) at 48 weeks.

Predictors of neurocognitive impairment at week 48

By multivariate analysis, having NCI at baseline [odds ratio (OR), 3.8; 95 % CI, 1.4–10.5] and having fewer years of educational attainment [OR, 3.1; 95 % CI, 1.1–8.5] predicted NCI at 48 weeks. Age, gender, transmission route, income, CDC class, time on NNRTI-based cART, nadir CD4 or current CD4 T lymphocyte count and plasma HIV RNA at week 0, treatment arm, CD4 T lymphocyte count, and plasma HIV RNA at week 48 were not associated with the development of NCI (Table 2).

HIV RNA in CSF and plasma at baseline and 48 weeks

At baseline, 20 participants underwent lumbar puncture (8 in the mLPV/r arm and 12 in the triple therapy arm; Table 3). All

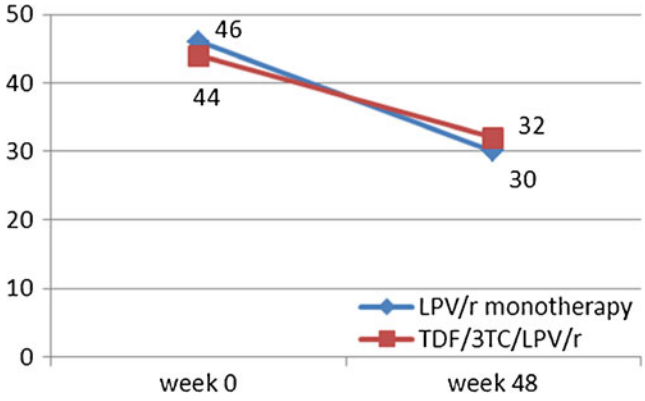

Fig. 2 Prevalence of neurocognitive impairment at weeks 0 and 48. No statistical difference between arms; p>0.05 both at weeks 0 and 48

had baseline plasma HIV RNA >1,000 copies/ml with a median (IQR) plasma HIV RNA of 4,840 (3,100–26,300) copies/ml. The median (IQR) CSF HIV RNA was 97 (40–411)copies/ml with 13/20 participants having CSF HIV RNA >50 copies/ml. In all cases, the CSF HIV RNA was lower than that in plasma with a mean (SD) difference of 16,166 (23,560) copies/ml. No differences of median (IQR) baseline CSF HIV RNA between arms were seen: 207 (70.5–938.5) in mLPV/r vs. 60.5 (40–308.5) in TDF/3TC/LPV/r arm (p=0.13). At baseline, plasma HIV RNA did not correlate with CSF HIV RNA (coefficient, 0.37; 95 % CI, −0.16 to 0.90; p=0.16). The mean $\log_{10}$ CSF HIV RNA did not correlate to NCI at baseline (coefficient, 0.35; 95 % CI, −0.17 to 0.88 and p=0.17).

At 48 weeks, 11 agreed to lumbar puncture (7 in the mLPV/r arm and 4 in the triple therapy arm; Table 3). CSF HIV RNA <50 copies/ml at 48 weeks was observed in five out of seven in the mLPV/r arm vs. three out of four in the TDF/3TC/LPV/r arm. Two patients in mLPV/r had plasma HIV RNA <50 copies/ml but had detectable CSF HIV RNA. Both met NCI criteria at baseline, and one remained with NCI at week 48. One patient in the TDF/3TC/LPV/r arm had plasma HIV RNA above 1,000 copies/ml, detectable CSF HIV RNA, and met NCI criteria at week 48.

Depressive symptoms

Ninety-one participants, 42 in the mLPV/r and 49 in the TDF/3TC/LPV/r arms, completed the TDI at weeks 0 and 48. At baseline, the mean (SD) of depression scores in mLPV/r vs.TDF/3TC/LPV/r arms were 10.6 (7.5) vs. 12.8 (8.5), respectively (p=0.20). The proportions of participants with different degrees of depressive symptoms suggestive of mild/moderate/major depression were 10:2:0 % in the mLPV/r arm vs. 4:10:2 % in the TDF/3TC/LPV/r arm (p=0.26).

At 48 weeks, the mean (SD) depression scores in mLPV/r vs.TDF/3TC/LPV/r arms were 9.4 (7.1) vs. 10.6 (8.8), respectively (p=0.47). The mean change in depression scores from baseline to week 48 did not differ by study arm (p=0.43). The proportions of participants with different degrees of depressive symptoms suggestive of mild/moderate/major depression were 10:0:0 % in the mLPV/r arm vs. 6:4:0 % in the TDF/3TC/LPV/r arm (p=0.36). Three new cases developed symptoms consistent with mild depression in the mLPV/r arm but none in the TDF/3TC/LPV/r arm.

Discussion

We observed NCI in about 50 % of patients failing first-line NNRTI-based cART in this study. Over 48 weeks, there were no significant differences in the rates of developing NCI between patients randomized to mLPV/r vs. TDF/3TC/LPV/r treatments. The frequency of NCI did not differ by study arm at baseline or after 48 weeks of treatment. Predictors of NCI at 48 weeks were NCI at baseline and fewer years of educational attainment.

Several publications of NCI prevalence in HIV-infected patients have been reported, but mainly in patients on stable cART with virologic suppression (Pumpradit et al. 2010; Valcour et al. 2011; Harezlak et al. 2011; Ciccarelli et al. 2011). The prevalences of NCI in studies conducted in resource-rich settings are reported to be as high as 50 % (Valcour et al. 2011; Harezlak et al. 2011; Ciccarelli et al. 2011). Limited data exist for NCI prevalence in HIV-infected patients from Asia and particularly in Thailand, where circulating recombinant CRF01_AE predominates. We previously reported an NCI frequency of 38 % among 64 HIV-infected Thai adults with virologic suppression on first-line NNRTI-based cART for more than 5 years (Pumpradit et al. 2010). Half of the patients in the current study of Thais virologically failing first-line NNRTI-based regimens had NCI. The more frequent NCI of the current study may be related to failure and HIV viremia, although NCI itself, particularly through compromise of prospective memory, could have contributed to poor medication compliance and subsequent failure (Zogg et al. 2010). Depression could also adversely impact neuropsychiatric test scores. The Thai Depression questionnaire used in this study is a culturally appropriate instrument for measuring the severity of depressive symptoms (Lotrakul and Sukanich 1999). The proportion of patients with any grade of depression was generally low in both study arms, and we did not observe its effect on NCI.

Data related to the predictive capacity of the CNS penetration effectiveness (CPE) score on cognitive improvement among patients changing therapy remain mixed (Marra et al. 2009; Valcour et al. 2010). Our study cannot conventionally employ the CPE paradigm since CPE is designed to compare regimens that are constructed similarly, namely with similar number and classes of antiretroviral medications (Letendre et al. 2010). Instead, our study can inform outcomes of mono vs. triple therapy, where we did not

Table 2 Predictors of neurocognitive impairment at 48 weeks

Variables	Univariate analysis			Multivariate analysis		
	Odds ratio	95 % CI	*p*	Odds ratio	95 % CI	*p*
Age (years)						
≤40	1					
>40	0.57	0.19–1.75	0.33			
Gender						
Male	1					
Female	1.10	0.45–2.69	0.83			
Education						
Higher than primary school	1			1		
Primary school or no certificate	3.51	1.33–9.28	0.01	3.06	1.11–8.45	0.03
Transmission route						
Heterosexual	1					
Homosexual/intravenous drug use	1.54	0.40–5.96	0.53			
Monthly income (USD)						
>150	1					
≤150	0.92	0.36–2.37	0.87			
CDC class						
A	1		0.09			
B	1.02	0.32–3.20				
C	0.36	0.11–1.18				
Time on NNRTI	1.06	0.86–1.32	0.567			
NCI before switch to PI regimen						
No	1			1		
Yes	4.24	1.66–10.87	0.003	3.83	1.40–10.51	0.01
Nadir CD4 count (cells/mm^3)						
>100	1					
≤100	0.73	0.28–1.94	0.54			
CD4 count (cells/mm^3) at switch to PI regimen						
>200	1					
≤200	2.02	0.81-5.02	0.13			
HIV-RNA (log10 copies/ml) at switch to PI regimen						
≤4	1					
>4	1.74	0.71–4.26	0.26			
Current regimen						
mLPV/r	1					
TDF/3TC/LPV/r	1.84	0.73–4.65	0.20			
CD4 count (cells/mm^3) at 48 week						
>500	1					
≤500	1.41	0.35–5.67	0.62			
HIV-RNA (log10copies/ml) at 48 week						
≤1.7	1					
>1.7	3.15	1.07–9.28	0.04			
Depression at week 0						
No	1					
Yes	2.59	0.81–8.24	0.11			

NCI neurocognitive impairment, *PI* protease inhibitor, *mLPV/r* lopinavir/ritonavir monotherapy

demonstrate a difference in the frequency or the development of NCI between arms. Similarly, we cannot adequately investigate efficacy of antiretrovirals in monocytes/macrophages, proposed by some to impact CNS effectiveness as

Table 3 HIV-RNA (copies/ml) in cerebrospinal fluid and plasma

Participant number	mLPV/r						Participant number	TDF/3TC/LPV/r					
	Week 0			Week 48				Week 0			Week 48		
	CSF	Plasma	NCI	CSF	Plasma	NCI		CSF	Plasma	NCI	CSF	Plasma	NCI
1	40	3,070	No	<40	<50	Yes	9	40	14,000	No	8,580	>100,000	Yes
2	265	8,930	Yes	<40	<40	No	10	40	4,690	Yes	<40	<50	Yes
3	89	18,300	Yes	<40	2,064	Yes	11	883	100,000	No	<40	<40	No
4	52	3,950	No	<40	57	Yes	12	105	1,440	Yes	<40	<40	No
5	149	2,020	Yes	154	<40	Yes	13	81	29,800	No	NA	<40	Yes
6	1,498	47,400	Yes	<40	<40	No	14	40	4,320	No	NA	<40	No
7	842	27,200	Yes	110	<40	No	15	350	4,840	No	NA	<40	No
8	1,035	6,640	Yes	NA	<40	N0	16	472	2,760	Yes	NA	<40	Yes
							17	267	3,100	Yes	NA	<40	Yes
							18	40	4,720	Yes	NA	49,100	Yes
							19	40	10,200	Yes	NA	<50	N0
							20	40	26,300	No	NA	<40	No

CSF cerebrospinal fluid, *NCI* neurocognitive impairment, *NA* not available

these cells are proposed to seed the CNS with virus from the peripheral blood (Liu et al. 2000; Agsalda et al. 2012). Both treatment groups demonstrated improvement in the NPZ-5 at 48 weeks, but the degree of change did not differ between arms. This may be due to the similar rates of plasma HIV RNA suppression or test–retest learning effects (Gonzalez-Scarano and Martin-Garcia 2005).

There are limited data of neuropsychiatric events in patients using mLPV/r. In the OK04 trial, a randomized study of mLPV/r as maintenance therapy in virologically suppression patients, mLPV/r-treated patients did not have an increase in neuropsychiatric events after 2 years follow-up compared to those on triple therapy (Arribas et al. 2009). In contrast, in the MOST trial, six patients who failed mLPV/r had neurological symptoms as part of an acute retroviral syndrome (Gutmann et al. 2010). In our study, neuropsychiatric events were mostly reported in the triple therapy arm but not thought to be associated with study treatment.

Several publications report older age (Valcour et al. 2011) and low CD4 T lymphocyte nadir (Munoz-Moreno et al. 2008; Heaton et al. 2011) as predictors for NCI. The lack of correlation of these variables with NCI in our report may be due to limitations in sample size and few older patients.

Our study had some limitations. First, the neuropsychological testing battery is not extensive, and subtle neurocognitive deficits could have been missed. Second, the number of participants enrolled was small with few data of CSF HIV RNA. Several strengths are noted including: (1) the 48-week prospective and randomized design, (2) the availability of culturally appropriate normative neuropsychological testing data from nearly 500 healthy Thai controls, and (3) a lack of confounding due to intravenous drug use, hepatitis B and hepatitis C co-infections (Vivithanaporn et al. 2012).

In the main HIVSTAR study, we concluded inferiority of mLPV/r because it was associated with less undetectability of plasma HIV RNA (<50 copies/ml) compared to TDF/3TC/LPV/r (Bunupuradah et al. 2012). In the current analysis, we do not observe a difference in the frequency or development of NCI between study arms over 48 weeks. This does not exclude the possibility that more subtle differences could have been identified with more sensitive measures, a larger sample size, and more cases agreeing to lumbar puncture at follow-up. Several studies of mLPV/r with cognitive measures are currently underway to provide additional information on this critical issue (Paton et al. 2011; Clotet and Gomez 2011).

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