

# Lopinavir with Ritonavir Reduces the HIV RNA Level in Cerebrospinal Fluid

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**Background.** Combination antiretroviral (ARV) therapy can reduce human immunodeficiency virus (HIV) RNA levels in cerebrospinal fluid (CSF) and plasma and improve immunocompetence. However, HIV-associated neurocognitive disorders persist, possibly because some ARV drugs do not reach therapeutic concentrations in the brain. The primary objective of this study was to determine whether lopinavir plus ritonavir (LPV-rtv) used alone reduced the HIV RNA level in CSF.

**Methods.** The study was an open-label, 24-week trial of sequential ARV therapy. Fifteen subjects were enrolled and received LPV-rtv therapy. Ten subjects reached the primary study end point at week 3, before at least 2 other ARV drugs were added to the treatment regimen. CSF and blood samples were obtained before treatment and after 3, 12, and 24 weeks of treatment.

**Results.** LPV-rtv therapy alone reduced the HIV RNA level in CSF in all subjects (median change in HIV RNA level,  $-1.42 \log_{10}$  copies/mL), including 5 who had slower decreases in HIV RNA level in CSF than in plasma—an indicator of autonomous central nervous system infection. Among 9 subjects who completed 12 weeks of LPV-rtv-containing therapy, the HIV RNA level was below quantitation in the CSF samples from 8 subjects and in the plasma samples from 6 subjects. By week 24, HIV RNA levels were below quantitation in samples of both fluids from all 8 subjects.

**Conclusions.** LPV-rtv therapy alone for 3 weeks consistently reduces the HIV RNA level in CSF by at least 10-fold in most individuals, including those likely to have autonomous HIV replication in the central nervous system. Because it penetrates the central nervous system in therapeutic concentrations and appears to reduce HIV replication in the central nervous system, LPV-rtv may benefit subjects who receive a diagnosis of or are at risk for HIV-associated neurocognitive disorders.

HIV-associated neurocognitive disorders (HANDs), including subsyndromic neuropsychological (NP) impairment, minor cognitive motor disorder, and HIV-associated dementia, profoundly affect the quality of life of persons living with HIV infection [1]. Antiretroviral (ARV) therapy has reduced the incidence of HAND, likely by decreasing HIV replication in the

CNS. Despite this, the prevalence of HAND has increased, possibly because ARV drugs fail to completely suppress HIV replication in the brain [2, 3]. Ongoing replication may enable adaptation to neural cells, progressive brain injury, and ARV drug resistance.

In the context of HAND, improvement is associated with treatment with ARV drugs that more effectively penetrate the CNS [4]. ARV drugs may fail in the CNS, because an important component of many regimens, protease inhibitors, can extensively bind to plasma proteins [5, 6], leaving little unbound drug to penetrate into the brain and CSF. This negative property is balanced by the potency of the drugs, many of which can inhibit HIV replication at nanomolar concentrations [7].

Lopinavir (LPV) is an excellent example of such a drug. Although up to 99% of LPV is bound to plasma proteins, concentrations of the drug in CSF exceed the

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population median inhibitory concentration for wild-type HIV by >5-fold [8]. Lafeuillade et al. [9] demonstrated that treatment with LPV plus ritonavir (rtv) alone reduced HIV RNA levels below detectable levels in 3 individuals. Yilmaz et al. [10] provided further supportive evidence of the effectiveness of LPV-rtv in the CNS by demonstrating that LPV-rtv-containing combinations reduce the HIV RNA level in CSF. Similar to prior studies, however, these investigators initiated all ARV drugs simultaneously, preventing analysis of the independent effect of LPV-rtv on HIV replication in CSF.

The pharmacokinetics, potency, and high barrier to resistance of LPV-rtv enable safe administration without other ARV drugs for limited durations. We administered LPV-rtv to ARV drug-naïve individuals for 3 weeks and then added other ARV drugs to the treatment regimen, similar to a published study that demonstrated the safety of this approach [11]. Our primary objective was to determine whether LPV-rtv therapy independently reduced the HIV RNA level in CSF.

## METHODS

The study was an open-label, 24-week trial of sequential ARV therapy. The Human Research Protections Program at the University of California, San Diego, approved the study. Eligibility criteria included ARV therapy-naïve adults (age, 18–65 years) who were capable of providing informed consent, had HIV RNA levels >2000 copies/mL in plasma and >200 copies/mL in CSF, had the absence of phenotypic and genotypic resistance to LPV and at least 2 nucleoside analogue reverse-transcriptase inhibitors, and were willing to undergo the study procedures. Subjects who had evidence of severe cognitive impairment were excluded.

Nineteen ARV therapy-naïve subjects underwent screening assessments, which included measurement of HIV RNA levels in CSF and plasma samples and screening for antiretroviral drug resistance in plasma samples. Fifteen subjects were eligible, provided informed consent, enrolled, and were reassessed at a pretreatment (baseline) visit. Subjects then initiated LPV-rtv treatment; 10 completed the 3-week assessment, which was the primary study end point. Subjects who continued in the study then had at least 2 other ARV drugs added to their treatment regimen and were assessed again at weeks 12 ( $n = 9$ ) and 24 ( $n = 8$ ). Subjects were excluded after enrollment because of loss to follow-up ( $n = 2$ ), refusal of lumbar puncture ( $n = 1$ ), or poor adherence ( $n = 1$ ). One subject mistakenly initiated all ARV drugs simultaneously, which precluded the use of the data from the week 3 visit, because use of LPV-rtv only was required for this visit; the data from weeks 12 and 24 were included, because use of LPV-rtv and at least 2 other ARV drugs was required for these visits. The investigators withdrew 2 subjects after 3 weeks; 1 was withdrawn because of an increase

in hepatic transaminase levels that exceeded predefined study criteria, and 1 was withdrawn because of virologic failure.

Standardized assessments included neuromedical exams, phlebotomy, and lumbar puncture. Six subjects also consented to optional comprehensive NP testing. All assessments were performed at the University of California, San Diego, HIV Neurobehavioral Research Center (San Diego, CA).

**Neuromedical and laboratory assessments.** All subjects underwent standardized neuromedical assessments. Blood samples were obtained by venipuncture, and CSF samples were obtained by lumbar puncture. HIV RNA levels were quantified in plasma and CSF samples by RT-PCR (Amplicor; Roche Diagnostics) using the ultrasensitive assay (nominal limit of quantitation, 50 copies/mL). HIV RNA levels were truncated at the lower limit of quantitation for the purpose of analysis. CD4<sup>+</sup> cell counts were measured by flow cytometry. At screening, samples from all subjects were tested for evidence of phenotypic and genotypic resistance using the PhenoSense GT assay (Monogram Biosciences).

**NP assessment.** Fourteen subjects underwent an abbreviated NP assessment, which was constructed to provide a relatively focused assessment of the cognitive domains that are known to be impaired in HIV infection [12] and which included the following measures: (1) Hopkins Verbal Learning Test-Revised (total trials 1–3 and percent age retained) [13], (2) Trail Making Test (parts A and B) [14, 15], (3) Paced Auditory Serial Addition Test (50-item version) [16], and (4) Grooved Pegboard Test (dominant and nondominant hands) [17]. All NP tests were administered and scored by certified psychometrists in accordance with published procedures. Raw scores were converted to demographically adjusted  $\tau$  scores (mean  $\pm$  SD, 50  $\pm$  10) based on published normative data to account for the influence of age, education, sex, and ethnicity, when possible [18].  $\tau$  scores were then converted into deficit scores according to the following criteria: a  $\tau$  score >40 corresponded to a deficit score of 0, 39–35 to 1, 34–30 to 2, 29–25 to 3, 24–20 to 4, and  $\geq$ 19 to 5. The deficit scores from each of the NP test variables were then averaged to derive a global deficit score (range, 0–5) for each participant, whereas higher scores reflect greater levels of impairment. Global deficit scores  $\geq$ 0.5 were used to classify participants as globally NP impaired [12, 18].

**Statistical analysis.** Plasma and CSF HIV RNA levels were log<sub>10</sub> transformed prior to analysis to improve their distribution. Univariate analyses were performed using Fisher's exact tests for categorical variables (e.g., sex), Student's  $t$  tests for normally distributed continuous variables (e.g., age), or Wilcoxon rank-sum tests for skewed continuous variables (e.g., HIV RNA level). Because of the limited number of analyses and the sample size, the critical  $\alpha$  was set at 0.05 for all analyses.

All analyses were performed using JMP, version 6.0 (SAS Institute).

## RESULTS

Demographic and study data are summarized in table 1. Subjects were mostly middle-aged (median age, 38 years), white (53% of subjects), and male (87%) and had at least some college education (median duration of education, 13 years). Ten subjects (67%) had AIDS, and 5 (36%) of the 14 subjects who underwent NP testing had impaired global performance. For all subjects at baseline, the median CD4<sup>+</sup> cell count was 207 cells/ $\mu$ L, the median HIV RNA levels were 3.69 log<sub>10</sub> copies/mL in CSF and 5.16 log<sub>10</sub> copies/mL in plasma, the median leukocyte count in CSF was 2.5 cells/ $\mu$ L, and the protein concentration in CSF was 38.5 mg/dL.

After 3 weeks of LPV-rtv therapy alone, HIV RNA levels decreased in CSF (median change in CSF HIV RNA level,  $-1.42$  log<sub>10</sub> copies/mL; interquartile range,  $-0.99$  to  $-1.56$  log<sub>10</sub> copies/mL;  $P < .001$  by paired Student's *t* test) (figure 1A) and in plasma (median change in plasma HIV RNA level,  $-1.8$  log<sub>10</sub> copies/mL; interquartile range,  $-1.5$  to  $-2.1$  log<sub>10</sub> copies/mL;  $P < .001$  by paired Student's *t* test) (figure 1B). HIV RNA levels were below quantitation in the CSF samples from 2 subjects and in plasma samples from 1 subject. Among 9 subjects who completed 12 weeks of combination therapy, HIV RNA levels were below quantitation in CSF samples from 8 (89%) subjects and in plasma samples from 6 (67%). By week 24, HIV RNA levels were below quantitation in samples of both fluids from all 8 subjects.

To estimate the effectiveness of LPV-rtv in CSF, compared with that in plasma, we calculated the difference in HIV RNA levels between plasma specimens and CSF specimens at the baseline visit and compared this difference with that at the 3-week visit. We postulated that when HIV RNA levels decreased at similar rates in CSF and in plasma (i.e., the difference between CSF and plasma HIV RNA levels remained relatively constant, defined as a difference  $< 0.5$  log<sub>10</sub> copies/mL, between baseline and at week 3), HIV in CSF might derive predominantly from a blood-derived source, such as trafficking lymphocytes. Conversely, when the HIV RNA levels decreased at dissimilar rates (i.e., the difference between CSF and plasma HIV RNA levels between baseline and at week 3 was  $\geq 0.5$  log<sub>10</sub> copies/mL), HIV in CSF might derive predominantly from another source, possibly from longer-lived cells within the CNS. The differences between HIV RNA levels in CSF and plasma remained relatively constant between baseline and at week 3 in 5 subjects (figure 2A) but decreased in the other 5, reflecting slower decrease in HIV RNA level in CSF than in plasma. Because autonomous CNS infection is more likely to occur in subjects with more advanced immunosuppression, we postulated that subjects who had slower decrease in HIV RNA level

in CSF than in plasma would also have lower pretreatment CD4<sup>+</sup> cell counts. The subjects who had a slower decrease in HIV RNA level in CSF than in plasma trended towards having lower pretreatment CD4<sup>+</sup> cell counts (median CD4<sup>+</sup> cell count, 197 cells/ $\mu$ L vs. 328 cells/ $\mu$ L;  $P = .068$ , by 1-sided Student's *t* test) and greater differences between pretreatment HIV RNA level in CSF and that in plasma (2.26 copies/mL vs. 1.14 copies/mL;  $P = .07$ , by 1-sided Student's *t* test). In fact, lower pretreatment CD4<sup>+</sup> cell counts correlated with slower decreases in HIV RNA level in CSF, relative to the decrease in HIV RNA level in plasma (i.e., greater differences between HIV RNA levels in CSF and plasma at week 3, compared with baseline;  $\rho = -0.71$ ;  $P = .02$ ) (figure 2B). The groups did not differ with regard to age, sex, ethnicity, pretreatment HIV RNA level in CSF or plasma, CSF leukocyte count, CSF protein concentration, or Centers for Disease Control stage.

Among the 14 subjects who completed NP testing, 5 met criteria for impaired global performance at baseline. Two of the impaired subjects were among those who did not complete the primary study end point, and 3 continued in the study until week 12. When testing was performed again at week 12, the NP performance of the 3 impaired subjects improved, reaching the normal range. Subjects who had normal NP performance at baseline were not tested again.

## DISCUSSION

This open-label study demonstrated that LPV-rtv therapy alone reduced HIV replication in CSF and that LPV-rtv-containing combination therapy reduced HIV RNA levels below quantitation in the CSF. Our study is unique, because it was designed to address a problem that many previous studies have not addressed—identifying the contribution of a single drug to reduction of the HIV in CSF. Because previous CSF studies initiated all components of a combination regimen simultaneously, determining the contribution of a single drug was not possible. By administering a single drug with a high viral genetic barrier to resistance, our study was able to demonstrate that the study drug alone, not other drugs in the regimen, reduced HIV RNA levels in the CSF. More specifically, LPV-rtv therapy alone for 3 weeks reduced HIV RNA levels in the CSF of all subjects; in 80% of them, HIV RNA levels were reduced by  $> 10$ -fold.

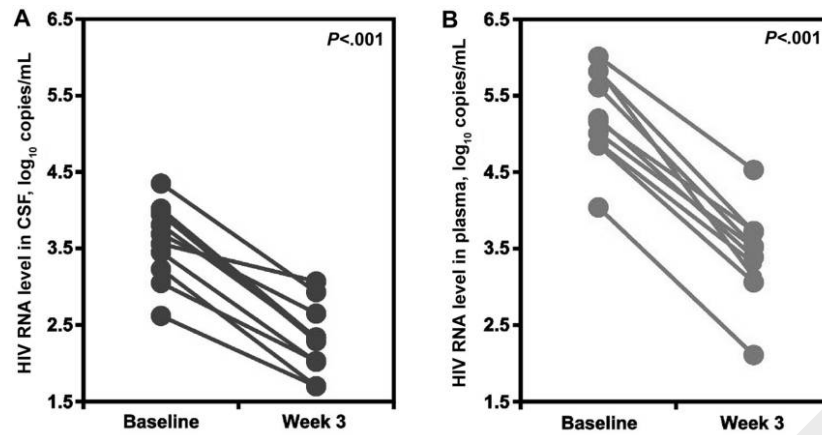
Another important concern that is often not addressed in neurologic effectiveness studies is the cellular source of HIV found in CSF. HIV in CSF is thought to be a mixture from blood-derived and CNS-derived sources, and this mixture varies on the basis of factors that include CD4<sup>+</sup> cell count and CSF leukocyte count. Individuals with higher CD4<sup>+</sup> cell counts are more likely to have blood-derived HIV in CSF, and those with lower CD4<sup>+</sup> cell counts are more likely to have HIV in CSF that derives from another source, presumably the CNS

**Table 1. Demographic and laboratory data on HIV-infected subjects who received 3 weeks of therapy with only lopinavir plus ritonavir.**

Subject	Age, years	Sex	Ethnicity	CDC stage	GDS	CD4 <sup>+</sup> cell count, cells/ $\mu$ L	Baseline			Week 3			
							Plasma HIV RNA level, log <sub>10</sub> copies/mL	CSF HIV RNA level, log <sub>10</sub> copies/mL	CSF WBC count, cells/ $\mu$ L	Plasma HIV RNA level, log <sub>10</sub> copies/mL	CSF HIV RNA level, log <sub>10</sub> copies/mL	CSF WBC count, cells/ $\mu$ L	Plasma-CSF group <sup>a</sup>
1	44	M	W	B3	0.00	76	5.84	3.23	1	3.13	1.70	0	Slower
2	46	M	W	B2	0.41	197	5.82	3.56	4	3.72	3.07	9	Slower
3	46	M	W	A2	0.29	243	5.61	3.81	3	3.53	2.34	2	Slower
4	29	F	W	C3	0.00	14	6.01	3.05	1	4.53	2.03	1	Similar
5	31	M	H	A3	0.19	207	4.88	2.62	2	3.31	1.70	0	Slower
6	42	M	W	B3	0.06	582	4.04	3.95	19	2.11	2.29	12	Similar
7	36	M	W	B3	1.00	328	4.85	3.45	6	3.06	2.02	0	Similar
8	34	M	H	C3	0.00	21	5.20	3.69	2	3.39	2.65	2	Slower
9	40	M	W	B2	0.53	347	5.16	4.02	3	3.73	2.33	2	Similar
10	37	M	W	A2	0.12	299	5.01	4.35	1	3.52	2.93	4	Similar
11	39	F	H	C3	0.71	521	3.86	2.66	2	3.97	2.51	3	...
12	39	M	W	A3	0.35	180	5.67	3.70	2	3.99	...	...	...
13	36	M	H	C3	1.59	69	5.29	4.47	3	...	...	...	...
14	36	M	H	C3	...	4	5.08	4.71	5	...	...	...	...
15	32	M	B	A1	...	647	4.82	2.53	...	...	...	...	...
All, median (IQR)	39 (34–43)	...	...	...	0.29 (0.06–0.53)	207 (72–338)	5.16 (4.87–5.64)	3.69 (3.14–3.99)	2.5 (2–4)	3.46 (3.18–3.67)	2.31 (2.02–2.57)	2 (0–4)	...

**NOTE.** Summary descriptive measures of baseline data include all 15 subjects who enrolled. Summary measures of data from the 3-week visit include only the 10 subjects who completed that visit. Boldface type designates subjects who were included in the analysis. B, black; CDC, Centers for Disease Control and Prevention; GDS, global deficit score; H, Hispanic; IQR, interquartile range; W, white.

<sup>a</sup> The difference in the rate of change between CSF and plasma HIV RNA levels, with “slower” indicating that the HIV RNA level decreased more slowly in CSF than in plasma and “similar” indicating that the HIV RNA levels decreased at a similar rate in CSF and in plasma.



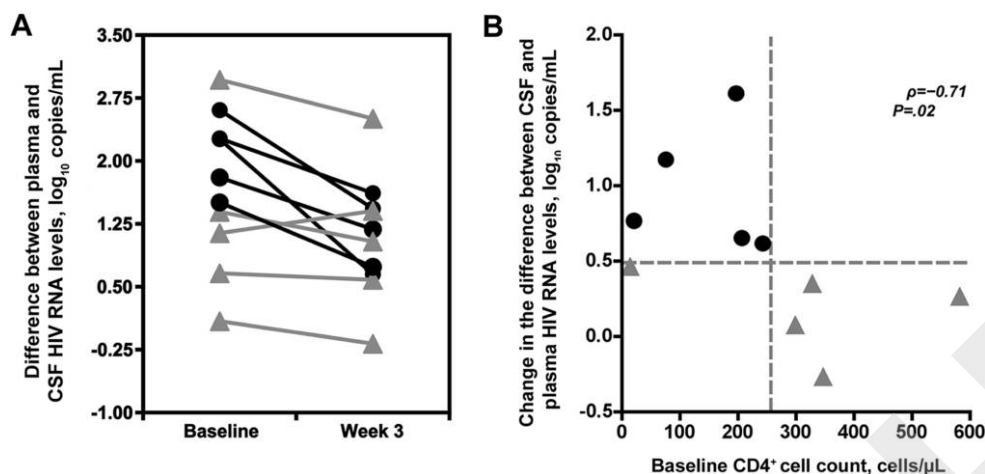
**Figure 1.** Changes in HIV RNA levels. HIV RNA levels decreased in CSF (A; median change,  $-1.42 \log_{10}$  copies/mL) and in plasma (B; median change,  $-1.8 \log_{10}$  copies/mL) in response to 3 weeks of lopinavir plus ritonavir therapy alone.

itself [19]. Demonstrating that an ARV drug reduces HIV levels in CSF would not clearly establish the effectiveness of the drug in CSF if the virions derived predominantly from the peripheral circulation, because reducing the HIV RNA level in plasma would also reduce the HIV RNA level in CSF (i.e., HIV is trafficking into the CNS from the blood). The effectiveness of an ARV drug in the CNS would be more clearly established when HIV in CSF is derived from a CNS source. When HIV in CSF derives predominantly from cells within the CNS, only a drug that penetrates the blood-brain barrier is able to reduce HIV replication in the CNS. One approach to identifying the source of CSF virions is to compare the slopes of decrease of HIV RNA levels in CSF and plasma with the hypotheses that HIV RNA levels in CSF and plasma would decrease at (1) similar rates if the virions had a similar source or (2) different rates if the virions had different sources [19, 20]. We found that one-half of the subjects who reached the primary study end point had similar decreases of HIV RNA levels in CSF and in plasma, and the other one-half had slower decreases of HIV RNA levels in CSF than in plasma. Because autonomous CNS infection [21] typically occurs in persons with advanced immunosuppression, the observation that those with slower HIV RNA level decreases in CSF, compared with plasma, had substantially lower CD4<sup>+</sup> cell counts provides additional supportive evidence for the hypothesis that differences in slopes of decrease reflect differences in cellular sources. HIV RNA levels in CSF decreased both in the subjects who had a slower decrease in HIV RNA level in CSF than in plasma (median change in HIV RNA level in CSF,  $-1.04 \log_{10}$  copies/mL) and in those who had a similar decrease in HIV RNA level in CSF and in plasma (median change in HIV RNA level in CSF and in plasma,  $-1.43 \log_{10}$  copies/mL); HIV RNA levels were actually reduced below quantitation in 2 of the subjects who had a slower decrease in

HIV RNA level in CSF than in plasma after treatment with LPV-rtv alone.

Previous studies [22, 23] have identified that the HIV RNA level can, in some individuals, decrease more rapidly in CSF than in plasma—a finding that contrasts with our findings that the HIV RNA level in CSF either decreased at rates similar to or slower than the rates of decrease in plasma. Importantly, these contrasting findings were derived primarily from individuals who had substantial prior ARV drug exposure (in contrast with our subjects, who had no prior ARV drug exposure). The resulting resistance to multiple ARV drugs caused partial responses in plasma. The more substantial responses in CSF in these individuals have been attributed to discordant ARV drug resistance between CSF and plasma or to reductions in immune activation that can occur in subjects who receive partially effective therapy.

This study provides strong evidence that LPV-rtv itself reduces the HIV RNA level in CSF but has several limitations. First, because there was no contemporaneous comparison group receiving an alternate ARV regimen, no conclusions can be reached about the relative magnitude of LPV-rtv-induced HIV RNA level reduction in CSF. Second, because treatment assignment was not randomized, unintended biases in subject selection may limit the generalizability of the findings. Third, 5 of 15 subjects did not complete the primary study end point at week 3. This probably did not influence the findings, because subjects who completed 3 weeks of the study did not differ from those who did not complete 3 weeks of the study with regard to age, education, sex, ethnicity, CD4<sup>+</sup> cell count, or HIV RNA level in CSF or in plasma (data not shown). Finally, factors other than the cellular source of HIV, such as interindividual differences in LPV concentrations, may have accounted for the



**Figure 2.** Changes in HIV RNA levels in CSF, compared with changes in HIV RNA levels in plasma. *A*, The difference between HIV RNA levels in CSF and those in plasma remained relatively constant in 5 subjects from baseline to week 3 visits (*triangles*), but the difference decreased in 5 subjects (*circles*), indicating that HIV RNA levels decreased more slowly in CSF than in plasma. *B*, Lower baseline CD4<sup>+</sup> cell counts correlated with slower decreases in HIV RNA level in CSF than in plasma. The horizontal dashed line signifies the criterion that was used to define decreases in HIV RNA level in CSF as either similar to or slower than that in plasma. All subjects who had slower decreases in HIV RNA level in CSF than in plasma had CD4<sup>+</sup> cell counts <250 cells/μL (signified by the vertical dashed line).

observed differences between decreases in CSF and plasma HIV RNA levels.

Thus, 3 weeks of LPV-rtv therapy alone reduced HIV replication in CSF after 3 weeks, even in individuals with more advanced HIV disease or impaired NP performance, and LPV-rtv-containing combinations durably suppressed HIV RNA levels in CSF for up to 24 weeks. As more studies support the importance of blood-brain barrier penetration to the control of HIV replication in the CNS [4, 24, 25], the value of the study's findings will increase, because the study demonstrates 2 design elements that may enhance the ability of future neurologic effectiveness studies to address their objectives. First, sequential introduction may be a safe method for determining the effectiveness of a single ARV drug to reduce HIV RNA levels in CSF. This method requires that the study drug have a high genetic barrier to resistance; therefore, it is probably a less useful option for studies of current nonnucleoside reverse-transcriptase inhibitors, such as efavirenz and nevirapine, which have low genetic barriers to resistance. Second, slower decreases in HIV RNA level in CSF than in plasma may be a useful and inexpensive surrogate for identifying individuals in whom HIV in CSF is predominantly produced in CNS cells. Compared with individuals who have similar decreases in HIV RNA levels in CSF and in plasma, subjects who have slower decreases in HIV RNA level in CNS than in plasma may better demonstrate the true neurologic effectiveness of a particular drug or regimen and may more accurately predict the benefits of that drug or regimen in cognitively impaired subjects in the clinic.

In conclusion, this study confirms our pharmacologic analyses, which demonstrated that LPV concentrations in CSF ex-

ceeded the median inhibitory concentration for HIV by >5-fold [8]. We conclude that LPV-rtv therapy reduces the HIV RNA level in CSF and, therefore, may benefit individuals who are at risk for or receive a diagnosis of HAND.

## HIV NEUROBEHAVIORAL RESEARCH CENTER

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