Journal of NeuroVirology, 12: 403–406, 2006

ISSN: 1355-0284 print / 1538-2443 online
DOI: 10.1080/13550280600981695

informa
healthcare

Short Communication

Valproic acid does not affect markers of human immunodeficiency virus disease progression

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Valproic acid (VPA) reduces latent human immunodeficiency virus (HIV) reservoirs by activating resting CD4+ cells. This retrospective case-control study ($n = 30$) examined effects of VPA on markers of HIV progression. VPA was not associated with changes in cerebrospinal fluid viral loads (VL), plasma VL, or neuropsychological performance. VPA patients had a trend towards lower CD4+ cells ($P = .08$) at follow-up. Concurrent antiretrovirals did not alter these relationships. VPA does not induce viremia or promote disease progression and may be safe for clinical intervention. *Journal of NeuroVirology* (2006) **12,** 403–406.

Keywords: CD4+ cell; HIV; latent virus; valproic acid; viral load

Antiretroviral therapy (ARV) can suppress both plasma and cerebral spinal fluid (CSF) human immunodeficiency virus (HIV) RNA levels to undetectable and improve CD4+ cell counts. However, latent DNA provirus can remain in resting CD4+ cells (Ylisastigui *et al*, 2004). Valproic acid (VPA), a histone deacetylase inhibitor (HDACI), is often prescribed for clinical conditions such as seizures, headaches, or mood disorders. Lehrman and colleagues demonstrated that VPA can induce activation of resting CD4+ cells, depleting latent HIV provirus when used in combination with intensified ARVs (Lehrman *et al*, 2005). However, this proof of principle study had limited numbers of subjects (four) and no controls for comparison (Smith, 2005).

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The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, nor the United States Government.

This work was supported by University of California Universitywide AIDS Research Program Fellowship (CF05-SD-301; B.A.) and amFAR Fellowship (106729-40-RFRL; B.A.). The HIV Neurobehavioral Research Center (HNRC) is supported by Center award MH 62512 from the National Institute of Mental Health (HIV Neurobehavioral Research Center, S.L., T.M., I.G., R.E).

This work was presented at the American Academy of Neurology 58th Annual Meeting.

Received 5 June 2006; revised 18 August 2006; accepted 26 August 2006.

Few studies have investigated the affect of VPA on the progression of HIV immune or neurologic disease (Schifitto *et al*, 2006). In addition, questions persist concerning the effectiveness of this medication within HIV infected individuals who do not take ARVs. Activation of latent provirus within these patients may accelerate HIV replication or deplete CD4+ cells, both of which would be clinically deleterious (Robinson *et al*, 2006). We performed a retrospective chart and database analysis of the effects of VPA on markers of HIV disease progression in both the immune (plasma viral load [VL], CD4+ cell counts) and nervous CSF VL, neuropsychological performance [NP]) systems of individuals initiating VPA compared to matched controls not taking this medication.

A retrospective chart and database analysis was performed of over 2500 patients evaluated at the HIV Neurobehavioral Research Center (HNRC) at the University of California San Diego (UCSD) (see Appendix). From this group, 80 patients were identified who had been administered VPA for clinical indications, including seizures, migraines, or mood disorders. From this set, only subjects with laboratory values both before and at least 3 months after starting VPA were included. To qualify for analysis, subjects must have maintained the exactly same ARV regimens (either on or off therapy for both visits) with the only difference being VPA. A total of 15 HIV-infected (HIV+) individuals were successfully

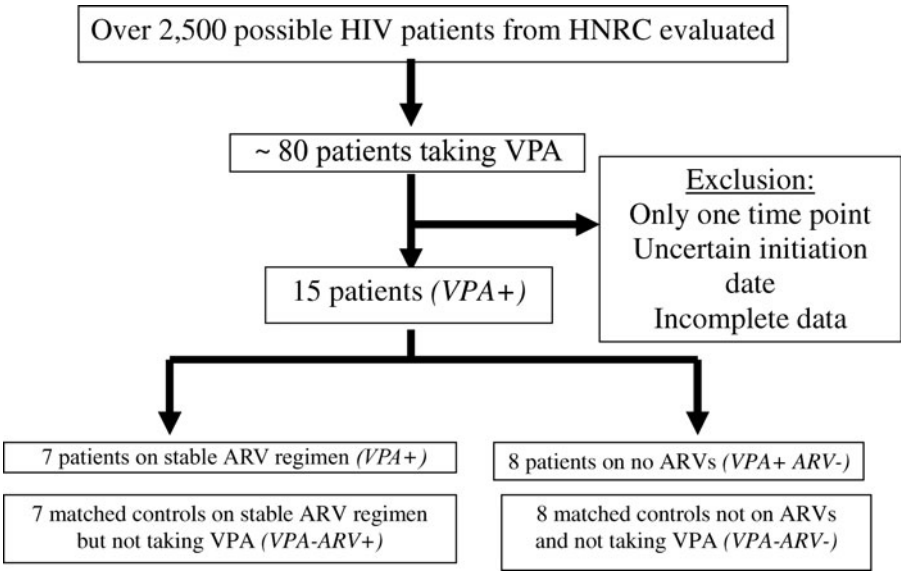

Figure 1 Flow diagram outlining selection criteria used for determining valproic acid patients (VPA+) taking medications (ARV+) or on no therapy (ARV−) compared to controls not taking valproic acid (VPA−) and either taking medications (ARV+) or no therapy (ARV−).

identified (VPA+). Fifteen HIV+ controls (VPA−) were selected who continued maintenance of ARVs (either on or off therapy for both visits), did not use VPA, with matching to cases by disease stage, plasma VLs, and CD4+ counts at the first visit (Figure 1).

Commercially available ultra sensitive assays of the CSF VL, plasma VL, and CD4+ lymphocyte counts were assessed for all patients at the two time points. In addition, 21/30 (70%) subjects (10/15 VPA+, 11/15 VPA−) completed a comprehensive, standardized NP battery at both time points. The NP battery and the approach to analysis have been described elsewhere (Carey *et al*, 2004; Heaton *et al*, 2004). This study used the global deficit score (GDS) as the primary NP outcome. Nonparametric paired *t* tests were performed for changes in laboratory values and NP performance between the two groups with *P* values significant if $P < .05$.

VPA+ and VPA− did not differ in baseline characteristics, including age, sex, ethnicity, and nadir CD4+ counts, with the median duration between visits was 14 months in both groups (Table 1). Dosage administration was determined within 12/15 patients in the VPA+ group with the average total daily dose greater than 1000 mg. VPA+ and VPA− did not differ in regards to changes in plasma or CSF VLs from baseline to follow-up. A trend towards a reduction in CD4+ counts (from 420 cell/μl to 331 cells/μl, Figure 1A) ($P = .08$) was seen for VPA+ compared to VPA− . On NP testing, VPA+ had significantly worse performance prior to initiation of medications compared to VPA− (GDS of 0.90 for VPA+ compared to 0.30 for VPA−). However, no significant differences were seen in changes in the GDS for the two groups (−0.04 for VPA+ and −0.03 for VPA−).

To further study the effects of VPA in HIV+ individuals not taking ARVs, we performed a subset analysis comparing cases taking VPA but not ARV (VPA+/ARV−) ($n = 7$) to controls on neither VPA nor ARV (VPA−/ARV−) ($n = 7$). Similar to the overall group analysis results, no significant changes were seen in plasma or CSF VL. The VPA+/ARV− group also had a trend ($P = 0.07$) towards a decrease in CD4+ counts (from 419 cell/μl to 342 cells/μl; Figure 1B). When comparing VPA+/ARV+ cases to VPA−/ART+ controls yielded similar results (data not shown). These effects were seen throughout the group and were not influenced by a single patient.

Table 1 Demographics of patients taking valproic acid (VPA+) and controls (VPA−)

	VPA+ (n = 15)	*VPA− (n = 15)*
Mean age (year old) (SE)	41 (2)	40 (2)
Sex (% male)	85%	80%
Ethnicity (% Caucasian)	67%	67%
Median CD4 nadir (cells/μl) (IQR)	271 (78–347)	250 (183–285)
Baseline CD4 (cells/μl) (IQR)	420 (287–596)	387 (292-536)
Baseline plasma viral load (copies/ml) (IQR)	12,245 (474–24,890)	9764 (51–15,389)
Baseline cerebral spinal fluid viral load (copies/ml) (IQR)	8390 (0–5221)	10,080 (0–6427)
Baseline global deficit score (SE)	0.90 (0.20)	*0.30 (0.10)
Median no. months between visits (SE)	14 (1)	14 (2)
Mean total daily VPA dose (mg) (IQR)	1155 (688–1750)	0

*$P < .05$ for VPA+ compared to VPA− at baseline.

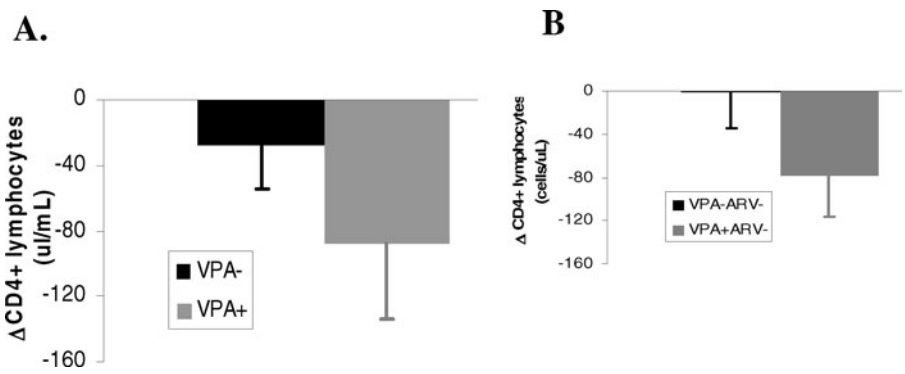

Figure 2 Changes in CD4+ cells within VPA+ and VPA− groups (**A**) and within a subgroup not on therapy (ARV−) (**B**). A trend towards a decrease in CD4+ cells was observed for both groups ($P = .08$).

No differences in NP were seen within either of the subgroups (data not shown).

In this small, retrospective, case-control study, the initiation of VPA led to no significant adverse effects on markers of HIV disease progression. In particular, plasma and CSF VL did not change among subjects initiating VPA, including those who did not take ART. Among the 21 subjects who underwent NP testing, no differences were seen between VPA+ and VPA−. Overall our results are in agreement with a recent placebo-controlled study (Schifitto *et al*, 2006) and suggest that VPA is a relatively safe medication even in individuals who not virologically suppressed.

We did observe a possible reduction in CD4+ counts following VPA initiation. This reduction did not reach statistical significance but this may reflect the limited power of this small study. Subgroup analyses supported that the effect was attributable to VPA because CD4+ counts did not decline in controls who did not take ARVs even though they had similar plasma VLs and CD4+ counts at baseline. The decline may reflect the expected loss of latently infected lymphocytes or VPA associated hematologic toxicity (Acharya and Bussel, 2000). In either case, a decrease in lymphocytes may reduce immunocompetence and may hasten initiation of ARV.

This study has a number of limitations, including its retrospective design and small sample size. Additionally, VPA levels were not measured to account for inter-individual differences in dosing, adherence, and metabolism. VPA dosages were greater than a previous placebo controlled trial (Schifitto *et al*, 2006) but similar to those used for expression of latent provirus (Lehrman *et al*, 2005; Ylisastigui *et al*, 2004). These differences may account for some of the observed discrepancies in results between the various studies. Finally, the inclusion of individuals who were not completely virologically suppressed may have masked small changes in viral loads attributable to VPA in those HIV patients who were on ARVs and were virologically suppressed.

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Appendix

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