Increased Human Immunodeficiency Virus Loads in Active Methamphetamine Users Are Explained by Reduced Effectiveness of Antiretroviral Therapy

Ronald J. Ellis,1,2 Meredith E. Childers,1,2 Mariana Cherner,2,3 Deborah Lazzaretto,2,3 Scott Letendre,2,4 Igor Grant,2,4 and the HIV Neurobehavioral Research Center Group

1Department of Neurosciences, 2HIV Neurobehavioral Research Center, and Departments of 3Psychiatry and 4Medicine, University of California San Diego, San Diego

Abuse of methamphetamine (METH) is a frequent comorbidity among individuals infected with human immunodeficiency virus (HIV) type 1. In cell cultures and animal models, METH accelerates retroviral replication. To determine whether METH increases HIV replication in humans, we evaluated HIV loads in HIV-positive METH users and nonusers. We studied 3 groups: Tox+, active METH use and positive urine toxicology results; METH +Tox, previous METH dependence/abuse and negative urine toxicology results; METH -Tox, no METH dependence/abuse and negative urine toxicology results. Tox+ subjects’ plasma virus loads were significantly higher than METH +Tox and METH -Tox subjects; cerebrospinal fluid virus loads showed a similar but nonsignificant trend. Stratification by use of highly active antiretroviral therapy (HAART) revealed that virus loads were higher only in those Tox+ subjects who reported receiving HAART. In contrast, abstinent former METH abusers (METH +Tox) receiving HAART effectively suppressed viral replication. These data suggest that abstinence programs are a key component of effective treatment of HIV in METH-abusing populations.

Recreational methamphetamine (METH) use is common in many areas of the United States, and its prevalence continues to increase [1]. METH use and human immunodeficiency virus (HIV) infection frequently co-exist, perhaps, in part, because of the association of METH use with behaviors that carry a high risk for infection [2–5]. Interactions between METH use and HIV infection are of public health concern for 3 principal reasons. First, experimental evidence from cell cultures and animal models suggests that METH exposure can accelerate feline immunodeficiency virus (FIV) replication [6], potentially hastening progression to AIDS and death. Second, the specific pathogenic mechanisms by which METH influences replication may be amplified in the central nervous system (CNS) [6], raising the possibility of additive or synergistic neurological damage and disability in HIV-infected METH users. Third, factors such as reduced access to medical care and inadequate adherence to the therapy regimen may limit the ability of METH users to benefit from highly active antiretroviral therapy (HAART). In the present study, we evaluated potential interactions between METH use and HIV infection by measuring HIV loads in current METH users and abstinent former abusers and comparing them to subjects with no history of METH dependence or abuse. To address the possibility that the effects of METH use on virus load are amplified in the CNS, we measured virus load in cerebrospinal fluid (CSF) as well as in blood plasma. To assess the potential influence of METH use on HAART...
efficacy, we grouped subjects according to current use of HAART and analyzed their self-reported adherence to the therapy regimen.

SUBJECTS AND METHODS

Subjects. Participants in the present study comprised 230 volunteers who were enrolled in various longitudinal studies at the HIV Neurobehavioral Research Center, University of California, San Diego, between 1996 and 2002. A subset of this group (n = 142) participated in a study conducted to determine whether and by what mechanisms abuse of METH enhances CNS injury in the context of HIV infection. Data from subjects in this subset were obtained at baseline visits. All other subjects were participating in other studies, which required multiple visits. Data from these subjects were obtained at the first visit at which study criteria were met. All subjects had HIV infection documented by serologic testing. Informed consent was obtained according to a protocol approved by the institutional human-subjects review panel.

For purposes of analysis, subjects were classified into 3 groups: (1) METH ‘Tox’, (2) METH ‘Tox’, and (3) ‘Tox’. The METH ‘Tox’ group (n = 66) comprised subjects who were former METH users and who met criteria for METH dependence at some time in the past but who, at the time of evaluation, reported being free of METH dependence for at least 30 days and had negative urine toxicology results for METH at the time of lumbar puncture and blood sampling. Former METH users were defined as individuals who received a diagnosis of lifetime METH dependence at some point in the individual’s life, on the basis of the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV) criteria [7], as ascertained by the Structured Clinical Interview for Substance Abuse and Dependence. In addition, members of this group had received a diagnosis of METH dependence or abuse during the preceding year, on the basis of DSM-IV criteria. The METH ‘Tox’ group (n = 76) comprised subjects who were never METH dependent and had negative urine toxicology results at the time of evaluation. The ‘Tox’ group (n = 88) comprised subjects who had positive urine toxicology results at the time of study evaluation.

Clinical evaluations. Each subject underwent a comprehensive neuromedical evaluation that was performed by use of structured clinical data forms that assessed medical history, history of medication use, antiretroviral medications, self-reported adherence to the therapy regimen, neurological and general physical examinations, and laboratory studies, including CD4+ lymphocyte (CD4) counts, routine hematology, and chemistry measurements. Participants were assessed to ensure that there was no clinical evidence of CNS opportunistic disease. From a subset of 175 subjects, 5–15 mL of CSF was obtained by lumbar puncture, and samples were aliquoted and stored at −70°C. The subset of subjects with available CSF was included as a convenience sample on the basis of having undergone a lumbar puncture. Among the groups, 29% of METH ‘Tox’ subjects had no CSF sample obtained, 18% of METH ‘Tox’ subjects had no CSF sample obtained, and 24% of ‘Tox’ subjects had no CSF sample obtained; these differences were not statistically significant (χ² = 2.81; P = .34). HIV disease stage was assigned according to the Centers for Disease Control and Prevention’s (CDC) classification scheme, which categorizes HIV-infected adolescents and adults on the basis of clinical conditions associated with HIV infection and CD4 count [8]. Adherence to antiretroviral medications was assessed among a subset of 116 subjects by use of the AIDS Clinical Trial Group’s brief self-report instrument [9]. HAART was defined as an antiretroviral drug regimen containing ≥3 antiretroviral medications.

Laboratory measures. We measured HIV RNA loads in plasma and CSF by reverse-transcriptase polymerase chain reaction (RT-PCR), using the Amplicor HIV-1 Monitor Test (Roche Molecular Systems). For CSF, an ultrasensitive version of the assay, with a nominal detection limit of 50 copies/mL, was used; whereas, for plasma, the standard assay, with a nominal detection limit of 400 copies/mL, was used. CD4 counts were quantified by a fluorescence-activated cell sorter. CSF white blood cells were measured by manual microscopy. Urine toxicology was assessed by use of the Rapid Drug Screen system (Phamatech). Urine toxicology results were determined for amphetamines, cocaine, barbiturates, tetrahydrocannabinol (THC), opiates, benzodiazepines, and phencyclidines. In this assay, the detection limit for METH is 500 ng/mL [10, 11].

Statistical analyses. To compare continuous variables among the 3 groups, 1-way analysis of variance (ANOVA) was used. When the overall group effect was significant (P < .05), pair-wise group comparisons were performed by post hoc Tukey honest significant difference test. For categorical variables, χ² test was performed; significant results were explored further by post hoc, pair-wise comparisons. HIV RNA values were log10 transformed before analysis. The assay nominal detection limits for each fluid were used as lower limit cutoffs for HIV RNA values (plasma, 2.60 copies/mL; and CSF, 1.70 log copies/mL). Although some deviation from normality on the log-transformed virus loads still existed, the large sample properties of the sampling distribution of the ANOVA and analysis of covariance (ANCOVA) estimators permitted parametric analysis methods. F values are reported. When the assumptions of an ANOVA are met, the F test (variance ratio test), which is the ratio of the between-groups variability to the error variability (taking into account their respective degrees of freedom), follows an F distribution.
RESULTS

Virus load differences among the groups. To assess possible effects of METH use on virus load, we performed ANOVA, comparing plasma and CSF virus loads among the 3 groups. METH-use status was significantly related to plasma virus load (n = 230; F = 7.91; P < .001). Post hoc, pair-wise comparisons demonstrated that the overall group effect was due to higher plasma HIV RNA loads in Tox− subjects (4.06 log10 copies/mL), compared with subjects in each of the other 2 groups (METH−Tox−, 3.45 log10 copies/mL [P = .001]; and METH+Tox−, 3.57 log10 copies/mL [P = .01]). The difference between plasma virus loads in METH−Tox− METH+Tox− subjects was not significant (P = .76). A parallel ANOVA examining CSF virus load in relation to METH-use status showed a similar trend, which did not reach statistical significance (n = 175; F = 2.51; P = .08).

Next, we evaluated potential interactions between antiretroviral therapy (ART) and METH use, by a 2-factor ANOVA in which plasma virus load was the outcome variable and HAART status (not receiving HAART vs. receiving HAART) and METH-use status (METH−Tox−, METH+Tox−, and Tox+) were the predictors. The overall ANOVA yielded a significant result (F = 20.88; P < .001). There was a significant main effect for METH-use status (F = 3.33; P = .04), as well as for HAART status (F = 82.23; P < .001), and a trend for a HAART/METH-use status interaction (F = 2.65; P = .07). Additional post hoc comparisons were performed to further assess these effects.

To assess the effects of HAART status, the cohort was divided by HAART status into 2 subgroups: 1 group included all subjects receiving HAART and the other included all subjects not receiving HAART. Plasma HIV RNA loads were compared by METH-use status separately within each HAART-status subgroup. The subgroup of subjects not receiving HAART (n = 97) comprised 82 subjects not receiving ART and 15 receiving mono- or dual-drug therapy. The subjects receiving mono- or dual-drug therapy were distributed among the groups as follows: METH−Tox−, 3 subjects (4%); METH+Tox−, 2 subjects (3%); and Tox+, 10 subjects (11%). Among these subjects, METH-use status was not related to plasma virus load (F = 0.12; P = .89). In addition, the percentages of subjects in the subgroup not receiving HAART with undetectable plasma HIV RNA loads were similar among the 3 METH-use-status groups: METH−Tox−, 13%; METH+Tox−, 12%; and Tox+, 11% (χ2 = 0.064; P = .97). By contrast, among the subgroup of subjects receiving HAART (n = 133), METH-use status was significantly related to plasma virus load (F = 7.08; P = .001). Pair-wise comparisons showed that the mean plasma virus load in Tox− subjects (3.70 log10 copies/mL) was significantly higher than that in either METH+Tox− subjects (3.06 log10 copies/mL; P = .006) or METH−Tox− subjects (3.06 log10 copies/mL; P = .10). The difference between METH−Tox− and METH+Tox− subjects was not significant (P = 1.00). Results are summarized in figure 1. Among the subgroup of subjects receiving HAART, the percentages of subjects with undetectable plasma HIV RNA loads were dissimilar among the 3 METH-use-status groups, with the lowest percentage in the Tox− group: METH−Tox−, 62%; METH+Tox−, 59%; and Tox+, 39% (χ2 = 5.24; P = .07).

We performed parallel analyses to assess potential interactive effects of HAART and METH-use status on CSF HIV RNA loads; 175 subjects had data available on CSF. An overall 2-factor ANOVA with CSF virus load as the outcome variable and HAART status and METH-use–status group as the predictors was performed. The results of the overall 2-factor ANOVA were significant (F = 12.44; P < .0001). There was a significant main effect for HAART status (F = 55.20; P < .0001) but not for METH-use status (F = .93, P = .40). The cohort was again divided by HAART status into 2 subgroups (not receiving HAART and receiving HAART), and CSF HIV RNA loads were compared among the METH-use–status groups within both HAART-status subgroups. Within the subset of 173 subjects for whom data on CSF were available, the subgroup of subjects not receiving HAART (n = 73) comprised 63 subjects not receiving ART and 10 receiving mono- or dual-drug therapy, and the remaining subjects were receiving HAART (n = 102). CSF HIV RNA loads were compared by METH-use–status group within the subgroup of subjects not receiving HAART. There was no significant effect of METH-use–status group on CSF HIV RNA loads (F = .54; P = .59). The group of 102 subjects receiving HAART was com-

Figure 1. Relationship of highly active antiretroviral therapy (HAART) to plasma virus load (log10 copies/mL) in the 3 study groups. Box-and-whisker plots show the median (center line), interquartile range (box), and 5th and 95th percentiles (whiskers) for subjects receiving HAART and for those not receiving HAART. HIV, human immunodeficiency virus; METH−Tox−, no METH dependence/abuse and negative urine toxicology results; METH+Tox−, previous METH dependence/abuse and negative urine toxicology results; Tox−, active METH use and positive urine toxicology results.
pared by METH-use–status group. There was no statistically significant difference in CSF virus loads ($F = 2.62$; $P = .08$).

**Comparability of the subject groups.** Table 1 compares demographic and medical characteristics of subjects in the 3 groups. The groups were comparable with respect to age, sex, education, percentage of subjects at CDC stage C, nadir CD4 count, length of infection, self-reported adherence to ART, and CSF leukocyte counts. There was a significant difference in the proportion of subjects receiving HAART among the groups ($F = 4.63$; $P = .01$). A significantly smaller proportion of ‘Tox’ subjects were receiving HAART, compared with METH ‘Tox’ subjects ($P = .04$) and METH ‘Tox’ subjects ($P = .003$). Among subjects receiving HAART, there was no difference in percentages of protease inhibitor (PI)–containing regimens among the 3 groups ($\chi^2 = 3.45$; $P = .18$). There was no significant difference in proportion of subjects receiving mono- or dual-drug therapy among the groups ($\chi^2 = 2.54$; $P = .28$). Because subjects were studied during a period of 5 years, we considered the possibility that HAART regimens might differ by period. However, subjects enrolled between 1996 and 1999 did not differ from those enrolled between 2000 and 2002, in the percentages of PI–containing regimens ($\chi^2 = 0.00$; $P = .99$). There was a difference in CD4 counts at time of evaluation ($F = 4.6$; $P = .01$). This result was attributable to CD4 counts being significantly lower in ‘Tox’ subjects than in METH ‘Tox’ subjects ($P = .009$).

Because ‘Tox’ subjects differed from subjects in the other 2 groups with respect to an important medical characteristic, CD4 count, we performed ANCOVA to determine whether this difference might account for the observed effects on group-related plasma virus load. Since there were significant differences in plasma virus loads only among subjects receiving HAART, ANCOVA was performed only within the group receiving HAART. The METH-use–status group was tested as a predictor of the outcome variable, plasma virus load, with CD4 count as a covariate. The results of the overall model were significant ($F = 6.55$; $P < .001$). The covariate, CD4 count, was independently significant ($F = 8.03$; $P = .005$), showing the expected inverse relationship to plasma virus load. After adjusting for CD4 count, the METH-use–status group main effect remained significant ($F = 3.44$; $P = .04$). In post hoc, pairwise comparisons, the ‘Tox’ group still showed higher virus loads than either the METH ‘Tox’ group ($P = .02$) or the METH ‘Tox’ group ($P = .03$).

In addition to screening for METH, we performed urine toxicology screening for other nonprescription drugs of abuse, including other amphetamines, cocaine, barbiturates, THC, opiates, benzodiazepines, and phencyclidines. Predictably, ‘Tox’ subjects were more likely to be positive for these other substances ($n = 14$) than were either METH ‘Tox’ ($n = 1$) or METH ‘Tox’ ($n = 2$) subjects. To evaluate whether use of these other drugs might explain increased virus loads in the ‘Tox’ subjects, we performed secondary analyses. Excluding subjects positive for drugs of abuse other than METH did

### Table 1. Demographic and clinical characteristics of the 3 methamphetamine (METH)–use–status groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All subjects</th>
<th>Group 1, METH ‘Tox’</th>
<th>Group 2, METH ‘Tox’</th>
<th>Group 3, ‘Tox’</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>230</td>
<td>88</td>
<td>66</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Age, mean, years</td>
<td>39</td>
<td>41</td>
<td>38</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Male sex, %</td>
<td>90</td>
<td>86</td>
<td>92</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>Education, years</td>
<td>13</td>
<td>13</td>
<td>12</td>
<td>13</td>
<td>.29</td>
</tr>
<tr>
<td>CD4 count, cells/µL$^b$</td>
<td>376</td>
<td>383</td>
<td>426</td>
<td>310</td>
<td>.01$^a$</td>
</tr>
<tr>
<td>CDC stage C, %</td>
<td>32</td>
<td>34</td>
<td>26</td>
<td>35</td>
<td>.42</td>
</tr>
<tr>
<td>Nadir CD4 count, cells/µL$^c$</td>
<td>222</td>
<td>220</td>
<td>253</td>
<td>196</td>
<td>.29</td>
</tr>
<tr>
<td>Length of infection, years$^d$</td>
<td>7.33</td>
<td>7.83</td>
<td>6.42</td>
<td>7.42</td>
<td>.36</td>
</tr>
<tr>
<td>Receiving HAART, %</td>
<td>58</td>
<td>68</td>
<td>62</td>
<td>46</td>
<td>.009$^a$</td>
</tr>
<tr>
<td>Self-report on adherence available, no.</td>
<td>119</td>
<td>52</td>
<td>43</td>
<td>24</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Self-reported ≥95% adherence, %</td>
<td>69</td>
<td>71</td>
<td>65</td>
<td>71</td>
<td>.65</td>
</tr>
<tr>
<td>CFV WBC count, cells/µL</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>.32</td>
</tr>
<tr>
<td>Plasma HIV RNA load, copies/mL</td>
<td>3.72</td>
<td>3.45</td>
<td>3.57</td>
<td>4.06</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CSF HIV RNA load, copies/mL</td>
<td>2.38</td>
<td>2.32</td>
<td>2.20</td>
<td>2.57</td>
<td>.08</td>
</tr>
</tbody>
</table>

**NOTE.** $^a$ by χ² test was used for proportions; analysis of variance with post hoc Tukey honest significant difference test was used for means. CD4, CD4⁺ lymphocyte; CDC, Centers for Disease Control and Prevention; CSF, cerebrospinal fluid; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; METH ‘Tox’, no METH dependence and negative urine toxicology results; METH ‘Tox’, previous METH dependence and negative urine toxicology results; ‘Tox’, active METH use and positive urine toxicology results; WBC, white blood cells.

$^b$ Denotes statistically significant results.

$^c$ CD4 counts were not available for 3 subjects.

$^d$ $n = 191$.

$^e$ $n = 222$. 

Increased HIV Loads Due to METH • JID 2003:188 (15 December) • 1823
not substantively alter the findings described above. Plasma HIV RNA loads differed significantly among the METH-use-status groups (F = 9.42; P < .001). Virus loads in the Tox group differed significantly from those in the METH ‘Tox’ group (P < .001) and the METH’’Tox’’ group (P = .004). There was no significant difference between the METH ‘Tox’ and METH’’Tox’’ groups (P = .71). As in the previous analysis, CSF HIV RNA loads did not differ significantly among the METH groups (P = .08).

DISCUSSION

METH stimulates secretion of tumor necrosis factor (TNF)-α in splenocytes from retrovirus-infected mice [12]. Similarly, cocaine, a recreational stimulant with prominent dopaminergic effects that are similar to those of METH, increases production of TNF-α and HIV replication in human peripheral blood mononuclear cells [13] and stimulates viral replication in human peripheral blood leukocytes implanted into severe combined immunodeficient mice [14]. These findings suggest that stimulants such as METH might increase virus loads in humans by dysregulating inflammatory cytokine production. The present study has found that, in fact, plasma virus loads were higher in Tox subjects than in METH ‘Tox’ subjects or METH’’Tox’’ subjects. Although this intriguing finding is consistent with the in vitro data, further analyses demonstrated a compelling alternative explanation for the increased virus loads seen in Tox subjects.

More than half of the subjects in this study were receiving HAART. HAART is prescribed to suppress viral replication, and its effects on virus load typically are very significant. Thus, declines of 100–1000-fold from baseline are quite common. We therefore considered it important to assess whether HAART effects modified the influence of METH use on virus load. Indeed, subgroup analyses demonstrated that, compared with subjects in the other groups, Tox subjects had increased plasma virus loads only if they were receiving HAART. Untreated Tox subjects and those receiving suboptimal therapy had virus loads statistically indistinguishable from those of subjects in the other groups. This is not consistent with a direct biological effect of METH use itself on viral replication. Rather, it suggests that recent METH use and ART interact in their effects on virus load.

Antiretroviral medications suppress viral replication only if drug concentrations are maintained at levels greater than a certain, drug-specific threshold. Inadequate adherence to strict medication administration schedules can allow concentrations to fall below these thresholds, resulting in a rebound of viral replication [15, 16]. Enhanced elimination of antiretrovirals via metabolic pathways due to drug-drug interactions also may lower concentrations below these thresholds. Thus, the increase in virus load that we found among Tox subjects receiving HAART may be due to poor adherence or to altered metabolism of antiretroviral medications. Although no consistent reports of altered drug metabolism related to METH use exist, there is substantial literature on impaired adherence to the therapy regimen among stimulant users [17, 18]. Impaired adherence to the therapy regimen, in turn, is believed to contribute to less-effective inhibition of viral replication and to the development of resistance to antiretroviral drugs. We collected self-reports of adherence to the HAART regimen and found these to be similar in Tox subjects, compared with subjects in the other groups. However, self-reports of adherence to the therapy regimen are frequently inaccurate.

It is possible that some METH ‘Tox’ subjects falsely reported abstinence from METH during the 30 days before evaluation. If so, virus loads in these subjects would be expected to be similar to those of Tox subjects. Including these subjects would therefore introduce a conservative bias, favoring the null hypothesis of no group differences. In fact, we observed a robust and statistically significant difference.

Recreational drug users typically do not limit themselves to 1 substance, but instead use drugs that are available and affordable. This raises the possibility that use of substances other than METH might explain the increased virus loads seen in our subjects. To address this possibility, we replicated our initial analysis after excluding subjects who tested positive for any drugs of abuse other than METH (excluding marijuana). Comparable results were obtained. Although this approach does not eliminate the possibility that these subjects had used other substances recently, it does diminish the possibility that other drugs could account for the observed effects on virus load.

For several reasons, the CNS is a particularly important site for interactions between METH and HIV. METH penetrates the brain and CSF rapidly because of its lipid solubility and is sequestered in the CNS [26, 27]. Virus-infected cells in the CNS may be selectively affected by METH. Thus, Gavrilin et al. [6] showed that METH exposure dramatically enhances FIV replication in infected brain astrocytes expressing the chemokine receptor CXCR4. Both FIV and HIV are able to use this receptor, which is expressed on astrocytes and immune system cells [6]. Additionally, METH may injure the brain microvascular endothelium, potentiating CNS tissue infiltration by HIV-infected monocytes [28]. These observations suggest that the effects of METH on immune dysregulation and stimulation of virus replication are likely to be enhanced in the brain. Indeed, previous research has found that HIV encephalitis is more prevalent among drug users, compared with nonusers [29]. Despite these observations, we found no evidence of increased CSF virus load in METH users. We plan to address the effects of METH use on cytokine and chemokine concentrations in CSF in separate studies.

We have found that HAART, as expected, effectively lowers
virus loads in METH“Tox” subjects, but not in Tox” subjects. Understanding HAART efficacy in METH users is important for a number of reasons. First, HIV-infected substance abusers frequently have diminished access to health care [19–21], and health care providers may be less motivated to treat them [22–24]. Comorbid conditions associated with drug use, such as higher rates of mood disorders and hepatitis than among non-using peers, can present obstacles to effective treatment [5, 25]. Despite concerns that the complexities of HAART therapy make it impractical for persons with a history of drug abuse, our findings demonstrate that former METH users who maintain abstinence can effectively suppress HIV replication with potent ART. These data suggest that providers involved in the clinical care of HIV-infected persons who are METH users will need to make efforts to get their patients into substance abuse treatment programs to assist them in achieving stable abstinence. Once abstinence is achieved, the responses to ART by former METH-dependent persons are similar to those of non–substance abusing control subjects.

SAN DIEGO HIV NEUROBEHAVIORAL RESEARCH CENTER GROUP

The San Diego HIV Neurobehavioral Research Center group is affiliated with the University of California, San Diego, the Naval Hospital, San Diego, and the San Diego Veterans Affairs Health-care System, and includes the following: Igor Grant (director); J. Hampton Atkinson and J. Allen McCutchan (codirectors); Thomas D. Marcotte (center manager); Mark R. Wallace (Naval Hospital San Diego); J. Allen McCutchan, Ronald J. Ellis, Scott Letendre, and Rachel Schrier (neuromedical component); Robert K. Heaton, Mariana Cherner, Julie Rippeth, Joseph Sadek, and Steven Paul Woods (neurobehavorial component); Terry Jernigan, John Hesselink, and Michael J. Taylor (imaging component); Eliezer Masliah and Dianne Langford (neuropathology component); J. Allen McCutchan, J. Hampton Atkinson, Ronald J. Ellis, and Scott Letendre (clinical trials component); Daniel R. Masys (data management unit); Michelle Frybarger (data systems manager); and Ian Abramson, Reena Deutsch, Deborah Lazzaretto, and Nupur Roy (statistics unit).

References

25. Shoptaw S, Reback CJ, Freese TE. Patient characteristics, HIV serostatus, and risk behaviors among gay and bisexual males seeking treat-
methylamphetamine (V-111) in the body. Acta Physiol Acad Sci Hung
27. Baselt R. Disposition of toxic drugs and chemicals in man. 2nd ed.
28. Lee YW, Hennig B, Yao J, Toborek M. Methamphetamine induces AP-
1 and NF-κB binding and transactivation in human brain endothelial
29. Bell JE, Brettle RP, Chiswick A, Simmonds P. HIV encephalitis, proviral
load and dementia in drug users and homosexuals with AIDS. Effect