Antiretroviral Therapy in HIV Infection

Are Neurologically Active Drugs Important?

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Background: The effect on neuropsychological function of antiretroviral drugs that are able to penetrate into the brain in effective concentration (neuroactive drugs) remains unclear.

Objective: To investigate whether highly active antiretroviral therapy (HAART) containing neuroactive drugs is associated with better neuropsychological performance in patients with human immunodeficiency virus disease.

Design: Cross-sectional survey.

Setting: Tertiary referral hospital outpatient clinics.

Patients: The study population consisted of 97 individuals positive for human immunodeficiency virus (stage C3, 1993 Centers for Disease Control and Prevention classification) whose condition had been stable on their current HAART regimen for a mean ± SD of 18.5 ± 16.5 months and who were aged 48.14 ± 9.38 years. The patient groups were analyzed according to whether their regimen contained 3 or more neuroactive drugs (neuro-HAART group; n = 41) or not (HAART group; n = 56).

Main Outcome Measure: Neuropsychological performance on 7 cognitive domains.

Results: The neuroHAART and HAART groups did not differ from one another on neuropsychological performance, but both patient groups were impaired compared with controls. Impaired patients in each treatment group were compared, and the neuroHAART group showed significantly better memory performance, unrelated to plasma viral load, than the HAART group.

Conclusion: No direct benefit of neuroactive HAART therapy was found in patients with advanced human immunodeficiency virus infection. However, in neuropsychologically impaired patients, there was a benefit in memory function. This suggests that a threshold of neuropsychological impairment is required for the benefit of neuroactive HAART.

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Despite the introduction of highly active antiretroviral therapy (HAART) and its initial benefit on neuropsychological (NP) function, NP impairment associated with human immunodeficiency virus (HIV) remains common. One possible explanation for this is that HAART regimens either do not contain or do not contain enough antiretroviral drugs that penetrate the central nervous system (CNS) in effective concentration.

Several antiretroviral drugs have been identified as being more neurologically active on the basis of their capacity to reduce cerebrospinal HIV viral load to an undetectable level2,4 and ameliorate neurologic and NP deficits.5 However, the effect on NP function of HAART regimens that contain 1 or more so-called neurologically active antiretroviral drugs remains unclear. A 3-year study6 showed no difference in motor and psychomotor functioning between patients receiving HAART regimens that include single or multiple CNS-penetrant drugs. However, another study7 demonstrated that a HAART regimen that included 2 neuroactive HAART drugs was associated with a transient improvement in motor and psychomotor speed in individuals with moderately advanced AIDS.

Because of these controversial results and because several important points have not been previously addressed (the comprehensiveness of NP measures, the level of impairment and drug interactions, and especially the boosting effect of ritonavir8 on blood concentrations of protease
The exclusion criteria were psychiatric disorders (past or current psychotic disorders, current major depressive disorder, substance use disorder, posttraumatic stress disorder), neurologic disorders (current neurologic disease), and current neurologic disease (current CNS opportunistic infection), current AIDS-dementia complex, current neurologic disorder unrelated to HIV, head injury with loss of consciousness, and current drug use disorder. Patients with a previous brain HIV-related infection were included as long as there had been clinical resolution with HAART at least 6 months before study entry. These patients were equally represented in both treatment groups and did not differ from other patients in their NP performance.

Demographic, clinical, and laboratory characteristics are presented in Table 1. Ninety-seven patients agreed to participate. Forty-one HIV-positive individuals were on a neurologically active HAART regimen (neuroHAART group), while 56 HIV-positive individuals were on a less neurologically active regimen (HAART group). A neurologically active regimen was defined as one with 3 or more antiretroviral drugs known to penetrate the CNS in effective concentration. A threshold of 3 neuroactive drugs was chosen on the basis of the higher probability of reaching an undetectable cerebrospinal viral load. Seven antiretroviral drugs were defined as neuroactive drugs: nevirapine, efavirenz, stavudine, didanosine, lamivudine, abacavir, and indinavir. The patient’s physician, who was unaware of the NP results, made the choice of which drugs were included in the HAART regimen according to the patient’s history of tolerability and resistance to individual antiretroviral drugs.

Thirty seronegative men were selected as controls matched for age and education level from a study on sexual behavior in gay men and from advertisements in the gay press. They had to have been seronegative at least 3 months before the examination on a screening test (enzyme-linked immunosorbent assay) for HIV-1 specific antibody. They were screened for significant neurologic or psychiatric diseases.

HISTORICAL AND MEDICAL INFORMATION

Before the NP examination, participants were interviewed to obtain demographic and substance use information. Medical information (date of HIV diagnosis, mode of infection, antiretroviral treatment, year of HAART initiation, current HAART initiation) was recorded. Immunologic markers (current and nadir CD4 cell count, plasma viral load) were obtained within 1 month of the examination.

NEUROPSYCHOLOGICAL EXAMINATION

All subjects were examined with a standard NP battery assessing 7 cognitive domains that have been shown to be relevant in the study of HIV–1–infected individuals. These include attention (Digit Span, Wechsler Adult Intelligence Scale–Revised III), psychomotor speed and complex attention (Trail-Making Test A and B; Symbol Digit Modalities Test, written and oral procedures), motor coordination (Grooved Pegboard Test, dominant and nondominant hand), verbal memory (California Verbal Learning Test, total of 5 trials; learning and short-term and long-term recall), visual memory (Rey-Osterrieth Complex Figure,

Table 1. Demographic, Clinical, and Laboratory Measures for the NeuroHAART, HAART, and Control Groups

<table>
<thead>
<tr>
<th></th>
<th>NeuroHAART (n = 41)</th>
<th>HAART (n = 56)</th>
<th>HIV-Negative Control (n = 30)</th>
<th>F or t</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>48.31 (9.62)</td>
<td>48.27 (9.36)</td>
<td>47.4 (9.29)</td>
<td>0.12</td>
<td>.88</td>
</tr>
<tr>
<td>Education, y</td>
<td>13.87 (3.17)</td>
<td>14.17 (2.67)</td>
<td>15 (3.08)</td>
<td>1.31</td>
<td>.27</td>
</tr>
<tr>
<td>Estimated IQ (NART FSIQ)</td>
<td>115.12 (8.96)</td>
<td>116.14 (8.58)</td>
<td>117.4 (6.61)</td>
<td>0.65</td>
<td>.52</td>
</tr>
<tr>
<td>Sex, No. M/F</td>
<td>41/0</td>
<td>55/1</td>
<td>30/0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>DASS score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>7.96 (8.03)</td>
<td>6.91 (7.47)</td>
<td>4.83 (5.95)</td>
<td>1.54</td>
<td>.21</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4.87 (5.59)</td>
<td>5.19 (5.65)</td>
<td>3.33 (5.31)</td>
<td>1.14</td>
<td>.32</td>
</tr>
<tr>
<td>Stress</td>
<td>8.87 (7.77)</td>
<td>9.16 (6.65)</td>
<td>9.53 (8.23)</td>
<td>0.06</td>
<td>.93</td>
</tr>
<tr>
<td>Estimated disease duration, y*</td>
<td>9.07 (5.4)</td>
<td>12.67 (3.8)</td>
<td>ND</td>
<td>3.6</td>
<td>.001</td>
</tr>
<tr>
<td>Year of HAART initiation</td>
<td>1997.2 (0.2)</td>
<td>1996.1 (0.1)</td>
<td>ND</td>
<td>3.2</td>
<td>.002</td>
</tr>
<tr>
<td>Current HAART duration, mo</td>
<td>21.9 (2.5)</td>
<td>16.1 (2.2)</td>
<td>ND</td>
<td>1.7</td>
<td>.09</td>
</tr>
<tr>
<td>Nadir CD4 count, cells/µL</td>
<td>77.6 (10.34)</td>
<td>69.07 (7.77)</td>
<td>ND</td>
<td>0.67</td>
<td>.50</td>
</tr>
<tr>
<td>Current CD4 count, cells/µL</td>
<td>389.51 (33.51)</td>
<td>335.78 (32.17)</td>
<td>ND</td>
<td>1.13</td>
<td>.25</td>
</tr>
<tr>
<td>Plasma HIV RNA, log₁₀ copies/mL</td>
<td>2.31 (1.16)</td>
<td>3.17 (1.52)</td>
<td>ND</td>
<td>3.04</td>
<td>.003</td>
</tr>
</tbody>
</table>

Abbreviations: DASS, Depression Anxiety Stress Scale; FSIQ, Full Scale IQ; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; NA, not applicable; NART, National Adult Reading Test; ND, not done; NeuroHAART, HAART composed of at least 3 neuroactive drugs.

*Time since date of first HIV diagnosis.
delayed recall), and visuconstructional ability (Rey-Osterrieth Complex Figure, copy). Premorbid intelligence level was estimated by means of the National Adult Reading Test with the Full Scale IQ. The Depression Anxiety Stress Scale16 was administered to measure mood status. All participants signed an informed consent form, and the affiliated research institutions and ethics committees approved the research protocol.

DATA ANALYSIS
Demographic, clinical, laboratory, and treatment data were compared by independent samples t test, analysis of variance, and χ² test. The distribution of plasma viral load was log₁₀ transformed because of a significant positive skew. The NP raw scores were compared between the neuroHAART and HAART groups and between HIV-positive patients and controls by t test. These comparisons reflected the hypotheses that (1) patients receiving neuroHAART would show superior NP performance to patients receiving HAART and (2) patients with advanced HIV disease in general would have worse cognitive function than seronegative controls. In addition, measures of effect size15 were calculated between the 2 HAART groups to determine the magnitude of any differences in performance. Five composite NP scores were created to reflect attentional function, memory function, motor function, psychomotor function, and visuconstruction. These composite scores were derived from the 13 NP measures by averaging the standard scores within each domain. Correlational analyses were conducted to explore the relationship between the number of neuroactive drugs and ritonavir-PI combinations (Table 2) and NP performance. Analyses of covariance were conducted to adjust for variables that differed between the patient groups (eg, disease duration, year of HAART initiation, log₁₀ plasma HIV RNA level, and treatment duration showing a trend) and separately to further investigate the effect of HAART containing ritonavir-PI combinations. Finally, to address the issue of level of impairment, we selected patients in each treatment group who were impaired according to a standard criterion16: −2 SDs in 2 NP measures. Impaired patients signed an informed consent form, and the affiliated research institutions and ethics committees approved the research protocol.

In the NeuroHAART and HAART Groups

Table 2. Numbers of Neuroactive Drugs and Ritonavir-PI Combination Composing the HAART Regimens in the NeuroHAART and HAART Groups

<table>
<thead>
<tr>
<th>Combination Composing the HAART Regimens</th>
<th>NeuroHAART (n = 41)</th>
<th>HAART (n = 56)</th>
<th>χ²</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroactive drugs, No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>0</td>
<td>97.00</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>0</td>
<td>0.00</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>27</td>
<td>0.00</td>
<td>4</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>25</td>
<td>0.00</td>
<td>4</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0.00</td>
<td>4</td>
</tr>
<tr>
<td>Ritonavir-PI combination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
<td>36</td>
<td>97.00</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No</td>
<td>28</td>
<td>20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HAART, highly active retroviral therapy; NeuroHAART, HAART composed of at least 3 neuroactive drugs; PI, protease inhibitor.

RESULTS

GROUP COMPARISONS

Significant group differences were found for Digit Span forward, Verbal Memory learning, Verbal Memory recall, Grooved Pegboard Test dominant hand, Trail-Making Tests, and Symbol Digit Modalities Test written and oral measures (Table 3). However, for all of these measures, while HIV-positive patients (neuroHAART and HAART groups) performed worse than controls, no significant differences in cognitive performance were found between the patient treatment groups. Effect sizes of the magnitude of differences between the patient treatment groups were small across all measures. Treatment groups did not differ significantly on adjusted analyses for disease and treatment variables.

NUMBER OF NEUROACTIVE DRUGS IN RELATION TO NP MEASURES

There was no significant association between the number of neuroactive drugs used (defined as an ordinal variable, 0-4 neuroactive drugs) and the NP composite scores. The presence of a ritonavir-PI combination showed a trend for a negative association with motor performance (r = −0.19, P < .06).

EFFECT OF RITONAVIR-PI COMBINATION

Adjusted analyses showed that ritonavir-PI combinations had a significant negative effect on motor performance (β = −0.49; t = 2.41; P < .02). The neuroHAART group showed lower motor performance compared with the HAART group (F₁,₉₄ = 3.72; P < .05).

COMPARISONS FOR IMPAIRED PATIENTS IN THE NEUROHAART AND HAART GROUPS

Subgroups did not differ in demographic, mood, clinical, laboratory, and treatment measures with the exception that the neuroHAART group had a lower log₁₀ plasma viral load than the HAART group (t₁₅ = −2.78; P = .009). Nevertheless, the comparison of patients with undetectable vs detectable viral load in each treatment group showed only a trend (P = .07). The neuroHAART group showed significantly better memory learning (t₁₅ = −2.15; P = .04), short-term recall (t₁₅ = −2.30; P = .03), and long-term recall (t₁₅ = −2.37; P = .02) (Table 4). Subsequent analyses to control for differences in plasma viral load demonstrated that impaired patients in the neuroHAART group still showed significantly better memory score (F₁,₃₄ = 7.42; P < .01), while plasma viral load was not associated with the memory performance. When a milder degree of impairment was chosen (−2 SDs in one
NP measure), the treatment groups did not differ on NP performance.

The aim of our study was to explore the impact of a neurologically active HAART regimen on a wide range of NP functions. We found no differences in NP function between patients with advanced HIV infection who were receiving HAART regardless of whether this included 3 neuroactive drugs. Additionally, the number of neuroactive drugs was not associated with NP performance. However, when impaired patients were compared in each treatment group, the neuroHAART group demonstrated better memory performance even after control for plasma viral load.
Some limitations may have reduced our ability to detect differences between patients groups. The post hoc study design did not allow us to control exactly all clinical and laboratory factors. However, patients were well matched on demographic characteristics as well as mood status. Additionally, when analyses were conducted to control for these variables, the treatment groups remained statistically not different in their NP performance.

Second, it could be argued that patients receiving neuroHAART were actually on such a drug regimen because they were known to have or suspected of having NP deficits and that this may have confounded the results. This is unlikely: the choice of antiretroviral drugs was made by the patient’s physician, who was unaware of the NP results, and patients with clinical AIDS-dementia complex were excluded.

Third, there is the possibility that the presence of previous damage in some of the patients may have confounded the results. Again, this is very unlikely, as the number of patients with previous HIV-related brain diseases represented a minority (10% in each treatment group), and those patients were included only if their symptoms had clinically resolved for at least 6 months before study entry. In addition, after further subanalyses, their NP performance was not different from that of the other patients.

Fourth, the results may have been confounded by differences in adherence between the 2 groups. While adherence was not formally assessed, it is an improbable confounding factor. Immune and viral load markers have been shown to be associated with measures of adherence. In our group, 55% had an undetectable viral load and 23% had a plasma viral load greater than 30,000 copies/mL, suggesting that a majority of patients were adherent. Additionally, in impaired patients, the number of patients with detectable and undetectable viral load did not statistically differ between treatment groups. Finally, plasma viral load was not a significant covariate in all adjusted analyses.

The results are largely in accord with what has been published, showing that patients with advanced HIV infection show poorer NP performance than seronegative controls. Indeed, controls showed better performances than both patient groups on immediate memory, verbal memory, motor coordination in the dominant hand, psychomotor speed, and complex attention.

Our results confirm the notion that in patients with moderate to advanced HIV-AIDS who receive long-term HAART treatment, having a higher number of neuroactive drugs composing the HAART does not influence NP performance. A positive effect, however, may be transiently observable shortly after HAART initiation.

However, in NP impaired patients, a positive effect of neuroactive drugs was observed on verbal memory. This included a small number of patients, and as such it should be considered suggestive rather than definitive. Nevertheless, the differences observed showed large effect sizes that represent clinically meaningful trends.

REFERENCES


22. Brew BJ. Evidence for a change in AIDS dementia complex in the era of highly active antiretroviral therapy and the possibility of new forms of AIDS dementia complex. AIDS. 2004;18(suppl 1):S75-S78.