Human immunodeficiency virus-type 1 (HIV-1) infection causes a spectrum of neurocognitive syndromes ranging from minor cognitive impairment, detectable on neuropsychological (NP) testing, to frank dementia. Most reports assessing NP performance in HIV-infected patients have been conducted as multicentre studies and are usually composed of self-selected participants.

**ABSTRACT: **Background: Neurocognitive impairment is a frequent complication of HIV infection and heralds a poor survival prognosis. With the availability of highly active antiretroviral therapy (HAART), survival times for HIV-infected patients have markedly increased although the effects of HAART on the prevalence of neurocognitive impairment remain uncertain. **Objective:** To determine the relationship between self-reported neurocognitive symptoms and neuropsychological (NP) performance together with the impact of HAART among HIV-infected patients. **Methods:** A cross-sectional study was performed in which patients without previously documented neurocognitive impairment attending an HIV community clinic were questioned about neurocognitive symptoms and a NP test battery was administered. **Results:** Of the eighty-three patients examined, neurocognitive symptoms were reported by 34% of patients and were associated with a shorter duration of HAART and higher viral loads. Patients reporting neurocognitive symptoms were also more likely to exhibit impaired NP performance (p<0.005) with NP impairment being detected in 46% of all patients examined (12% with HIV-associated dementia). Neuropsychological impairment was directly correlated with age (p<0.001), plasma viral load (p<0.005) and inversely correlated with the number of prescribed antiretroviral drugs (p<0.01). **Conclusions:** These results suggest that neurocognitive symptoms are predictive of impaired NP performance and that NP impairment remains a frequent finding among older patients with higher viral loads. An increased number of antiretroviral drugs may be neuroprotective.

**RéSUMÉ: **Symptômes neurocognitifs et invalidité chez les patients d’une clinique communautaire anti-VIH. **Introduction:** Le déficit neurocognitif est une complication fréquente de l’infection par le VIH et comporte un mauvais pronostic quant à la survie. Avec l’arrivée de la thérapie antirétrovirale hautement efficace (HAART), la survie des patients infectés par le VIH a augmenté de façon appréciable, bien que l’influence de HAART sur la prévalence du déficit neurocognitif demeure inconnue. **Objectif:** Déterminer la relation entre les symptômes neurocognitifs rapportés par les patients et la performance neuropsychologique (NP) ainsi que l’impact de HAART chez les patients infectés par le VIH. **Méthodes:** Dans cette étude transversale, on a questionné des patients d’une clinique communautaire anti-VIH sans déficit neurocognitif documenté sur leurs symptômes neurocognitifs et on leur a administré une batterie de tests NP. **Résultats:** Parmi les quatre-vingt-trois patients examinés, des symptômes neurocognitifs ont été rapportés par 34% et ils étaient associés à une administration plus brève de HAART et à une charge virale plus élevée. Les patients qui avaient rapporté des symptômes neurocognitifs étaient également plus susceptibles d’avoir une performance NP altérée (p < 0.005); une altération NPa été détectée chez 46% de tous les patients examinés (démence associée au VIH chez 12%). Le défictpNétait directement corrélé à l’âge (p < 0.001), la charge virale plasmatique (p < 0.005) et inversement corrélé au nombre de médicaments antirétroviraux prescrits (p < 0.01). **Conclusions:** Ces résultats suggèrent que les symptômes neurocognitifs sont indicateurs d’une performance NP altérée et que l’altération NP demeure une constatation fréquente chez les patients plus âgés qui ont une charge virale plus élevée. Un nombre croissant de médicaments antirétroviraux puissent être neuroprotecteurs.
volunteers who are motivated to remain in a longitudinal study. These circumstances may not reflect the circumstances for many HIV community clinics and neurology referrals from such clinics. To date, there has been limited evaluation of NP impairment following use of highly active antiretroviral therapy (HAART) with variable results. Furthermore, few studies have addressed the relationship between neurocognitive symptoms and impairment in the setting of an HIV community clinic among patients receiving HAART. The purpose of this cross-sectional study was to examine the relationship between neurocognitive symptoms and NP impairment among patients receiving HAART in a community clinic.

METHODS

The Southern Alberta Clinic (SAC) is a community HIV clinic that serves all HIV seropositive patients (n=780) in southern Alberta. All patients attending SAC receive free antiretrovirals and are followed regularly with viral loads and CD4 counts. During routine visits to SAC, patients and/or primary care givers were randomly selected and subsequently questioned, by a registered nurse or a social worker, about symptoms indicative of (1) memory and concentration dysfunction, (2) difficulty with gait and coordination, (3) change in behavior or social interactions and (4) related difficulties with activities of daily living including self-care (cooking, dressing, management of financial issues) or employment. Patients were designated as symptomatic or asymptomatic depending on the self-reported presence or absence, respectively, of at least two of the above neurological symptomatologies. Patients were excluded from the analysis if they exhibited CNS opportunistic infections, depression confirmed by the clinic psychiatrists (DSM-IV definitions), debilitating neuropathy, or had a previous diagnosis of cognitive impairment, including previously diagnosed HIV-associated dementia (HAD). After questioning about neurocognitive symptoms, patients underwent routine NP testing including Grooved Pegboard (dominant and non-dominant hands), Trail Making Test: Parts A and B, and Symbol Digit Modalities Test, administered in a standardized manner. These tests were selected because of their proven utility in previous studies of HIV-related NP performance.

Results of these NP tests were assessed in relation to previously reported normative data according to age and education. The mean deficit score (MDS) was calculated, as previously reported, using the Symbol-Digit Modalities, Trail Making: Part B and Grooved Pegboard (non-dominant hand) Tests. To ensure reliability of the categorization of NP impairment, two definitions were used including (1) a MDS value of greater than 0.50 or (2) a single test score two standard deviations or any two scores one standard deviation below the demographically corrected normative mean for those tests. Relevant demographic and clinical data from the medical records were recorded. The diagnosis of HAD was predicated on testing with the HIV Dementia Scale and established criteria, following administration of the NP test battery. Univariate comparisons were made using the Fisher exact test for categorical variables, the Mann-Whitney or Welch-corrected unpaired t tests for continuous variables, and derivation of correlation coefficients by multiple and single regression analyses (Instat2, Graphpad).

RESULTS

Ninety-five patients were screened regarding the presence of neurocognitive signs and symptoms, of which 83 were included in the present analysis, while the remaining met the predefined exclusion criteria. Fifty-five patients (66%) were classified as asymptomatic and 28 (34%) as symptomatic, based on the presence of at least two or more self-reported symptoms. Comparison of demographic and clinical characteristics (Table) revealed that the symptomatic group had a shorter median duration of antiretroviral drug treatment (p<0.005) with higher viral loads (p<0.05) and a greater number of individuals diagnosed with HAD (p<0.0001). The prevalence of HAD was 12% (10/83) with a median HIV Dementia Scale score of 8 (range: 4-12) based on the criteria outlined in the Methods section. The asymptomatic and neurocognitively symptomatic groups did not differ significantly in the frequencies of head injury, presence of cytomegalovirus, hepatitis C or B viral infections, antidepressant use, median time since AIDS diagnosis, median nadir CD4 counts and the median number of antiretroviral drugs taken at the time of testing.

Analysis of NP findings revealed that symptomatic patients performed significantly worse on all tests although these differences were least apparent for the Grooved Pegboard tests.

Table: Demographic and clinical features of patients who were neurocognitively asymptomatic and symptomatic

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Asymptomatic (N=55)</th>
<th>Symptomatic (N=28)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Age (yr) (Range)</td>
<td>42 (27-66)</td>
<td>45.5 (24-55)</td>
<td>NS</td>
</tr>
<tr>
<td>Gender, No. (%) Male</td>
<td>51 (92.7)</td>
<td>26 (92.8)</td>
<td>NS</td>
</tr>
<tr>
<td>No. (%) Homo/Bisexual</td>
<td>38 (69.1)</td>
<td>17 (60.7)</td>
<td>NS</td>
</tr>
<tr>
<td>No. (%) IVDrug Users</td>
<td>4 (7.3)</td>
<td>5 (17.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Median (Range) Education (yr)</td>
<td>16 (8-21)</td>
<td>13 (10-21)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Range) Time of HIVseropositivity (mo)</td>
<td>89 (15-168)</td>
<td>71.5 (6-189)</td>
<td>NS</td>
</tr>
<tr>
<td>Median (Range) Log_{10} Viral Load (copies/ml)</td>
<td>1.59 (1.59-6.86)</td>
<td>3.24 (1.59-6.28)</td>
<td>0.0346*</td>
</tr>
<tr>
<td>Median (Range) Nadir CD4 (Count/µl)</td>
<td>76 (1-582)</td>
<td>81 (2-537)</td>
<td>NS</td>
</tr>
<tr>
<td>Median (Range) Present CD4 (Count/µl)</td>
<td>285 (1-1332)</td>
<td>244.5 (4-924)</td>
<td>NS</td>
</tr>
<tr>
<td>No. (%) on HAART*</td>
<td>49 (89)</td>
<td>20 (71)</td>
<td>NS</td>
</tr>
<tr>
<td>Median (Range) Time on HAART (mo)</td>
<td>20 (0-69)</td>
<td>3.5 (0-118)</td>
<td>0.0073*</td>
</tr>
<tr>
<td>No. (%) HIV Dementia</td>
<td>1 (1.8)</td>
<td>9 (32.1)</td>
<td>0.0002*</td>
</tr>
</tbody>
</table>

* highly active antiretroviral treatment (minimum of three antiretrovirals)
* statistically significant difference, NS-nonsignificant
More recent studies suggest that plasma viral loads may be higher in patients with NP impairment who receive HAART. Since the number of antiretrovirals taken was also inversely related to the severity of NP impairment, with a predominant effect on improved psychomotor efficiency, which is in agreement with earlier studies.6,12

Although median plasma viral loads did not differ significantly between the NP impaired and unimpaired groups, there was a trend towards an increased viral load among the NP impaired group. Moreover, the present findings indicate that viral load was correlated with MDS among all eighty-three patients. This latter observation is at odds with earlier studies, performed prior to the availability of HAART in which plasma viral load was not correlated with neurocognitive impairment.13,14 More recent studies suggest that plasma viral loads may be higher in patients with NP impairment who receive HAART.5,7 Since the number of antiretrovirals taken was also correlated with NP performance, the implication of these findings is that HAART-associated reductions in viral load might have a beneficial effect on NP performance. Indeed, this may reflect combined therapeutic effects on viral replication in the brain and plasma and perhaps, neurocognitive symptoms and impairment may be useful surrogate indicators of rising viral load and/or drug resistance. Within the Southern Alberta Clinic, there is preference towards using CNS penetrating drugs including stavudine, zidovudine, abacavir and lamivudine to minimize lipodystrophy occurrence. The effects of the predominant use of these drugs on CNS function remains uncertain.

Group ages differed between the NP impaired and unimpaired groups with the impaired patients tending to be older and similarly, MDS was also significantly correlated with age. Earlier studies show conflicting results on the effect of age on HIV-related NP impairment1,15,16 with one study showing no effect and the other showing a positive correlation. However, several concerns in the current study should be considered. The cross-sectional design and relatively small sample size may...
predispose to biased results. Although a limited, highly-selected NP battery is practical on day-to-day basis as shown in the present study, a small NP test battery (less than nine tests) has been shown to miss subtle deficits. Nonetheless, the present study battery was sufficient to identify patients that had previously unrecognized HAD. Finally, since this study was performed in a Canadian HIV community clinic, the impact of universal health care may result in findings that differ from those in the United States where optimized HAART regimens may not be as available to all patients.

We conclude that in the setting of an HIV community clinic, it is useful to assess HIV/AIDS patients who report neurocognitive symptoms because these symptoms are frequently associated with impaired NP performance, which may respond to an increased number of antiretroviral drugs. Future prospective studies examining the relationship between HAART use and the development of neurocognitive symptoms and NP impairment may identify optimal HAART regimens that are neuroprotective and elucidate some of the neuropathogenic mechanisms underlying HIV-induced NP impairment.

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REFERENCES