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Neurological evaluation of untreated human immunodeficiency virus infected adults in Ethiopia

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Human immunodeficiency virus (HIV) has been implicated in neurological complications in developed countries. Developing countries have different viral clades and potentially different genetic and social risks for these complications. Baseline neurological performance measures associated with HIV infection have rarely been available from developing countries. The authors carried our a cross-sectional neurological evaluation of a cohort of community-dwelling treatment-naïve HIV-infected patients and similar control subjects from the same communities in Ethiopia. Blinded evaluation using standardized structured questionnaires and a neurological examination was performed by neurologists and treating physicians trained by an HIV neurology specialist. Quantitative performance measures for cognitive and motor function were employed. Data were analyzed with descriptive statistical methods, standard contingency table methods, and nonparametric methods. HIV-positive and control groups were similar by age, gender, and job site. Participants included 73 HIV-positive and 87 HIV-negative controls. Fingertapping speed in the dominant hand was more poorly performed in HIV positives than negatives ($P = .01$) and was significantly associated with HIV viral load levels ($P = .03$). Other quantitative neuropsychiatric tests including timed gait, grooved pegboard, task learning, and animal naming did not show significant differences between the two groups. The overall prevalence of central nervous system (CNS) and/or peripheral nervous system (PNS) disease did not significantly differ in the two populations. HIV patients had slowed fingertapping speed correlating with viral load. Other measures of CNS and/or peripheral nervous performance did not differ from controls. The unanticipated minor evidence of HIV-associated neurocognitive and peripheral nerve deficits in this untreated HIV-positive population invite further investigation. *Journal of NeuroVirology* (2007) **13,** 67–72.

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Introduction

Ethiopia is a country severely affected by HIV. In 2005, Ethiopia had an estimated adult human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) prevalence rate of 4.7% nationwide; the epidemic is focused in urban areas, with estimated prevalence of 12.5%, but is projected to grow most rapidly in rural areas, with estimated prevalence of 3.0%. There are estimated to be 1.7 million people living with HIV/AIDS in Ethiopia,

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and the impact on this developing nation is extremely severe (CDC-Ethiopia, personal communication). The major root of HIV transmission (>85%) in Ethiopia is through heterosexual contact (Ministry of Health of the Federal Democratic Republic of Ethiopia, 2000). Studies showed that the prevalent viral type prevailing are HIV clades C and C' (Abebe *et al*, 2000). The advent of successful multidrug antiretroviral therapy (ART) has transformed the course of HIV/AIDS infection in developed nations, decreasing morbidity and mortality, improving quality of life, and restoring hope to persons living with HIV/AIDS. ART is just becoming available in Ethiopia, and evaluation of the consequences of therapy will need to be monitored in this new population. Institution of ART routinely has resulted in improved neurological performance and decreased neurological complications in other populations (Sacktor *et al*, 2003; Schmitt *et al*, 1988).

The Ethio-Netherland AIDS Research Project (ENARP) of the Ethiopian Health and Nutrition Research Institute (EHNRI) was established in 1994, and since then has been a major source for tracking the epidemiology and biology of HIV-related disease in Ethiopia. ENARP established a modern research laboratory facility, and a longitudinal cohort study that has contributed greatly to knowledge of HIV in Ethiopia. Since 1997, ENARP has studied the natural history of HIV infection in over 1400 factory workers in Akaki (a textile factory located 20 km outside of Addis Ababa) and Wonji (a sugarcane producing town located 100 km outside of Addis Ababa). The Akaki and Wonji cohorts consist of approximately 1460 factory workers who have been followed for over 7 years, and who have had, together with their families, access to free medical care through the project. At ENARP's cohort sites, health clinics are staffed by physicians supported by essential healthcare providers (councilors, technicians, and nurses).

HIV infection was found in 11% and 5% of subjects at the Akaki and Wonji sites, respectively, closely reflecting the urban and rural demographics in Ethiopia. The population has been an important resource for learning about the HIV clade C infection encountered in Ethiopia (Rinke de Wit *et al*, 2002). Deaths during the course of the study have reduced the total HIV positive subjects from 155 to ~100 total in the cohort.

No neurological evaluation had been performed with this population. Some hospital based studies focused on the prevailing secondary complications of HIV, including toxoplasmosis (Woldemichael *et al*, 1998) and syphilis (Tsegaye *et al*, 2002), but primary neurological involvement had not been evaluated. This study was performed as a baseline anticipating the introduction of ART to this cohort. The fact that all of the cohort subjects were untreated with antiviral drugs gave opportunity to learn more about the natural course and degree of neurological impairment found in a clade C virus–affected population.

Results

There were a total of 160 cohort subjects evaluated with a median participation in the ENARP cohort of 5 years. We report the results of cross-sectional neurological testing performed for the first time on this group of the ENARP cohort participants. Seventy-three (45.6%) of them were HIV positive. Table 1 shows the demographic characteristics of the participants. Demographic parameters including age, marital status, educational level, income, and other comorbid diseases were very similar. The potential to work full time showed a slight trend favoring the HIV-negative group but did not reach clinical significance. A history of syphilis of 10% in the HIV-positive group and 8% in the HIV-negative group was noted.

The clinical status had been followed through the past 5 years as a part of the ENARP study. The most recent viral load and CD4 count, within 6 months of this evaluation, were known. Table 2 shows viral load, CD4 count, and the Karnofsky score. The median CD4 count was 260 and 737 cells/dl in HIV-positive and -negative subjects, respectively. CD4 counts correlated

Table 1 Baseline characteristics by HIV status

		HIV status		
	Total $N = 160$	HIV negative $N = 87$	HIV positive $N = 73$	P value[a]
Age at baseline				NS
Median	38	38	39	
Sex				NS
Male	104 (65%)	55 (63%)	49 (67%)	
Female	56 (35%)	32 (37%)	24 (33%)	
Marital status				NS
Single	13 (8%)	5 (6%)	8 (11%)	
Married ever	147 (92%)	82 (94%)	65 (89%)	
Read or write				NS
Yes	126 (80%)	69 (80%)	56 (79%)	
No	32 (20%)	17 (20%)	15 (21%)	
Educational level	$N = 142$	$N = 69$	$N = 73$	NS
Median years	8	8	7	
Income				
Mean birr/month		642	552	NS
Potential working status				NS
Full time	144 (91%)	83 (95%)	61 (86%)	
Less than full time	14 (9%)	4 (5%)	10 (14%)	
Diabetes				NS
No	156 (98%)	84 (97%)	72 (99%)	
Yes	4 (3%)	3 (3%)	1 (1%)	
Hypertension				NS
No	136 (95%)	73 (94%)	62 (97%)	
Yes	7 (5%)	5 (6%)	2 (3%)	
Syphilis				NS
No	127 (91%)	72 (92%)	57 (90%)	
Yes	12 (9%)	6 (8%)	6 (10%)	

[a]Unknowns excluded. Exact test or Kruskal-Wallis test as appropriate.

Table 2 Base line CD4 count, viral load, and Karnofsky score by HIV status

	Total $N = 142$	HIV status: HIV negative $N = 69$	HIV status: HIV positive N = 73	P value[a]
CD4 count (cells/mm^3)				<.01
Median	494	737	260	
Q1, Q3	262, 744	556, 824	168, 451	
HIV RNA viral load				NA
Mean log 10 copies/ml		—	4.3	
Karnofsky score				NS
Mean	95.9	97.2	95.7	
Median	100	100	100	

[a]Kruskal-Wallis test.

with logRNA as anticipated ($P < .01$). The mean HIV RNA viral load was 4.3 log copies/ml in the HIV-positive population studied. There was a comparable Karnofsky score distribution in both groups.

Neuropsychiatric and psychomotor exam results by HIV status are found in Table 3. Finger-tapping performance with the dominant hand index finger (FTD) was significantly slower in HIV-positive than -negative subjects ($P < .01$) and did not correlate with CD4 counts ($P = .13$). Other measures, including timed gait, grooved pegboard, and verbal fluency performance, did not show significant difference between the two groups. There was a positive correlation between higher viral load and worsening mean FTD performance ($P = .03$).

The International HIV Dementia Scale results are found in Table 4. We failed to find evidence to suggest between group differences in performance using this measure.

Table 3 Neuropsychiatric and psychomotor examination by HIV status

	Total	HIV status: HIV negative	HIV status: HIV e positive	P value[a] P value[a]
Finger tapping (average)				.01
N	160	87	73	
Mean (SD)	42.1 (8.4)	43.6 (8.2)	40.3 (8.3)	
Min, max	21.4, 68.4	21.4, 68.4	24.4, 64.4	
Median	42.3	44.0	39.8	
Timed gait (average) (s)				.70
N	155	85	70	
Mean (SD)	12.2 (3.9)	12.5 (4.6)	11.9 (2.9)	
Min, max	7.7, 45.0	8.6, 45.0	7.7, 28.1	
Median	11.5	11.5	11.3	
Grooved pegboard (s)				.85
N	152	81	71	
Mean (SD)	124.6 (48.3)	123.2 (46.7)	126.1 (50.3)	
Min, max	14.0, 240.0	14.0, 240.0	71.0, 240.0	
Median	111.0	111.5	108.0	
Verbal fluency (total average)				.44
N	159	87	72	
Mean (SD)	15.0 (5.5)	15.3 (4.8)	14.7 (6.4)	
Min, max	0, 29	0, 22	0, 29	
Median	16	16	15	

[a]Kruskal-Wallis test.

Table 4 International HIV Dementia Scale by HIV status

	Total	HIV status: HIV negative	HIV status: HIV positive	P value[a]
Motor speed				
N	160	87	73	.48
Mean (SD)	3.6 (0.6)	3.7 (0.6)	3.6 (0.7)	
Min, max	1, 4	1, 4	2, 4	
Median	4	4	4	
Timed Alternating Hand Sequence				
N	159	87	72	.86
Mean (SD)	3.3 (1.1)	3.3 (1.1)	3.3 (1.1)	
Min, max	0, 4	0, 4	0, 4	
Median	4	4	4	
IHDS score				
N	158	87	71	.28
Mean (SD)	10.6 (1.8)	10.7 (1.8)	10.4 (1.8)	
Min, max	2, 12	2, 12	6, 12	
Median	11	11	11	

[a]Kruskal-Wallis test.

Neuropathy was evaluated by the investigators including targeted history seeking distal sensory loss or pain, ankle jerk evaluation and evaluation of vibratory sense in the great toe both with a 128-Hz tuning fork, and with a Rydel Seiffer quantitative tuning fork. Table 5 summarizes the neuropathy evaluation using the tuning fork in both toes of lower extremities. There was no statistical difference between the groups.

After completing the neurological history and exam, physicians evaluated the overall neurological status for abnormalities in the central nervous system (CNS) and/or peripheral nervous system (PNS). There was no significant HIV+ versus HIV− between-group difference in the proportions of subjects with

Table 5 Vibration sensation and overall neurological impairment by HIV status

	Total	HIV status: HIV negative	HIV status: HIV positive	P value
Tuning Fork (right toe ave.)				.51[a]
N	147	84	63	
Mean (SD)	6.2 (1.0)	6.3 (0.9)	6.1 (1.1)	
Min, Max	2.5, 8.0	4.3, 8.0	2.5, 7.8	
Median	6.5	6.3	6.5	
Tuning Fork (left toe ave.)				.25[a]
N	149	84	65	
Mean (SD)	6.2 (1.0)	6.2 (0.9)	6.0 (1.1)	
Min, Max	2.5, 8.0	4.3, 8.0	2.5, 7.8	
Median	6.3	6.4	6.3	
Any CNS or PNS abnormalilty				.16[b]
No	113 (71%)	66 (77%)	47 (66%)	
Yes	44 (28%)	20 (23%)	24 (34%)	

[a]Kruskal-wallis test.
[b]Fisher's Exact Test.

any CNS or PNS abnormality ($P = .16$, Fisher's Exact Test).

Discussion

In many studies of untreated HIV subjects, neuropsychological performance measures demonstrate a negative impact of infection on performance, particularly in more advanced patients (Grant *et al*, 1987). We anticipated that this would be the case in the untreated Ethiopian cohort with a median CD4 <300 cells/dl, but our data suggested only a very modest impact of the infection on performance in this population. We believe our study has some features that may make its results more reliable than other studies reported from developing countries. Few reports are available of quantitative evaluation of performance in well-matched HIV-positive and control groups. An intrinsic problem with neuropsychometric testing is that norms are generally unavailable for application in developing countries. It can be anticipated that cultural and educational differences would impact performance on these measures. The differences of genetics, diet, schooling, language, and other factors make performance norms from developed nations inappropriate to this setting. Thus, a well-selected control group appears the safest way in which to evaluate the impact of HIV on performance. This study had a remarkably similar control group that had been followed for the same period of time, with the HIV-positive group as part of a cohort study in Ethiopia. The control group was working at the same jobs, in the same communities, and distribution of gender, age, and community were similar with the HIV-infected population. We believe this is superior in design to control and HIV groups drawn from separate pools (e.g., testing center versus treatment clinic). Because subjects were scheduled for investigators randomly, the evaluations were performed without knowledge of HIV status, further making the control group informative. Finally, the same group of physicians, trained at the same sessions, performed all of the examinations in random order on the control and infected populations. It is notable that relative to Western norms performance in this cohort differs substantially both in the control and the HIV-affected group, affirming the necessity of local controls for such testing.

Of all the parameters used to detect early nervous system impairment, only the mean and median score of finger-tapping speed demonstrated statistically poorer performance by HIV-positive subjects, and this result correlated with viral load. We suspect that this measure may have been more sensitive than others we used, but consider this finding preliminary because we have only one measure that showed significant performance decrement associated with viral disease status. The lack of performance decrements in many motor speeded tasks that have proved informative in studies performed in the developed world was unanticipated and could be explained in several ways (Tross *et al*, 1988). Not all studies of asymptomatic HIV-infected subjects support the idea that performance decrements are common, which likely is due to either selection of controls, or of subjects (Clifford *et al*, 1990). Patient selection could be an explanation. Sicker HIV-positive subjects may not have reported for examination. Although a similar bias for less healthy controls to report for testing also exists, if the HIV-positive subjects are sicker overall, this could result in differences in the population reporting for examination. We have no evidence that this occurred, and indeed employment status and income were quite closely matched, suggesting similar health in the populations even in the face of significant untreated HIV disease in the HIV population. Approximately 75% of the available HIV positives subjects in the cohort were examined. Given the negative impact of HIV in other studies, even in relatively healthy populations, this explanation is unlikely to completely justify absence of a deficit in a HIV population with substantial immunodeficiency. It is possible that controls were more comparable to HIV-positive subjects in our cohort than in most clinical-based cohort studies where selection of interested, mobile, altruistic people may make the controls "above average" in performance. Similarly, the impact of prescription drugs and drugs of abuse was virtually absent from this population, whereas these drugs negatively impact neurocognitive studies in other countries and might augment differences between the populations based on factors other than HIV. It is possible that the relative lack of healthcare in Ethiopia also contributes to early death of impaired subjects, removing them from the sample studied. However, the ENARP cohort specifically was performed at centers where general medical care was provided for subjects and their families. Finally it is possible that clade C virus found in Ethiopia is less neurotropic than the viral strains in the West, or those in the nearby Uganda where recent studies suggested impairment comparable to historical standards in the developing world in subjects likely harboring clades A and D. The ENARP cohort has been carefully studied and it is known that the virus present in these subjects is either clade C or the closely related C' (Abebe *et al*, 2000; Rinke de Wit *et al*, 2002).

There have been very few careful studies of the neurocognitive status of HIV-infected subjects in the developing world. One of the most careful efforts in this regard has been the recently reported work in Kampala,Uganda (Sacktor *et al*, 2005). In Uganda, the International HIV Dementia Score (IHDS) appeared to be sensitive to neurological deficits in an HIV-infected populations, in contrast to a control group. The HIV-affected group in the Uganda study had more advanced disease according to the Karnofsky score, suggesting that the HIV-affected group was more disabled. The Ugandan study also was not age matched, having controls significantly younger than

the HIV+ subjects. Although the difference between HIV-affected and controls in the Uganda population likely represents the more advanced disease status, the quantitative motor testings such as timed gait and grooved pegboard also showed no difference in this cohort, which is somewhat puzzling for tests that had previously reflected HIV-associated performance deficits.

Development of the IHDS is an important effort that requires close examination and validation. We anticipated that it should reflect the impact of HIV on patients with untreated and moderately advanced disease such as was seen in our population, but found that it was insensitive to differences even at this moderate stage of HIV disease. The statistical difference reported with this measure in the Ugandan population could be interpreted as resulting from a poorly matched (superior performing) control population that was healthier, younger, and better educated than the test population, in association with a somewhat more advanced HIV-positive group. Our results with a better matched control population bring into question whether HIV-specific performance changes will be reliably detected with this appealing instrument.

In comparing the Ugandan report with our own, tests probing the cognitive domain were more sensitive to dysfunction. We had not included these tasks in our testing because we were concerned about the social, educational, and language differences that would more severely impact these measures than motor tasks. Future evaluations will need to include verbal learning, digit span testing, and symbol digit tasks as was done in the Uganda trial to augment our information about potential early cognitive changes not reflected in motor performance tasks.

The possibility of a difference in neurotropism between different clades of HIV is a very important finding that could provide the opportunity to understand the mechanism and impact of neurotropism in great molecular detail (Power, 2001; Power *et al*, 1994). To date, efforts to understand genetic predilection of the virus or of affected patients has not been conclusive but this is a key property of HIV infection with tremendous impact that requires further detailed study.

The results of our study also have implications in the discussion on when it is important to start HIV therapy. In the developing world, the limitation of resources has conspired to dictate starting therapy only when the risk of complications from immunodeficiency become great (e.g., when the CD4 lymphocyte count falls below 200 cells/mm^3). However, there is concern that delay of antiretroviral therapy may expose patients to hidden injury, such as brain damage, that could be ongoing from an earlier stage of infection, as well as to greater risks of transmission of the virus and opportunistic complications. If the brain performance is relatively preserved even to more advanced disease, as seems to be the case in the Ethiopian population, one of the theoretical concepts suggesting early therapy should not be valid. Clearly this work deserves careful follow-up, with more extensive measures before it is used to drive health policy.

Methods

The study was approved by the national ethics board of Ethiopia and the Institutional Review Board (IRB) of Washington University School of Medicine as an addition to ongoing consent of the cohort population followed by ENARP. HIV status was determined in all subjects at enrollment, and retesting of seronegative subjects occurred annually, resulting in detection of 21 seroconverters, yielding a total of 155 HIV+ subjects over the history of the cohort. All available HIV+ subjects were scheduled for history and examination by the coordinating center of ENARP. For each known HIV+ subject, controls from the same study site, gender, and age were identified from the known seronegative population by the coordinating center and scheduled for examination. Examiners were not told the HIV+ status of subjects, thus obviating bias on the part of examiners as to the possible impact of HIV status on performance. In some cases, by provision of the ENARP study, subjects had requested not to be informed regarding their own sero-status, so in some cases the evaluation was actually double blinded. A routine remuneration was provided to each subject for study visits by ENARP, and this was provided for the neurological visit.

Subjects were all antiretroviral therapy naïve because drugs were not yet available in their clinics at the time the study was performed. However, the subjects had all been under medical care as a part of the ENARP study for a similar period of time, and both they and their families had access to all routine health care. Both HIV subjects and controls were working in the community at similar tasks, with known and similar income status.

The evaluation was based on instruments from the International NeuroAIDS protocol (A5199 of the AIDS Clinical Trials Group; personal communication by Dr. Kevin Robertson) and by the International HIV Dementia Scale (Sacktor *et al*, 2005). The instrument was modified by the authors for use in Ethiopia, substituting words for recall that were not offensive to Ethiopians. The study physicians standardized the testing procedures, and practiced them together prior to administration to subjects under the direction of an HIV neurology expert.

The examiners included four physicians specializing in neurology in Ethiopia and two internists trained and supervised by the neurologists who had primary care responsibility for the cohort subjects. All examiners were observed in training performing each part of the examination. Examinations were

performed over an approximate 2-month period in the spring of 2004.

The study included:

- Description of the overall functional status related to working status, fatigability, and ambulation;
- Neurological cognitive/sensory examinations related to response slowing, concentration/speed of thought, memory and language, bladder control;
- Behavior/mood evaluation including history of mood, headache, and seizure;
- A 10-question neurological symptom screen and the Karnofsky Performance Scale (Karnofsky *et al*, 1948);
- International HIV Dementia Scale including memory registration for four common objects, motor speed on nondominant hand (NDH) documenting rapid tapping speed of the thumb and first digit, psychomotor speed measured by repetition of a three-position alternating hand sequence, and memory recall of the four objects (Sacktor *et al*, 2005);
- Neuropsychiatric and psychomotor examination including time gait (10 yard), finger tapping speed of the dominant hand (FTD), grooved pegboard (NDH), verbal fluency (animal naming);
- ENARC neurological screening examination including evaluation of neck stiffness, eye movement, facial strength and sensation, gait, tendon reflexes, plantar response, primitive reflexes, quantitative (using Rydel-Seiffer tuning fork) and qualitative vibration perception, limb coordination, motor tone and sensory examinations, tandem gait, and Romberg test;
- Over all clinical neurological assessment and abnormality pattern.

Data were compiled from score sheets to a computerized database containing the CD4 count and viral load of subjects involved in the project.

Descriptive statistics were used to describe the study sample. Exact tests were used to assess association with respect to categorical variables and the Kruskal-Wallis test was used to assess between arm differences with respect to continuous variables. All reported P values are two-sided without adjustment for multiple testing. Statistical significance was assessed using significance level of .05.

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