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Neuropsychiatric HIV-1 infection study: in Kenya and Zaire cross-sectional phase I and II

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SUMMARY

The objective of the study was to determine the prevalence and natural history of human immunodeficiency virus type 1 (HIV-1) associated psychiatric, neuropsychological and neurological abnormalities. A total of 408 subjects were recruited in Nairobi and Kinshasa. The study consisted of a cross sectional phase and a longitudinal follow up.

Assessment was made by a data collection instrument including six modules. The intercentre and intracentre reliability in the use of the each module have been formally evaluated. The mean global score on the Montgomery-Asberg Depression Rating Scale was significantly higher in symptomatic seropositive individuals than in matched seronegative controls.

In conclusion, these data suggest that the risk of subtle cognitive deficits may be increased in asymptomatic stages of HIV-1 infection.

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INTRODUCTION

The presence of psychological problems in people with human immunodeficiency virus type one (HIV-1) infection has been the subject of considerable attention recently. According to world wide estimates by the World Health Organization (WHO),[1] 85 pc of adults infected with HIV-1 live outside Western industrialized countries. Over 75 pc of infections in adults are transmitted through heterosexual intercourse and more than 45 pc of infected subjects are women.

Most of the available evidence comes from surveys of well educated, mostly White homosexual men[2-4], or gays and drug users.[5] A series of studies has shown an increased vulnerability to psychological distress and a significant prevalence of psychiatric disorders associated with HIV-1 infection, ranging from 30 to 63 pc.[6,7] Furthermore, infection with HIV-1 may lead to a number of neurological complications, one of the most important of which is AIDS dementia complex.[8]

The incidence of HIV-1 dementia is approximately seven per 100 patients per year following development of AIDS, with up to 20 pc of HIV-1 infected individuals receiving a diagnosis of HIV-1 dementia before death.[9,10] However, a recent study has found no significant decline in cognitive functions before AIDS, unless overt dementia is present.[11]

Concerns about generalization of the currently available information on the psychiatric, as well as the neuropsychological and neurological complications of HIV-1 infection has prompted the World Health Organization to implement the cross-cultural venture called World Health Organization Neuropsychiatric AIDS Study. The project's objective was to assess the prevalence and the natural history of the above mentioned complications in these two geographic areas, with respect to sex ratio and distribution of HIV-1 in at-risk groups.

MATERIALS AND METHODS

Subjects: A total of 408 subjects (n = 203 in Nairobi, Kenya and n = 205 in Kinshasa, Zaire) was recruited between October 1990 and August 1991, to participate in a cross-section (phase I and II) study. The drop outs

were 12 (5,5 pc) in Kinshasa and 15 (6,9 pc) in Nairobi. The drop outs did not differ significantly from the other subjects with respect to sociodemographic variables.

The Centres for Disease Control (CDC)[12] classification of HIV progression was used to classify the staging of illness among HIV-1 seropositive subjects. Three groups were defined, in each centre, for analytic purposes:

1. One hundred and eighteen symptomatic HIV-1 seropositive persons either had no symptoms (CDC stage II) or had persistent generalised lymphadenopathy (CDC stage III). It was conventional to regard these groups as asymptomatic in the absence of constitutional neurological, or AIDS-defining diseases.
2. One hundred and forty symptomatic HIV-1 seropositive persons with more severe HIV-1 complications (CDC stage IV). This group included those individuals, who had other diseases, such as neurological disease, secondary infectious disease (e.g. tuberculosis), *Herpes zoster*, Kaposi's sarcoma or other conditions.
3. One hundred and fifty HIV-1 seronegative controls, matched to seropositive persons by sex, age (± 5 years), education (± 3 years), and HIV-1 at risk group (homosexuals, intravenous drug users and blood recipients).

Assessments: The study was approved by the appropriate Ethics Committee, and all subjects gave informed consent. Every third subject who was attending the outpatient medical unit(s) of Kenyatta National Hospital in Nairobi and Mama Yomo Hospital in Kinshasa, aged older than 18 years, able to count from one to 25 in his or her native language, and able to read a series of 10 numbers were enrolled for the study. They received pre-test counselling, and had blood drawn for HIV-1 serological tests (enzyme-linked immunosorbant assay [ELISA], and confirmed with the Western blot test).

Two weeks later, at a return visit, test results and post test counselling were provided. The HIV-1 seropositive persons and the HIV-1 seronegative individuals, who were suitable for matching were definitively enrolled. In all these subjects a second blood sample was drawn (for CD_4 and CD_8 counts and for the VDRL test) and the sociodemographic survey module collected information on sex, age, education level, present work status, language, and HIV-1 at risk group (if any). Medical modules of the Comprehensive Instrument for the Collection of Neuropsychiatric Data were administered. The remaining modules of the instrument were applied one month later (based on the design of the study).[13]

The HIV-1 serostatus of recruited subjects was unknown to the examiners who performed cognitive/neuropsychological, psychiatric, and neurological assessments except the principal investigator. The design and rationale of the WHO neuropsychiatric AIDS study and its neuropsychological components have been described in detail elsewhere.[13,14] Relevant assessments are briefly summarised below.

Medical assessment: Physicians performed physical examinations targeted at HIV-related symptoms and signs. Subjects who met 1987 CDC criteria for AIDS at baseline were included in the study.

Neurological assessment: All neurological examinations were done by neurologists. Each neurological sign was coded separately so that individual signs could be examined and factor score could be created based on individual items. Finally, the neurological diagnoses were made according to the WHO[15] and the American Academy of Neurology (AAN) criteria, Minnespolis, Minn.[16]

Neuropsychological assessment:

1. The neuropsychological battery was administered to the subjects. The functional domains assessed by this battery are:

(a) motor speed/fine motor control (Time Gait, Colour Trials 1 & 2, the Wechsler Adult Intelligence Scale [WAIS][17] Block Design and Digit Symbol, Grooved Pegboard,[18] and Trail Making A[19]);
(b) sustained attention (Colour Trails 1 and 2 and Trail Making A;
(c) selective attention (Colour Trails 2 and WAIS Digit Symbol);
(d) cognitive flexibility (Colour Trails 2 and WAIS Digit symbol);
(e) perceptual-motor analysis (WAIS Block Design);
(f) verbal memory (WHO/UCLA[20] Auditory Verbal Learning Test);
(g) visual memory (WHO/UCLA Picture Memory and Interference Test;
(h) verbal fluency (Verbal Fluency Test, animals and first names[21]).

2. An adapted structured interview for the objective evaluation of cognitive performance (SIDAM)[22],

which incorporates algorithms for the diagnosis of dementia according to the ICD-10[23] and DSM-III-R[24];

3. A rating scale of performance in activities of daily living (ADL).[25]

Psychiatric assessment: All psychiatric assessments were performed by psychiatrists, using the Composite International Diagnostic Interview [CIDI],[26] which consists of the sections for psychotic, affective and anxiety disorders. It was a structured interview that incorporated algorithms for psychiatric diagnosis according to the :

(a) International Classification of Diseases, 10th Revision (ICD-10)[23], and DSM-III-R[24];
(b) the 18 item version[27] of the Brief Psychiatric Rating Scale (BPRS)[28];
(c) the Montgometery-Asberg Depression Rating Scale (MADRS),[29] which was administered to the subjects.

The laboratory test module collected the results of HIV-1 serological tests, CD_4 and CD_8 counts, VDRL, and specific diagnostic tests, as appropriate.

Analysis of the data.

The asymptomatic and symptomatic HIV-1 seropositive subjects assessed in each centre were compared separately with the HIV-1 seronegative controls with respect to the prevalence of psychiatric diagnoses according to ICD-10 and DSM-III-R, with the mean scores on the individual items of the BPRS and the MADRS, and with the mean global scores on the same scales. Also, the asymptomatic and symptomatic HIV-1 seropositive subjects with HIV-1 seronegative controls with respect to the prevalence of impairment on individual sections of neurological examination and the prevalence of current neurological diagnoses according to WHO and AAN criteria.

Furthermore, the asymptomatic and symptomatic HIV-1 seropositive subjects evaluated in each centre were compared separately with HIV-1 seronegative controls with respect to the prevalence of impairment on individual neuropsychological tests and global neuropsychological impairment. Impairment on each test was defined as a performance of two or more standard deviations worse than the mean of the seronegative group. Global impairment was defined as an impaired performance on at least three of 10 tests (impairment on one or both Grooved Pegboard tests or on one or both Verbal Fluency tests was counted as one impaired test).

Comparisons were made using the Scheffe test for continuous measures and the Chi-Squared (X^2) test (with a Bonferroni correction for multiple testing) for categorical measures. Within each centre and each serogroup, correlations between global scores on rating scales and the CD_4 count were explored by the Pearson Coefficient.

Table I: Sociodemographic characteristics of subjects.

	Kinshasa	Nairobi
HIV-1-	n = 85	n = 65
A/HIV-1+	n = 52	n = 66
S/HIV-1+	n = 68	n = 72
Sex Male pc		
HIV-1-	56,5 pc	75,4 pc
A/HIV-1+	63,5 pc	63,6 pc
S/HIV-1+	51,5 pc	66,7 pc
Age (mean ± SD)		
HIV-1-	33,9 ± 7,8	30,0 ± 8,6
A/HIV-1+	32,3 ± 7,6	30,7 ± 8,6
S/HIV-1+	33,8 ± 7,6	33,2 ± 9,6
Education (mean ± SD)		
HIV-1-	10,8 ± 2,4	8,2 ± 2,6
A/HIV-1+	9,6 ± 2,4	7,1 ± 3,9
S/HIV-1+	9,9 ± 2,7	7,1 ± 3,6
HIV-1 at-risk group pc [f]		
I.V. drugs users		
HIV-1-	0	1,5 pc
A/HIV-1+	0	0
S/HIV-1+	0	1,4 pc
Homosexuals/Bisexuals		
HIV-1-	1,2 pc	3,0 pc
A/HIV-1+	3,8 pc	0
S/HIV-1+	0	4,2 pc
Blood recepients		
HIV-1-	4,7 pc	1,5 pc
A/HIV-1+	1,9 pc	6,1 pc
S/HIV-1+	5,9 pc	6,9 pc

HIV-1 = human immunodeficiency virus type 1.
A/HIV-1+ = asymptomatic HIV type 1 seropositive subjects.
S/HIV-1+ = symptomatic HIV type 1 seropositive subjects.
HIV-1- = HIV type 1 seronegative subjects.
[f] = some subjects belonging to two at-risk groups counted twice.

RESULTS

Table I summarises the sociodemographic characteristics of the subjects in the two centres. The samples collected in the centres were obviously different as to males to females ratio and mean education level, whereas, they were very similar with respect to mean age. Homosexuals/bisexuals, intravenous (IV) drug users, and blood recipients were almost absent in both centres.

There were two cases of central nervous system opportunistic infections in Kinshasa (both of Cryptococcal meningitis), and none in Nairobi.

Prescribed psychotropic medications were taken by very few subjects, with the only exception being benzodiazepines used by a substantial proportion of individuals in Kinshasa, mainly at low doses, for the management of sleep disturbances. A previous diagnosis of malaria was very frequent in Kinshasa. The percentage of patients fulfilling CDC criteria for AIDS, within the group of symptomatic HIV-1 seropositive subjects, was 41,7 pc in Nairobi and 36,8 pc in Kinshasa (Table II).

The overall prevalence of lifetime mental disorders was not significantly increased in either symptomatic or asymptomatic HIV-1 seropositive subjects, compared with controls, in any centre.

Table III shows the mean MADRS global score was significantly higher in women than in men among symptomatic HIV-1 seropositive subjects who were assessed in Kinshasa ($p < 0,05$). The mean BPRS global score and the mean scores on the BPRS items "somatic concern", "anxiety", and "depressed mood" were significantly increased in symptomatic but not in

Table II: Background medical and immunological information on subjects.

	Kinshasa	Nairobi
HIV-1-	n = 85	n = 65
A/HIV-1+	n = 52	n = 66
S/HIV-1+	n = 68	n = 72
Malaria pc		
HIV-1-	97,6 pc	72,3 pc
A/HIV-1+	96,2 pc	84,8 pc
S/HIV-1+	98,5 pc	91,5 pc
Benzodiazepine pc		
HIV-1-	16,7 pc	0
A/HIV-1+	17,3 pc	1,5 pc
S/HIV-1+	33,8 pc	2,9 pc
CD_4 count X10⁹/4		
(mean ± S.D.)		
HIV-1-	1,15 ± 0,37	0,86 ± 0,43
A/HIV-1+	0,55 ± 0,27	0,58 ± 0,34
S/HIV-1+	0,28 ± 0,27*	0,38± 0,71*
CD_4 /CD_8 ratio		
(mean ± S.D.)		
HIV-1-	1,2 ± 0,6	1,1 ± 0,4
A/HIV-1+	0,3 ± 0,2	0,5 ± 0,4
S/HIV-1+	0,2 ± 0,2*	0,4 ± 1,0*

*Significant overall differences among serogroups. $p < 0,0001$ (by analysis of variances).
* Significant overall differences among serogroups. $p < 0,001$ (by analysis of variance).*

Table III: Mean scores on the MADRS and prevalence of current mental disorders in subjects.

	Kinshasa	Nairobi
HIV-1-	n = 85	n = 65
A/HIV-1+	n = 52	n = 66
S/HIV-1+	n = 68	n = 72
The mean global scores on MADRS		
F/M socres		
HIV-1-	2,4 ± 4,9	3,3 ± 7,9
A/HIV-1+	4,3 ± 7,7	5,5 ± 9,0
S/HIV-1+	11,5 ± 10,7*	10,1 ± 13,4*
ICD-10 Diagnosis pc		
Any mental disorders		
HIV-1-	1,2 pc	0
A/HIV-1+	1,9 pc	4,5 pc
S/HIV-1+	5,9 pc	7,1 pc
DSM-III-R Diagnosis pc		
Any mental disorders		
HIV-1-	1,2 pc	0
A/HIV-1+	1,9 pc	4,5 pc
S/HIV-1+	5,9 pc	6,9 pc

Significant differences (symptomatic seropositive VS seronegative subjects): $p < 0,01$.
MADRS = Montgomery-Asberg Depression Scale; F = Females; M = Males.

asymptomatic HIV-1 seropositive subjects, compared with those in seronegative controls, in both centres.

Symptomatic HIV-1 seropositive individuals differed significantly from controls on numerous neuropsychological measures (their performance was significantly worse on Time Gait, Colour Trails 2, WAIS Digit Symbol, Trail Making A, and Verbal Fluency, and animals). In Kinshasa and Nairobi the prevalence of global neuropsychological impairment was significantly higher in low, but not in high education, asymptomatic HIV-1 seropositive subjects compared with the corresponding subgroups of HIV-1 seronegative individuals. The most frequently involved tests were Colour Trails 1 ($p < 0,05$ among symptomatic subjects in Nairobi), and Grooved Peg Board, dominant ($p < 0,01$ among symptomatic individuals in Kinshasa; and $p < 0,05$ among asymptomatic subjects in Nairobi).

The proportion of symptomatic seropositive subjects presenting at least one subjective cognitive complaint was significantly higher than that of seronegative persons in both centres (1,2 pc, $p < 0,01$ in Kinshasa; 3,1 pc, $p < 0,05$ in Nairobi).

The association between the occurrence of at least one subjective cognitive complaint and the presence of prominent depressive symptoms was significant in asymptomatic seropositive subjects enrolled in Kinshasa ($p < 0,01$), and in Nairobi ($p < 0,05$), and in symptomatic seropositive individuals assessed in Kinshasa ($p < 0,01$) and in Nairobi ($p < 0,05$), Table IV. The mean total score on the ADL rating scale was significantly higher in symptomatic HIV-1 seropositive subjects than in controls in the two centres, and it was consistently not increased in asymptomatic HIV-1 seropositive subjects (Table IV). No case of dementia according to either ICD-10 or DSM-111-R was detected in HIV-1 seronegative and asymptomatic HIV-1 seropositive persons in any of the centres.

The prevalence of neurological impairment was significantly higher in symptomatic (but not in asymptomatic) HIV-1 seropositive individuals, compared with seronegative controls, in the two centres.

Table IV: Prevalence of impairment on individual NP tests in subjects.

	Kinshasa	Nairobi
HIV-1-	n = 85	n = 65
A/HIV-1+	n = 52	n = 66
S/HIV-1+	n = 68	n = 72
Impairment on NP Tests		
Time Gait		
HIV-1-	4,7	4,6
A/HIV-1+	5,8	6,0
S/HIV-1+	29,4*	22,2ǂ
Colour Trail-1		
HIV-1-	3,5	7,7
A/HIV-1+	7,7	9,0
S/HIV-1+	16,2ǂ	12.5
Performance in ADLs		
(mean ± S.D.)		
HIV-1-	34,2 ± 2,0	34,2 ± 4,2
A/HIV-1+	35,0 ± 4,1	34,6 ± 2,5
S/HIV-1+	40,2 ± 14,7**	39,2 ± 10,1**
Education		
Low education subjects, impairment pc		
HIV-1-	0	0
A/HIV-1+	25,0 pcǂǂ	22,7ǂǂ
S/HIV-1+	19,0	25,0ǂǂ
High education subjects, impairment pc		
HIV-1-	1,4 pc	5,1 pc
A/HIV-1+	2,8 pc	0
S/HIV-1+	19,1ǂ	10,4

**Significant differences (asymptomatic or symptomatic seropositive VS seronegative subjects) : p < 0,0001.*
ǂSignificant differences (asymptomatic or symptomatic seropositive VS seronegative subjects): p < 0,01.
ǂǂSignificant differences (symptomatic seropositive VS seronegative subjects): p < 0,05.

Table V: Findings on neurological examination in subjects.

	Kinshasa	Nairobi
HIV-1-	n = 85	n = 65
A/HIV-1+	n = 52	n = 66
S/HIV-1+	n = 68	n = 72
Antisaccadic eye movements		
HIV-1-	10,6	18,5
A/HIV-1+	17,3	22,4
S/HIV-1+	25,0*	30,6
Frontal lobe release sign		
HIV-1-	1,2	0
A/HIV-1+	7,7	0
S/HIV-1+	11,8*	9,7*

**Significant differences (symptomatic seropositive VS seronegative subjects): p < 0,05.*

Acute inflammatory demyelinating polyradiculoneuropathy was diagnosed according to AAN criteria (one case each in Kinshasa and Nairobi). No neurological diagnosis was made in HIV-1 seronegative subjects.

Comments: Several limitations of the current study should be considered. Some potential problems pertain to exclusion of the most severe cases of AIDS, which are unlikely to be seen in outpatient units.

Also, subjects, who were lacking in the minimum arithmetic skills necessary to perform neuropsychological tests, and those who were aged younger than 18 years (to simplify consent procedures) were excluded.

Contrary to many previous studies carried out in this research field, the WHO study did not rely on advertisements or contacts with specific communities for recruitment[2-3,5] (i.e. self-selected a sample of persons). Instead subjects were recruited from the respective outpatient clinic(s) where they had come for general medical assessment.

The main weakness of the existing studies is that they have almost exclusively involved cohorts or cross-sections of homosexual men.[2-5] Results in this population may not generalise to others, however, the WHO findings of the present study confirm and allow for generalization of results that neuropsychiatric HIV-1 infection and AIDS have similar complications worldwide.

In our symptomatic seropositive subjects the significant increase of the MADRS global score was a consistent finding across the centres, whereas, in the previous study,[3] the mean global score on the Hamilton Rating Scale for Depression,[30] was not significantly increased in seropositive subjects, compared with seronegative persons. The following explanations of this inconsistency can be proposed:

(a. The different structure of the adopted rating scales.
(b. The above mentioned differences in the recruitment procedures.

Subjective cognitive complaints of asymptomatic seropositive persons did not correlate significantly to the objective neuropsychological performance. This is in line with the finding from a previous report by Van Gorp *et al.*[31] The non-increased prevalence of dementia in the two centres is most likely due to the possible earlier onset of HIV-1 related cognitive impairment and the more rapid progression of the infection, in fact, may cause the death of several subjects before they are able to reach the most severe stages of cognitive deterioration, as reported elsewhere.[32]

In sub-Saharan African countries the prevalence of dementia among patients with AIDS in Northern Zone of Tanzania, figures as high as 54 pc,[33] and as low as 3,2 pc[34] in Central Africa can be found in the literature. These two African studies' findings hardly can be compared with each other or with those obtained in Western countries, owning to huge differences in population,sampling procedures and assessment.

Conclusion: On the whole, the results of the psychiatric evaluation performance within the cross sectional phase of the WHO Neuropsychiatric AIDS Study suggest that the significance of the psychological complications of symptomatic HIV-1 infection may have been under estimated by previous studies carried out on self-selected samples of well educated, middle class and mostly White homosexual men.

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