

# Determinants of Neurocognitive Impairment in HIV in a Cohort of Patients on Antiretroviral Therapy Followed in Bangui (Central African Republic)

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## Abstract

Infection with HIV is one of the deadliest epidemics of our time and its type is widespread in the Central African Republic. It is frequently accompanied by neurological complications. Objective: To contribute to a better understanding of neurocognitive disorders in patients living with HIV (PLHIV) in Bangui, and to identify associated factors using the International HIV Dementia Scale (IHDS) as a screening tool. We conducted a descriptive and analytical cross-sectional study from 1 December 2014 to 30 January 2015, in a cohort of patients seen on one of the supported sites in Bangui. A total of 400 patients were received in follow-up visit during the study period of which 244 met the inclusion criteria. The prevalence of neurocognitive disorders was 25%, 95% CI [19.70 - 30.92]. The mean age of subjects was  $42.77 \pm 9.58$  with extremes ranging from 24 - 64 years. The sex ratio (F/M) was 4.5 in. The average score for different tests was  $10.93 \pm 1.13$  with extremes of 7 and 12. The disorder was more about the gestural sequence. Determinants of neurocognitive disorders in the cohort were older age and lower educational level ( $p < 0.05$ ). It is useful to conduct further studies to confirm these results by combining a battery of neuropsychological tests to recommend this test for all the support sites of PLHIV in the country.

## Keywords

HIV, Neurocognitive Disorders, Determinants, Central African Republic

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## 1. Introduction

Infection with human immunodeficiency virus (HIV) is one of the deadliest epidemics of our time. According to the Antiretroviral treatment (ART) 2013 UNAIDS report, 35.5 million people were living with HIV worldwide in 2012 including 2.3 million new infections, a reduction of incidence of 33% over 2011. AIDS mortality records also down from 2.3 million in 2005 to 1,600,000 in 2012 [1]. It is a disease whose transmission is done either through sex, either through blood or from mother to child during pregnancy at the time of childbirth or during breastfeeding. High risk factors of its transmission are: sex homo/heterosexual unprotected, the use of contaminated equipment, blood exposure accidents. The diagnostic criteria in Central Africa based on two serological tests that are the Determine HIV 1 & 2 and HIV 1 & 2 Unigold. Both tests should be positive simultaneously to confirm the diagnosis of HIV/AIDS.

In Central African Republic, HIV is generalized type with a prevalence of 4.9% [2]. This has motivated the introduction of multi therapy 1996, causing the infection is better controlled but not always eliminated.

Having helped to restore a satisfactory immune function and control viral replication by ensuring that the viral load is undetectable. Thus the HIV infection has become a chronic disease. These treatments have also helped to reduce the opportunistic infections that can occur during infection.

HIV infection is frequently accompanied by neurologic complications [3]. It is shown from the beginning of the epidemic that HIV is present early in the central nervous system (CNS) [4]. Despite more effective ARV treatment, the virus can persist in the brain causing symptoms of neurological and psychological diseases. In addition, some ARV are toxic to the CNS. These neurological have neurocognitive disorders (NCD), which are highly prevalent among PLHIV. Before the era of highly active antiretroviral therapy (HAART), the incidence of HIV-associated dementia (DAV) is high. With the advent of ARTs, the prevalence of DAV dropped NCD phenotype has changed and is diagnosed more moderate neurocognitive disorders [5]-[7]. The first symptoms of dementia complex associated with HIV are mainly attention disorders and concentration associated with memory disorders in which patients are more or less aware. These symptoms are all the more precocious than the cultural level of patients which is very low, with reference to the hypothesis of brain reserve applied to Alzheimer's disease. Psychomotor retardation sets in parallel are often more obvious to the entourage for the patient himself. Sometimes, a manic state may inaugurate an HIV encephalopathy. At this early stage, the sensitivity, specificity and positive predictive value of a detailed neuropsychological evaluation proved to detect HIV encephalopathy are valued at respectively 67%, 92% and 95% [8]. After a few weeks or months, occur apathy, emotional indifference, loss of motivation with total disinterest and ambulatory difficulties characterize the status phase. At the advanced stage, the dementia is severe confining the patient in silence, with fecal and urinary incontinence and paraplegia related often associated myelopathy. There is no disturbance of consciousness until an advanced stage of dementia [9]. An international committee recently proposes a consensual revision of the diagnostic criteria for neurocognitive disorders associated with HIV [10]. The new classification of neurocognitive disorders has three levels of increasing severity: asymptomatic neuropsychological deficit, mild cognitive impairment and dementia associated with HIV [10].

These disorders have a negative impact not only on the achievements of the most demanding activities of daily living (housework, money calculation, driving etc.) in PLVIH associated with a loss of autonomy [11] but also adherence to treatment and social and professional integration of the latter [12]. Hence, the importance of their early detection to optimize their management and prevent progression to dementia as proven. That is why we invested in this work whose general objective was to contribute to a better understanding of neurocognitive disorders in people with HIV on one of the supported sites in Bangui, and to identify associated factors.

## 2. Methodology

We conducted a descriptive and analytical cross-sectional study from 1 December 2014 to 30 January 2015, in a cohort of patients seen on one of the supported sites in Bangui. The subjects were elderly PHIV 18+ included, treated with ARTs for at least one month with an updated medical record containing a CD4 count at initiation of ART and another in the last month study, the date of ART initiation. The study protocol was approved by the Scientific Committee responsible for the validation of study protocols and results which ethics committee office in Central Africa. All subjects gave informed consent and included signed an informed consent form.

Did not make the study, admitted PLHIV hospitalization, those with active disease of the CNS (meningitis, encephalopathy...) or intercurrent infection, or those whose health does not allow to undergo an interview. The

test used for screening NCD was that of the International HIV Dementia Scale (IHDS) which compute:

- The timed tapping finger which measures the driving speed (executive functions), during which the patient must type with the index and middle finger of non-dominant hand as quickly as possible on the table by five seconds;
- The sequence of Luria of repeating as many times as possible the next move: point/palm/slice by hand, with the non-dominant hand in 10 seconds and that tests programming ability and psychomotor speed;
- A repeat of four Dubois words given in the beginning of test, which tests the episodic memory.

Data collection was made during consultations followed with a single survey form, including socio-demographic, clinical (clinical stage of HIV infection (WHO), biological variables (rates current Nadir CD4 and CD4), antiretroviral regimens and duration, results IHDS test.

Data were analyzed using Epi data 7 software. Chi-square test and/or the Fischer were used to compare the proportions with a degree of significance set at 5%.

### 3. Results

A total of 400 patients were received in follow-up visit during the study period of which 244 met the inclusion criteria.

Of 224 patients enrolled, sixty had a disruption in neurocognitive tests matched hundred eighty three witnesses. The distribution by age and gender of the subjects included in the study is presented in **Table 1**. The prevalence of neurocognitive disorders was 25%, 95% CI [19.70 - 30.92]. The average age of the subjects was  $42.77 \pm \text{TNC } 9.58$  with extremes ranging from 24 - 64 years. The sex ratio (F/M) was 4.5 in NCD. The average score for different tests was  $10.93 \pm 1.13$  with extremes of 7 and 12. The disorder was more about the gestural sequence (psychomotor speed). Patients in couples accounted for 47.54%, while fourth was single; almost half of the patients had a secondary study (42.6%). The average duration of ART was  $29.06 \pm 21.02$  months. In 75% of cases, the patients had treatment duration of less than 39.70 months and the median duration was 28.76 months with extremes of 8 and 128.86 months; the average CD4 at initiation of treatment was  $175 \pm 126 \text{ CD4/mm}^3$  and was correlated with the non-performance of the subjects in IHDS. The Determinants of neurocognitive disorders in the cohort are shown in **Table 2**. The high age and low education were the factors associated with neurocognitive disorders ( $p < 0.05$ ).

### 4. Discussion

HIV infection in Central African Republic is generalized type with a national prevalence of 4.9% [13]. It mainly affects young individuals between 20 and 40 years, as evidenced by the very young age of the patients in our study whose median age was 38 years. This has been done in other African countries [14] [15] and Latin America [16]. This is explained partly by risky sexual behavior reported in the country [14]. Furthermore, the prevalence of HIV infection was twice as high among women (6.3%) than men (3%) in our [14], which we found in our cohort patients.

**Table 1.** Distribution by age and gender of the subjects included in the study.

Age (years)	Sex					
	Male		Female		Total	
	N	%	N	%	N	%
15 - 24	0	0	9	100	9	3.69
25 - 34	8	10.81	66	89.19	74	30.33
35 - 44	25	25.77	72	74.23	97	39.75
45 - 54	16	34.04	51	65.96	47	19.26
≥55	7	41.18	10	58.82	17	6.97
<b>Total</b>	56	22.95	188	77.05	244	100

**Table 2.** Factors determining neurocognitive disorders in the cohort.

Determinants Factors		NCD Presents (N = 61)		NCD absents (N = 183)		<i>p</i>
Sex						<b>0.29</b>
	Male	11	19.64	45	80.36	
	Female	50	26.6	136		
Age (years)						<b>0.0006</b>
	>40	24	18.45	109	81.95	
	≥40	37	33.33	74	66.67	
Marital status						<b>0.76</b>
	Couple	69	24.17	91	75.83	
	Single	32	28.91	92	74.49	
Social status						<b>0.32</b>
	Unemployed	41	27.15	110	72.85	
	Workers	20	21.5	73	78.5	
Instruction level						<b>0.018</b>
	Unschool/Primary	31	33.33	62	66.67	
	College/University	30	19.87	121	80.13	
Clinal stage WHO						<b>0.93</b>
	1 et 2	22	25.29	65	74.71	
	3 et 4	39	24.84	118	75.16	
ART at CD4 initiative (/mm <sup>3</sup> )						<b>0.053</b>
	<200	36	30	84	70	
	≥200	20	18.87	86	81.13	
Current CD4 (/mm <sup>3</sup> )						<b>0.13</b>
	<200	14	38.9	22	61.1	
	≥200	33	25.9	94	74.1	
Therapeutic protocol						<b>0.25</b>
	With EFZ	28	28.87	69	71.13	
	Without EFZ	33	22.45	114	77.55	
ART duration (in months)						<b>0.63</b>
	<24	24	23.76	77	76.24	
	≥24	36	26.47	100	73.53	

NCD: Neurocognitive disorders; N: Number; ART: Antiretroviral treatment; EFZ: Efavirenz.

The concept of neurocognitive disorders associated with HIV was early highlighted then categorized among AIDS symptoms [17] [18]. Thus several batteries of tests (test clock, 5 words Dubois etc.) have been proposed for screening of dementia in PLHIV [19] including the International HIV Dementia Scale-related or International HIV Dementia Scale [20]. The IHDS is a modification of the scale of dementia related to HIV or HIV Dementia Scale (HDS) developed by Power *et al.* [21]. It has recently been adapted by Sacktor *et al.* [22]. It is a tool whose sensitivity and specificity validated allow for screening of dementia among HIV positive populations.

This tool is easy to use does not require the direct involvement of healthcare professionals; less expensive because it does not require sophisticated instrument other than a watch with a second hand; finally IHDS is language independent and culture [21], thus it is transcultural. It helps identify patients at risk for neurocognitive disorders without the need for sophisticated neuropsychological tests. The specificity and sensitivity of the IHDS for the detection of dementia with a score less than or equal to 10 are 55% and 80% respectively in the Ugandan cohort [22] [23] and 57% and 80% in the cohort US [22]. In Brazil [24], the specificity is 55% and specificity of 80%; in South Africa 45% and 79% [25]. These data have confirmed our IHDS to use as a screening tool.

#### 4.1. Prevalence

In Central African Republic, the prevalence of neurocognitive disorders in the general population especially that of dementia was determined at 8.1% in the elderly [26]. But we do not have data on the prevalence of neurocognitive impairment in HIV in the country. The IHSD allowed us to find a prevalence of 25% among PLHIV. This percentage is in the range of the value of work done elsewhere that have reported rates ranging from 20% - 50% [5] [27]. Studies using the IHDS helped to bring a similar rate of 21% in Cameroon. As against our finding is slightly lower than the 38% prevalence found in Botswana and that of 33% in Guyana [15] [27] [28]. This demonstrates the extent of this phenomenon in HIV patients, especially since HIV has neurotropism with early dissemination to the central nervous system, the source of various complications [29]. Studies using another screening tool (basic test battery) also had results comparable to ours in Aquitaine [30] or 24%, while in the united states (38%) and Uganda (31%) rates well higher have been reported [11] [20]. But it is the IHDS is advised. Furthermore IHDS compared the MMSE (Mini Mental State Examination) detect much on the NCD HIV field [31]. Note that HIV-related dementia has an annual incidence of 7% after development of AIDS and ultimately affects 20% of people infected with HIV. If the incidence and severity of neurocognitive disorders have decreased, their prevalence continues to increase because of the elongation of the survival of patients and insufficient effectiveness of antiretroviral neurotoxicity induced by viral replication [5] [32]. Accurate and early diagnosis of HIV dementia can lead to treatment decisions and optimized management [21].

#### 4.2. The Performance of Patients to Different Tests

The average total score for the study population was 11. This average is identical to that found in Guyana [28]. Among PLHIV with NCD, the average score was 9 and in the US cohort (9.3) as well as in the Ugandan cohort when it was 9.9 [11]. Our finding is similar to that reported in Nigeria (8.36) by Oshinaike Olajumoke *et al.* [31], in Cameroon (9.4) by Njamnshi *et al.* [27]. This argues for the universality of the use of IHDS.

#### 4.3. The Performance for Each Neuropsychological Test

Concerning the under parts of the test, the sequence of Luria (concerning the gestural sequence) was difficult to achieve by our patients with NCD with a median score of 2. This score is similar to that reported in Guyana [28]. Moreover, this finding corroborates data reported in the literature [25] [27] [33]. This highlights the predominant involvement of the programming capacity by the patients in our study.

#### 4.4. Determinants

##### 4.4.1. Sex

Of the 61 patients with NCD, women were more numerous with a sex ratio (F/M) 4.5. But sex did not have a statistically significant effect ( $p = 0.29$ ) on the occurrence of disorders. This result goes in the same direction as that of the US and Ugandan cohort [22]. This can be a simple observation, because even for Alzheimer's disease in the general population, it has been reported that femininity is often associated with increased risk of this disease [34].

##### 4.4.2. Ages

Among patients with the NCD, the median age was 42 years. Patients older than 40 years were more likely to have these disorders (33.4%) for all subjects ( $p = 0.0060$ ). Our findings show that the higher the patient is elderly it is more likely to develop neurocognitive disorders. This fact was reported by African literature [27] [35]. In

our case, age over 40 years was associated with a risk of having a positive test. Similarly converging results have allowed us to confirm this correlation, especially in the Aquitaine cohort where age over 46 years was associated with a higher risk of having a positive test. At Bicêtre, the prevalence of NCD was high (50%) with a median age of 67 years [30]. A paper presented by Cross *et al.* also raised the link between age and the NCD [36]. For against Nakku *et al.* in their work on NCD risk factors in the population of Uganda reported that advanced age and neurocognitive disorders association was not demonstrated [37]. This phenomenon could be explained by certain stressful situations that seniors would face and which we have escaped. Because we have not administered batteries of neuropsychological tests to the subjects of the study, our objective is to test the IHDS for the rapid determination of the NCD in the cohort followed for PLHIV on the site.

#### 4.4.3. Education Level

Out of school sick or who left school at the primary level were more likely to develop the NCD ( $p = 0.018$ ). This finding reinforces the data from the study in India which had noted that the low level of education was significantly associated with the performance of The IHDS [38]. This result goes in the same direction as that presented by Bonnave in Guyana [39]. Cross *et al.* 2013 in an article also showed a low level of education was associated with the occurrence of a NCD [36]. These findings corroborate the studies already conducted in the general population on dementia [40]-[42]. Thus, the low educational level reduces, in addition to the neuronal degeneration induced by the virus, neuronal plasticity phenomenon that would protect against dementia [43] [44].

#### 4.4.4. The CD4 Count at Treatment Initiation

We found that 30% of patients with NCD had fewer than 200 CD4/mm<sup>3</sup> before treatment and that this rate did not affect the performance of subjects with IHDS and therefore was not associated with the NCD. This finding is contrary to that reported by Gray indicating that the frequency of increased TNC when the CD4 count was lower than 200/mm<sup>3</sup> [45], as well Njamnshi *et al.* have shown that a low CD4 count was predictive of the NCD [27].

Furthermore, the current CD4 count at diagnosis had no impact on the performance of the NCD test we used. This finding has been reported in Botswana [15] and corroborates the facts reported that the CD4 count as well as other biomarkers such as plasma viral load and the cerebrospinal fluid are not correlated or are not predictive of neurocognitive disorders [46]. The finding that the current CD4 count is not associated with the performance on IHDS was predictable since most subjects received HAART.

#### 4.4.5. The Time on Treatment

Like all degenerative diseases, it is difficult for society and the family to take preventive measures, apart from accompanying the patient for his regular use of antiretroviral therapy.

We found that 28.9% of patients with NCD were under treatment containing the efavirenz for over 24 months. But they were no more affected by the unrest because it would be led to think otherwise holding the account of the toxicity of efavirenz on the brain [47]. The duration of ART does not intervene in the appearance of the NCD. This confirms the data reported in the literature that in the event of infringement of the cognitive functions of HIV, the standard treatment is based on a combination antiretroviral therapy involving at least three molecules, whose aim is to block viral replication in the periphery and in the central nervous system. Such a regimen has demonstrated its ability to improve, at least partially, cognitive deficit, although the assessment criteria vary from one study to another [48]. Several recent studies have shown that the preferential use of neuroactive called antiretrovirals, that is to say have a better level of penetration and efficiency in the cerebral compartment provides an additional benefit virological [49], cognitive [50] [51] and survival [52]. However, there are other controversies that taking highly active therapy for several years threatens to constitute all factors that can worsen or even be the cause of NCD, what we have found. This is in line with this assertion that prolonged exposure of the brain to TAR originally NCD was not shown.

## 5. Conclusion

Our data show that the IHDS is a rapid screening tool that can be used in Central Africa to identify people at risk of developing HIV-associated dementia or cognitive impairment associated with HIV. However, it cannot replace the neuropsychological tests adapted for the accurate diagnosis of dementia associated with HIV. But it is

useful to point to the diagnosis of NCD associated with HIV among at-risk patients and appears to be suitable for limited-resource countries such as Central African Republic. This first study in the country has successfully used IHDS worth pursuing by combining with a battery of neuropsychological tests. If the results are conclusive, the IHDS can be recommended for all supported sites PLHIV for screening NCD associated with HIV.

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## Abbreviations

AIDS: Acquis immunodeficiency syndrome  
 ART: Antiretroviral treatment  
 CNS: Central nervous system  
 DAV: HIV-associated dementia  
 HAART: Highly active antiretroviral therapy  
 HDS: HIV dementia scale  
 HIV: Human immunodeficiency virus  
 IHDS: International HIV Dementia Scale  
 NCD: Neurocognitive disorders  
 PLHIV: Patients living with human immunodeficiency virus  
 US: United State