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RESEARCH ARTICLE

Factors associated with verbal fluency in older adults living with HIV in West Africa: A longitudinal study

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Abstract

Objective: Verbal fluency decline, observed both in aging and HIV infection, has been related to lower quality of life. This study aimed to evaluate the factors associated with categorical fluency in people living with HIV (PLHIV) aged ≥60 years living in West Africa.

Methods: In this longitudinal study, PLHIV aged ≥60 years, on antiretroviral therapy (ART) for ≥6 months were included in three clinics (two in Côte d'Ivoire, one in Senegal) participating in the West Africa International epidemiological Databases to Evaluate AIDS (IeDEA) collaboration. Categorical fluency was evaluated with the Isaacs Set Test at 60 s at baseline and 2 years later. Factors associated with verbal fluency baseline performance and annual rates of changes were evaluated using multivariate linear regression models.

Results: Ninety-seven PLHIV were included with 41 of them (42%) having a 2-year follow-up visit. The median age was 64 (62–67), 45.4% were female, and 89.7% had an undetectable viral load. The median annual change in categorical fluency scores was −0.9 (IQR: −2.7 to 1.8). Low baseline categorical fluency performance and its decline were associated with older age and being a female. Low educational level was associated with low baseline categorical fluency performance but not with its decline. Categorical fluency decline was also associated with marital status and hypertension.

Conclusions: Among older West African PLHIV, usual socio-demographic variables and hypertension were the main factors associated with low categorical fluency performance and/or its decline. Interventions that focus on supporting cardiometabolic health are highly recommended to prevent cognitive disorders in PLHIV.

KEYWORDS
aging, ART, cognition, HIV, verbal fluency, West Africa

INTRODUCTION

Verbal fluency is a cognitive process requiring rapid, effortful search and retrieval from semantic memory stores to verbally generate as many words as possible within 60 s. It could be tested by searching words either from a specific letter (letter fluency) or belonging to a particular semantic category (e.g., animals, fruits; categorical fluency) [1, 2]. Verbal fluency also implies language and executive functions abilities. It relies on switching abilities (ability to switch between one lexico-semantic cluster to another relevant one—executive component) and clustering abilities (ability to generate words within specific semantic subcategories—semantic memory component) [3]. It relies on both frontal systems and executive processes, as well as medial temporal lobe networks [4–6].

Sustainable Development Goal: Good Health and Wellbeing

In western countries, aging is characterised by a decline in verbal fluency performance [7–9]. In a French population-based cohort, verbal fluency was the first cognitive performance to decline, up to 12 years before the clinical diagnosis of Alzheimer's disease [10]. Among People Living with HIV (PLHIV) on antiretroviral therapy (ART), cognitive impairment is more characterised by both cortical and subcortical features, with executive functioning and working memory being the most altered cognitive function [11]. Despite ART, impairment in semantic fluency has also been observed [2, 12, 13]. In the United States, older PLHIV had lower verbal fluency performance than older HIV-negative participants and young participants regardless of their HIV status [1]. The alteration was specifically found on the executive component of verbal fluency (i.e., switching abilities), which is consistent with a combined fronto-striatal neuropathological burden of aging and HIV [1]. In older US PLHIV, low baseline verbal fluency was one of the determinants of incident cognitive impairment at the 12-month follow-up [13].

In sub-Saharan Africa (SSA), some studies also evaluated the impact of HIV or ART on verbal fluency in middle-aged PLHIV. In adults PLHIV initiating ART in rural Uganda, declines in semantic verbal fluency are still observed after 2 years of treatment [14]. Other studies from South Africa [15] and Uganda [16] also found lower semantic verbal fluency performance in PLHIV compared to HIV-negative participants. In Cameroon, 23.8% of adult PLHIV (on ART or not) had impairment in verbal fluency vs 12.9% of HIV-negative participants [17], but the measure including semantic, letter and action fluency and no significant difference for semantic verbal fluency was observed. However, to our knowledge, no data are available in older PLHIV (i.e., aged 50 years or above) in SSA, except in a previous cross-sectional analysis conducted in Senegal and Côte d'Ivoire, where a non-linear effect of age was observed on categorical verbal fluency performance, suggesting the importance of evaluating what happens in the oldest ones [18]. As cognitive functioning, including verbal fluency, varies across cultures and education level, it is also important to understand what happens in the sub-Saharan African population.

Importantly, low verbal fluency is associated with a decline in everyday functioning in both aging [19, 20] and HIV infection [1, 21, 22], affecting communication with others. This association may highlight the role of behavioural initiation on everyday functioning. Indeed, in categorical fluency tasks, strategies of generation are required and evaluated, also involving constructs relevant for everyday functioning, such as planning [20]. As observed in previous findings, executive functions and frontal lobe integrity are crucial to execute daily tasks [19, 23, 24]. Understanding the determinants associated with low verbal fluency performance or its decline is important to identify older PLHIV vulnerable to loss of autonomy and decreased quality of life. Hence, based on a 2-year longitudinal study, we aimed to evaluate the factors associated with low categorical fluency performance at baseline (i.e., the lowest performance of the sample) and its annual change in PLHIV aged ≥60 years old and living in West Africa. In this study, we focused on categorical fluency, as it is the most used to evaluate verbal fluency in SSA [25].

METHODS

Study population

We focused our analyses on PLHIV aged ≥60 years who had been on ART for ≥6 months. This study is part of an ancillary study project ('NeuroAging project') nested within the West Africa network of the International epidemiological Databases to Evaluate AIDS (IeDEA) of the US National Institutes of Health [26]. The NeuroAging study is a 2-year longitudinal study evaluating different aspects of aging with HIV (cognition, physical function, depression and frailty). Information about inclusion and exclusion criteria of the NeuroAging study can be find elsewhere [27, 28].

The study was conducted in Côte d'Ivoire and Senegal, in three urban sites with a large caseload of PLHIV and selected by convenience: the infectious and tropical disease department of Treichville University Hospital, and the public referral clinic (CePReF) in Yopougon Attié Hospital (Abidjan, Côte d'Ivoire) and the infectious and tropical disease department of Fann National University Hospital (Dakar, Senegal). Patients were recruited at the time of their usual HIV clinical visit. Their follow-up visit had to be carried out 2 years ± 1 month after the inclusion visit.

The research was completed in accordance with the Helsinki Declaration. For each participating country, ethical clearance was obtained from the national ethics committee (Côte d'Ivoire: Comité National de l'Ethique et de la Recherche; Senegal: Conseil National d'Ethique de la Recherche en Santé). All patients gave written consent before inclusion in the study.

Categorical fluency

Categorical fluency was assessed at baseline and 2 years later, with the Isaacs Set Test (IST) [29]. This test is an easy-to-administer, short-term test that fits well into research studies that include many assessments (as ours). It was recommended few years ago in the cognitive evaluation for PLHIV [30]. In sub-Saharan Africa, it has already been used in a large cohort of older participants [31, 32] and in other studies in PLHIV [25, 33]. This test includes four semantic categories (colours, animals, fruits, cities/villages). For each semantic category, the patients must give as many words as possible belonging to this category in 60 s. Each given word that was correct counted as 1 point. The total score at 60 s, corresponding to the sum of the scores obtained for each category, was computed. Annual changes in categorical fluency performance were computed as followed: (score at follow-up - score at baseline)/delay in years between the two visits. The IST was administered to each subject by trained doctors or a nurse (only in Senegal) in a private room that was as quiet as possible. The test was administered in French and local language in some cases.

Health status

Participants were also asked if they had been diagnosed with the following comorbidities: diabetes, hyperlipidemia, hepatitis B or C, tuberculosis, migraine. Hypertension was defined by a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg (WHO/International Society of Hypertension criteria) or a previous diagnosis of hypertension. Severe depressive symptoms were defined as a total score ≥17 for men and ≥23 for women using the Center for Epidemiological Studies Depression scale (CES-D) 20 items [34, 35]. Pre-Frail and Frail PLHIV were identified if they presented at least one and two items, respectively, on the frailty index developed in the Mobilise Boston study (i.e., involuntary weight loss; muscular weakness; loss of energy) [36]. Hazardous drinkers were identified based on the AUDIT-C [37], with a score ≥3 in women or ≥4 in men. Tobacco and drug substance use (current, former, or never) were evaluated through basic questions. HIV clinical variables were documented: initial clinical stage (defined using the Centers for Disease Control and Prevention [CDC] definition [A, B, or C]) [38], Nadir CD4 (cells/μl) (i.e., lowest CD4 value during follow-up), the more recent CD4 (cells/μl), detectable viral load (based on local laboratory thresholds), duration of infection (i.e., delay in months between the first positive serology data and the study's inclusion date), and initial and current ART combinations. Viral load was considered as undetectable depending on the local laboratory threshold, which varied across sites and laboratory (<20, <50, or <100 cp/ml). Patients having undetectable viral load had a viral load <100 cp/ml. The composition of the initial and current ART treatment was presented through a categorical variable (TDF/3TC/EFV vs. other ART combinations). TDF/3TC/EFV was the first line treatment during the study period.

Sociodemographic data

The usual sociodemographic variables were obtained. Level of education was collected in four categories: no school, primary school, secondary school and superior level and then recoded as the variable 'level of education' in two categories 'primary or less' versus 'secondary and more'. Marital status was coded in two categories: 'married' (including cohabitation) and unmarried (including being single, divorced, separated, or widowed).

Statistical methods

The characteristics of the sample were described using median and interquartile range (IQR) for continuous variables and counts and proportion for categorical variables. A comparison of baseline characteristics according to follow-up status (i.e., 2-year follow-up: yes or no) was also performed using Wilcoxon rank test for continuous variables, and Chi-2 or Exact Fisher Test for categorical variables depending on the tests' conditions of applications.

To identify factors associated with raw categorical fluency performance at baseline and annual changes, we performed separate multivariate linear regression models (significance $p < 0.05$). In each multivariate model, we included the variables associated with the dependent variable with a p-value ≤0.2 in univariate analyses. The final models were obtained with a backward selection procedure. Inclusion centre variables were included as a confounder in each model. Unbalanced variables (85%/15%) were not included in the analyses. In the final model, all 2 × 2 interactions were checked for significance. The statistical tests were considered significant at $p < 0.05$. Statistical analyses were performed using SAS software (9.4 version).

TABLE 1 Characteristics of the participants at baseline

N	97		
Sociodemographic data			
Age (years)*	63.6	(62–67)	
Low educational level	53	(54.6)	
Female	44	(45.4)	
Marital status: unmarried	52	(53.6)	
Professional activity: unemployed	69	(71.1)	
Comorbidities			
Hypertension	48	(49.5)	
Tuberculosis	22	(22.7)	
Severe depressive symptoms	22	(22.7)	(mis. 1)
Frailty (pre-frail/frail)	18	(18.6)	(mis. 1)
Diabetes	10	(10.3)	
Migraine	9	(9.3)	
Hyperlipidemia	3	(3.1)	
Hepatitis B or C	2	(2.1)	
Substance use			
Smoking (current/previous)	21	(21.7)	
Hazardous drinking	5	(5.2)	
Drug use	1	(1.0)	
HIV clinical data			
Duration of HIV infection (months)*	114	(74–142)	
AIDS CDC clinical stage	12	(12.4)	(mis. 1)
NADIR CD4*	174	(96–279)	
CD4 (cells/μl)*	500	(317–720)	
Detectable viral load	10	(10.3)	(mis. 21)
Initial ART combination (3TC + TDF + EFV)	17	(17.5)	
Current ART combination (3TC + TDF + EFV)	51	(52.6)	

Note: Data are *n* (%), or median (Interquartile interval - IQR).
Abbreviations: ART, antiretroviral therapy; IQR, interquartile range; mis, missing values.
*Indicates variables presented with the median and (interquartile interval - IQR).

RESULTS

Characteristics of the sample

Ninety-seven PLHIV were included in this study (19.6% came from Senegal). The median age was 64 (IQR: 62–67; Table 1), 45.4% were female and 54.6% had a low educational level (i.e., primary or less); 49.5% had a CD4 count >500 cell/μl. The most prevalent comorbidities were hypertension (49.5%), tuberculosis (22.7%), severe depressive symptoms (22.7%), and frailty (18.6%). Concerning substance use, 21.7% were current or former smokers. Hazardous drinking and drug use were less prevalent (<5%). The participants experienced a long duration of HIV infection (median: 114 months), 12.4% were on AIDS stage at baseline and 10% had a detectable viral load. Among the study participants, 41 had a 2-year follow-up visit. The median delay between the baseline and the 2-year follow-up visits was 2.2 years (IQR: 2.1–2.3).

At baseline, the median IST 60 s score was 45 (IQR: 36–54). At the 2-year follow-up, the median IST 60 s score was 43 (IQR: 38–52). The median annual change in categorical fluency scores was −0.9 (IQR: −2.7 to 1.8).

PLHIV with a 2-year follow-up visit were compared with those who did not attend the follow-up visit (Table S1). The participants lost to follow-up (LFTU) were older (median age: 65 years old vs. 63 years old) and were less frequently unmarried (44.6% vs. 65.9%). There were no substantial differences between the 2 groups for the prevalence of comorbidities (including hypertension), substance use, or HIV-related characteristics, but patients lost to follow-up tend to have a higher frequency of migraine ($p = 0.07$) and a detectable viral load (p = 0.09). No significant difference was observed concerning the median IST 60 s performance with

TABLE 2 Factors associated with category fluency performance at baseline

	Univariate analyses			Multivariate analysis		
	β	*t*	*p*-value	*β*	*F*	*p*-value
Age[a]	−1.0	−3.0	**0.003**	−0.8	8.5	**0.005**
Low educational level	10.8	5.0	**<0.0001**	7.0	10.1	**0.002**
Female	−10.7	−4.9	**<0.0001**	−8.3	14.0	**0.0003**
Living alone	−5.7	−2.4	**0.02**			
Unemployed	−4.0	−1.5	0.14			
Hypertension	0.6	0.3	0.79			
Hyperlipidemia	10.7	1.5	0.13			
Diabetes	−2.3	−0.6	0.57			
Hepatitis B or C	7.7	0.9	0.37			
Tuberculosis	2.3	0.8	0.43			
Migraine	4.6	1.0	0.30			
Hazardous drinking	-4.9	−0.9	0.37			
Smoking (current/previous)	8.0	2.8	**0.006**			
Drug use	9.1	0.8	0.45			
Severe depressive symptoms	4.2	1.5	0.15			
Frailty (pre-frail/frail)	5.5	1.8	0.08			
Duration of HIV infection (months)[a]	0.02	0.7	0.47			
AIDS Clinical stage	4.1	1.1	0.26			
Nadir CD4[a]	0.004	0.8	0.42			
CD4 (cells/μl)[a]	−0.01	−1.7	0.09			
Detectable viral load	5.9	1.4	0.15			
Initial ART combination[b]	−2.9	−0.9	0.36			
Current ART combination[b]	−0.5	−0.2	0.8			

Note: Bolded *p*-values indicate significant results ($p < 0.05$).
Abbreviation: ART, antiretroviral therapy.
[a]Continue variables. All the other variables were categorical variables.
[b]Initial or Current ART combination other than 3TC + TDF + EFV.

TABLE 3 Factors associated with category fluency decline

	Univariate analyses			Multivariate analysis		
	β	*t*	*p*-value	*β*	*F*	*p*-value
Age[a]	0.2	1.4	0.16	0.3	4.3	**0.05**
Low educational level	−1.2	−1.3	0.21			
Female	1.4	1.4	0.16	2.0	4.3	**0.05**
Living alone	−1.6	−1.6	0.12	−2.2	4.4	**0.04**
Unemployed	0.6	0.6	0.53			
Hypertension	−1.8	−2.0	**0.05**	−2.0	5.6	**0.03**
Hyperlipidemia	3.1	0.9	0.33			
Diabetes	3.3	1.5	0.14			
Hepatitis B or C	−2.0	−0.9	0.36			
Tuberculosis	0.1	0.1	0.95			
Migraine	−3.3	−1.00	0.32			
Hazardous drinking	2.9	1.3	0.20			
Smoking (current/previous)	−0.2	−0.1	0.90			
Drug use	1.0	0.3	0.74			
Severe depressive symptoms	−1.5	−1.2	0.24			
Frailty (pre-frail/frail)	−2.0	−1.7	0.10			
Duration of HIV infection (months)[a]	−0.01	−0.7	0.46			
AIDS Clinical stage	0.4	0.2	0.84			
Nadir CD4[a]	−0.003	−1.7	0.10			
CD4 (cells/μl)[a]	0.001	0.3	0.78			
Detectable viral load	−6.3	−3.2	**0.003**			
Initial ART combination[b]	−0.5	−0.4	0.68			
Current ART combination[b]	−0.6	−0.7	0.51			

Note: Bolded *p*-values indicate significant results ($p < 0.05$).
Abbreviation: ART, antiretroviral therapy.
[a]Continue variables. All the other variables were categorical variables.
[b]Initial or Current ART combination other than 3TC + TDF + EFV.

PLHIV with a 2-year follow-up: 45 (37–54) versus PLHIV without a follow-up: 43 (35–53).

Factors associated with low categorical fluency performance at baseline

In univariate analyses (Table 2), age, low educational level, being female, unmarried, and not being a current or former smoker were significantly associated with low categorical fluency performance. In the multivariable model, only age, low educational level, and being female remained significantly associated with low categorical fluency performance. All possible 2 by 2 interactions were not significant.

Factors associated with categorical fluency performance annual change

In univariate analyses (Table 3), hypertension, and having a detectable viral load were significantly associated with categorical fluency decline. In the multivariable model, age, being female, unmarried, and having hypertension remained significantly associated with categorical fluency decline. All possible 2 by 2 interactions were not significant, except the Age * Gender interaction ($p = 0.05$). When included in the final model, only being unmarried living alone remained significantly associated with categorical fluency decline.

DISCUSSION

In this longitudinal study of older PLHIV under ART living in West Africa, we observed a negative median annual rate of change in categorical fluency performance after 2-year of follow-up, suggesting a categorical fluency decline during this period. At baseline, lower categorical fluency performance was associated with sociodemographic characteristics (i.e., older age, being female, and low educational level) whereas categorical fluency decline after a 2-year follow-up was associated with the same sociodemographic characteristics (except educational level), marital status, and hypertension.

The association between verbal fluency performance and sociodemographic factors is well-documented in the literature. Age is among the main factors associated with cognitive disorders both in the general population and PLHIV [39–45]. In the United States, addictive effects of HIV and aging were reported on verbal fluency, particularly on the executive components [1]. A recent study from West Africa reported a non-linear effect of age on categorical performance without interaction with HIV status [18]. Interestingly, educational level was associated with performance at baseline but not its decline. As observed in a systematic review and meta-analysis based on longitudinal cohorts in the aging population, even if the association between educational level and cognitive performance is robust, the association with cognitive changes is inconsistent [46]. For Tucker-Drob et al., the persistence of earlier differences in cognitive functioning could be reflected by cognitive reserve, influenced by educational level [47]. Verbal fluency is also related to cultural knowledge, as observed in Sosa et al. [48] leading to different levels of performance from one population to another. In SSA, some studies reported an association between low educational level and cognitive impairment in PLHIV but the studies were cross-sectional [49–54]. Verbal fluency performance also appeared to be sex-specific, as females showed lower performance at baseline and higher risk of verbal fluency decline than males. Data from the literature on middle-aged PLHIV show no consensus [49, 50, 53]. As this difference in performance remains unclear, future studies should examine cognitive performance, using appropriate normative data according to sex. Finally, marital status (i.e., being unmarried) was also associated with low categorical fluency performance at baseline and its decline. A recent meta-analysis reported that being married is associated with healthier lifestyle behaviours, lower mortality, and reduced risk of dementia [55]. In our sample, the majority of unmarried persons were widowers. Widowhood is also a stressful life event that could impact cognitive functioning and is associated with a higher risk of dementia [55].

Hypertension was also associated with verbal fluency decline. Even the pathway remains unclear [56], an association between hypertension and cognition with aging has already been observed [57–60]. In middle-aged PLHIV, the relationship appears to be more complex. In a multi-country cohort (Australia, North America, Brazil, and Thailand), a significant association between hypertension and cognitive performance was observed, but verbal fluency was not evaluated [61], whereas in other studies, the relationship between hypertension and cognitive performance or cognitive decline was significant only in unadjusted models [62–64]. In middle-aged US PLHIV (27.6% were aged >50), the interaction of age and cerebrovascular risk was associated with poorer verbal fluency [65]. The impact on cognition was more pronounced in the absence of cardiovascular risk treatment [65]. In the US study, among older PLHIV (median age 57 years old), it was reported that arterial wall thickness (i.e., influence by blood pressure) was significantly associated with global cognition, processing speed, and verbal fluency whereas only a trend was observed with hypertension [66]. In another study, hypertension and dyslipidemia were associated with a high probability of impairment across multiple domains [67]. In SSA, to our knowledge, few data are available on the relationship between cardiovascular risk and cognition. One recent study in Senegal reported an association between hypertension and brain atrophy among PLHIV aged 50 years old or above [68] but due to limited sample size, the authors could not go further in the analyses and no cognitive evaluation was included. As cardiovascular diseases/risks factors and aging are associated with neuronal injury and inflammation in PLHIV stable on ART, some researchers suggest a tripartite model of HIV infection, aging, and cardiovascular disease/

risk factors to explain neurocognitive impairment in PLHIV [69]. As the prevalence of hypertension was very high in our sample, hygieno-dietetics interventions are necessary to support the cardiometabolic well-being of these patients to limit or reverse declines in cognitive performance.

In this study, no association was observed between verbal fluency and HIV clinical data except for viral load. In Nigeria, a recent study reported a significant association between plasma viral load and cognitive performance, particularly in verbal fluency, at baseline and longitudinally (2-year follow-up) in middle-aged PLHIV initiating ART [70]. Because of the intrinsic characteristics of the viral load variable (i.e., unbalanced variable), we could not go further to describe the impact of detectable viral load on verbal fluency. Detectable viral load is associated with inflammation that could lead to cardiovascular disease and HIV-associated neurocognitive disorders, particularly in the context of aging [71, 72]. Further studies are needed to evaluate the impact of detectable viral load on cognition in older West African PLHIV.

The major strength of our study is the evaluation of the determinants associated with longitudinal changes in verbal fluency in PLHIV aged 60 years or older who were on ART and without major neurologic complications or addictive behaviours. To our knowledge, this is the first study on this topic in West Africa. However, some limitations must be mentioned. First, the limited sample size and the specific participants' characteristics (i.e., urban population, ART status, no neurologic complications or addictive behaviours, living in urban sites) limits the generalizability of our results. Hypertension was also defined based on a single measure or based on a previous diagnosis. Second, the lack of a 2-year follow-up assessment of a large number of participants is also a potential limitation. As this analysis was a part of a larger study also evaluating physical function (at each visit), loss to follow-up could be explained by the time- and energy-consuming study assessments, particularly for the oldest or sickest ones. Third, in the present study, we focused on categorical fluency but action fluency (although it is little used in aging) might be more sensitive to HIV-associated neurocognitive impairment [2, 73]. Further studies are needed to evaluate the determinants of action fluency performance in older PLHIV living in SSA. Fourth, the direct impact of illiteracy was not explored as we did not collect clear information about it.

CONCLUSION

Based on our longitudinal study, usual socio-demographic variables (i.e., age, gender, educational level) were the main factors associated with low categorical fluency performance at baseline whereas marital status and hypertension were the main factors associated with its decline in older PLHIV in West Africa. No association was observed with HIV-related factors. Factors associated with categorical fluency decline were remediable, particularly hypertension. These results highlight the need for diligent control of blood pressure and, the importance of hypertension treatment in this population. Because of the high prevalence of hypertension and other cardiovascular risk factors in this population, the long-term impact of its comorbidities on cognitive impairment needs to be further evaluated in a larger sample. Interventions that focus on supporting cardiometabolic health are highly recommended to prevent cognitive loss in PLHIV.

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DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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