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Cardiovascular risk and neurocognitive deficits in HIV-positive individuals

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ABSTRACT:

Background: Neurological disturbances are frequently reported by HIV-infected patients, in particular with aging. A multitude of physical comorbidities has been shown to affect cognition in general populations in particular age and cardio-metabolic disease. However, a mild clinical picture can escape detection without formal neurological assessment and neuropsychological testing (NCT). Screening can be done inquiring about symptoms and performing brief neurocognitive tests (bNCT) that can help clinicians for further investigations. Our aim was to apply bNCT to HIV-infected-individuals evaluated for cardiovascular and metabolic diseases for primary prevention and relate cardiovascular risk with bNCT performance.

Patients and Methods: Consecutive HIV-positive patients were prospectively enrolled. Anthropometric, clinical and biochemical data were recorded; 10-year cardiovascular risk score was calculated according to the ASCVD algorithm (<7.5%, 10-20%, >20%), 5 year D:A:D and 10 yy Framingham. The measurement of common carotid IMT was performed by the same operator at 1 cm from carotid bifurcation as the average of three measurements (abnormal >0.9 mm). Data are expressed as medians (interquartile ranges). Patients received bNCT as three questions (3Qs), the International HIV Dementia Score (IHDS) and Clock Drawing Test (CDT) and Frontal Assessment Battery (age and education adjusted, aFAB), used in Geriatric Medicine for dementia screening in both HIV- and HIV+ patients. Respectively 3Qs≥1, IHDS≤10, CDT≥3 and aFAB≤13.4 were considered abnormal.

Results: 420 patients were enrolled (89% on cART, 79% male, median age 49 years). Plasma HIV-RNA was <20 copies/ml in 302 patients (72%), with a continuous duration of HIV suppression of 3.3 years. Current and nadir CD4+ cell count were 522/uL (343-690) and 200/uL (86.5-323), respectively. CV risk strata were: 5yyDAD (low 86.8%, high 13.2%), 10yFramingham (low 42.6%, intermediate 27.7%, high 29.7%) and 10yyASCVD (low 57.4%, intermediate 26.9% and high 15.7%). bNCT were abnormal in 107 (32%), 109 (42.4%), 56 (13.3%) and 38 (9%) patients, according to 3Qs, IHDS, CDT and aFAB, respectively. HAND was diagnosed in 44 patients (51.7%): 31, 10 and 3 subjects with ANI, MND or HAD. Age, education, history of hypertension, dyslipidemia, diabetes, pathological IMT affected a worse performance at ≥ 1 bNCT (p<0.05). Patients in the intermediate/high CV risk strata (using the three algorithms) had significantly lower NC performances. According to HIV infection, previous exposure to old NRTIs, as didanosine or with current NNRTIs based regimen got a low IHDS score (p=0.007), while PIs and INI based regimes seem to be over-represented in patients with normal performances.

Conclusions: Our work confirm the need for an early neuropsychological and cardiovascular assessment for HIV-positive patients to guarantee a prompt risk factors identification: a patient with intermediate/high cardiovascular risk may benefit from neurocognitive testing even if asymptomatic. Studies assessing the impact of cardiovascular risk reduction on cognition in HIV-positive subjects are urgently needed.

Keywords: Neurocognitive impairment, Cardiovascular risk, Brief neurocognitive tests, HIV.

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INTRODUCTION

Changes in memory, mood, attention and motor skills are often reported by HIV-infected patients[1], in particular with the aging population. In its latest revision, the Diagnostic and Statistical Manual-(DSM-) 5 included HIV as possible explanations for cognitive dysfunction[2]. In clinical practice remains the ongoing challenge of establishing the impact of the virus as the source of impairment. A variety of clinical, social, and psychological factors may contribute to HIV-associated neurological diseases (HAND), including Asymptomatic Neurocognitive Impairment (ANI), Mild Neurocognitive Disorders (MND) and HIV-associated Dementia (HAD)[3-5].

Despite the use of combination antiretroviral therapy (cART), the prevalence of neurocognitive impairment remains high (up to 50%)[6] and HAND has shifted towards a milder clinical presentation[7].

A multitude of physical comorbidities has been shown to affect cognition in general populations[8]: age, cardiovascular/metabolic disease, sleep disorders, and coinfections, such as hepatitis C virus (HCV)[9,10]. Age is a major risk factor for dementia, with 0.8% of persons being 60-65 years old in the US reported to have dementia from any etiology[11]. In HIV-positive population, risk factors for the development of HAND include immunovirological features (with a large effect size associated with low nadir CD4 cell count)[6,12,13], possibly host genetic factors and common comorbidities to HIV negative population[14,15].

It's known how complex is the interaction between nervous and cardiovascular systems. The development of vascular cognitive impairment involves the interplay of traditional cardiovascular factors, such as hypertension, diabetes and hyperlipidemia, and behavioral ones, such as obesity and sedentary life style[3,16,17]. Mechanistically, they cause inflammation and oxidative stress to blood vessels and may cause cerebral hypoxia-ischemia and small vessel endothelium dysfunction. HIV infection, itself, can share these common pathways. This is associated with increased vascular morbidity through elevated levels of inflammatory and procoagulant factors, atherogenesis, and endothelial alterations[5,18-20]. Moreover, neurological disorders are frequently associated with ECG and structural cardiac changes, with various clinical manifestations. Both the underlying neurological disorder and the cardiovascular dysfunction may impose limitations in the optimal treatment of one another. Therefore, the high prevalence of cardiovascular makes it difficult to establish if the neurological injury is the cause or the consequence of cardiovascular dysfunction. Recent data have linked small vessel cerebral disease with lower cognitive performances in HIV-positive subjects[21].

However, a mild clinical picture may go undiagnosed without formal neurological assessment and neuropsychological testing (NCT), which are labor intensive and require trained personnel to administer and evaluate it. Furthermore, since clinical signs, imaging and cerebrospinal fluid (CSF) findings are often not explanatory. Proper screening has to be done inquiring about symptoms and performing brief neurocognitive tests (bNCT). Appropriate screening tests[13] as three questions (3Qs) proposed by EACS guidelines[22,23] and the International HIV Dementia Score (IHDS)[24-26] are associated with poor sensitivity and intermediate/good specificity in different population groups. Other quick and simple tests, as Clock Drawing Test (CDT)[27] and Frontal Assessment Battery (age and education adjusted, aFAB)[28-30], used in Geriatric Medicine for dementia screening in both HIV- and HIV+ patients can be used for a more specific assessment. The use of geriatric bNCT had been proposed because HAD clinical picture is a subcortical phenomenon, similar to cortical dementia as seen in Alzheimer disease[29,31] later reviewed through multiple drafts by the group, including additional experts and the members of the Neurocognitive Disorders Work Group of the fifth revision of Diagnostic and Statistical Manual (DSM-5).

Our aim was to apply bNCT to HIV-infected-individuals evaluated for cardiovascular and metabolic diseases for primary prevention and relate cardiovascular risk with bNCT performance.

PATIENTS AND METHODS

Consecutive HIV-positive patients followed routinely for HIV infection at Amedeo di Savoia Hospital, Torino, Italy underwent physical, clinical and neuropsychological assessments. Patients provided informed consent. Using a standard data collection form, sex, age, weight and height, targeted anthropometric measures, lifestyle habit (smoke, alcohol, illicit drug use), systolic blood pressure, abdominal circumference measurement were recorded. HIV-related data, as antiretroviral history, CD4 nadir value and laboratory tests included absolute CD4 lymphocytes count, HIV RNA, fasting total (T-COL), high-density lipoprotein (HDL-C) and low-density lipoprotein cholesterol (LDL-C), triglycerides (TG) and blood sugar were extracted from clinical records. Main cut offs are reported in Table 1.

A history of hypertension, hyperlipidemia, and diabetes was also noted and subsequently verified by medical records. According to the European Society Cardiology, hypertension was defined as systolic blood pressure of 140 mm Hg or previous prescription of antihypertensive medication. Type 2 diabetes was defined as a glycated hemoglobin level of 6.5% or higher or previous use of antidiabetic medication. Hyperlipidemia was defined as t-COL of 190 mg/dL or previous use of lipid-lowering medication. Metabolic syndrome was considered according to the International Diabetes Federation consensus.

Cardiovascular risk scores were calculated by ten-year risk for CVD using the Framingham equation (<10% – low risk; 10-20 moderate ≥ 20% – high risk) and The Pooled Cohort equation for ASCVD according to instructions in the 2013 ACC/AHA Guideline on

Table 1. Anthropometric parameters measured during the visit and available data in the medical file with cut off limits.

	Cut off	Population results
BMI kg/m^2 (med/IQR)	18.5-24.99	24.8 (22.4-27.8)
Abdominal waist – (M cm, med/IQR) – (F cm, med/IQR)	 <94 <89	 91 (84-99) 90 (84-102)
Systolic blood pressure (mmHg, med/IQR)	<140	120 (110-135)
Biochemical values – COL-T (mg/dL; med, IQR) – HDL-C (mg/dL; med, IQR) – LDL-C (mg/dL; med, IQR) – TG (mg/dL; med, IQR)	 <190 >39 <100<115<130 <180	 200 (168-229) 44 (37-54) 124 (97-151) 129 (87-176)
Fasting blood glucose	<90	91 (84-100)

Table 2. Population characteristics.

Age years (med, IQR)	49.3	42-58
Gender (male: n, %)	335	79.8
Race (caucasian: n, %)	396	94.3
Smokers (no., %)	199	47.4
PIs-based regimen	182	43.3
NNRTIs-based regimen	151	36
INSTI-based regimen	117	27.9
CCR5R antagonist-based regimen (no., %)	10	2.4
Current CD4 count (n/ml: med, IQR)	522	343-690
Nadir CD4 count (n/ml: med, IQR)	200	86-323
Treatment duration (years: med, IQR)	9.1	2.6-15.7
HIV RNA<20 cp/ml (no., %)	302	71.9
HCV co-infection (no., %)	93	22.1

the Treatment of Blood Cholesterol (<7.5% -low risk 7-5-20% moderate risk- >20% high risk) and DAD risk equation consider a 5-year CVD risk >10% high.

Intima-media-thickness (IMT) evaluation was performed by ultrasonography of the epiaortic vessels using a latest generation power color Doppler with 7.5 mHz probes by the same operator. The common carotid, the bifurcation and at least 1 cm of the internal and external carotid vessels were examined bilaterally in the short and long axes. Pathological findings were defined as the presence of plaques (focal echogenic structure with an IMT > 1.2 mm), or IMT > 0.9 mm in three different measurements.

3Qs, IHDS, CDT and aFAB were administered.

Respectively, 3Qs≥1, IHDS≤10, CDT≥3 (using Shulman 1-5 for scoring)[27] and aFAB≤13.4 were considered abnormal.

Data are expressed as medians (interquartile ranges) and tested through non-parametric tests.

A descriptive analysis of patients' characteristics was carried out using frequency tables of categorical variables and median interquartile range for continuous variables.

Chi-square test was used for categorical variables; Fisher's exact test was used in case of low frequency of the considered variable. The relationship between predictive variables was evaluated with a logistic regression analysis. Data analysis was performed using SPSS software for Windows (version 23.0, IBM Corp. Released 2011, Armonk, NY, USA). All tests were two-tailed and $p<0.05$ was considered significant.

RESULTS

From December 2012 to February 2017, 420 HIV patients were enrolled. Population characteristics are summarized in Table 2. Median age was 49.4 [IQR 42-58]; 335 (79.8%) were male, 396 (94.3) Caucasians. Current and nadir CD4+ cell count were 522/uL (343-690) and 200/uL (86.5-323). 377 patients (89.7%) were on HAART [PI-based (43.3%), NNRTI-based (36%), INSTI-based (27.9%)]; treatment duration was 9.1 years (2.6-15.7). HIV RNA was <20 copies/mL in 302 patients (72%), with a continuous duration of HIV suppression of 3.3 years (0.05-9.3).

According to anthropometric and biochemical parameters median BMI was 24.8 (22.3-27.8), abdominal circumference 91 cm (86-99) and 90 cm (84-102) in male and female, respectively, systolic blood pressure 120 mmHg (110-135), T-COL 200 mg/dL (168-229), HDL-C 44 mg/dL (37-54), LDL-C 124 mg/dL (97-151), TG 129 mg/dL (87-151), fasting blood glucose 91 mg/dL (84-100). In 256 patients median IMT was 0.8 mm (0.6-1.1). CV risk strata were: 5yyDAD (low 86.8%, high 13.2%), 10yFramingham (low 42.6%, intermediate 27.7%, high 29.7%) and 10yyASCVD (low 57.4%, intermediate 26.9% and high 15.7%). Screening tests were abnormal in 107 (32%), 109 (42.4%), 56 (13.3%) and 38 (9%) patients, according to 3Qs, IHDS, CDT and aFAB, respectively. HAND was diagnosed in 44 patients (51.7%): 31, 10 and 3 subjects with ANI, MND or HAD.

Multivariate analysis is summarized in Table 3. It showed a significantly worse performance in 3Qs and IHDS tests in the older population (respectively $p=0.01$ and $p=0.002$), not significant for CDT (50 yy *vs.* 55, $p=0.4$). Education conditioned only IHDS test (9.8 yy *vs.* 7.4, $p= 0.001$) while FAB was corrected for both age and education. Previous neuropsychological symptoms as anxiety and depression did not condition the bNCT score. Patients with history of hypertension, dyslipidemia, diabetes underscored IHDS test ($p=0.05$, $p=0.006$, $p=0.03$, $p=0.01$) and presented pathological IMT ($p=0.05$). Figure 1 represents patients with at least one altered bNCT split for 10 yyASCVD score, showing how patients with intermediate/high cardiovascular risk had a worse test performance ($p=0.02$). This result is reproducible for 10yyCuore score and 5yy DAD (both $p< 0.001$).

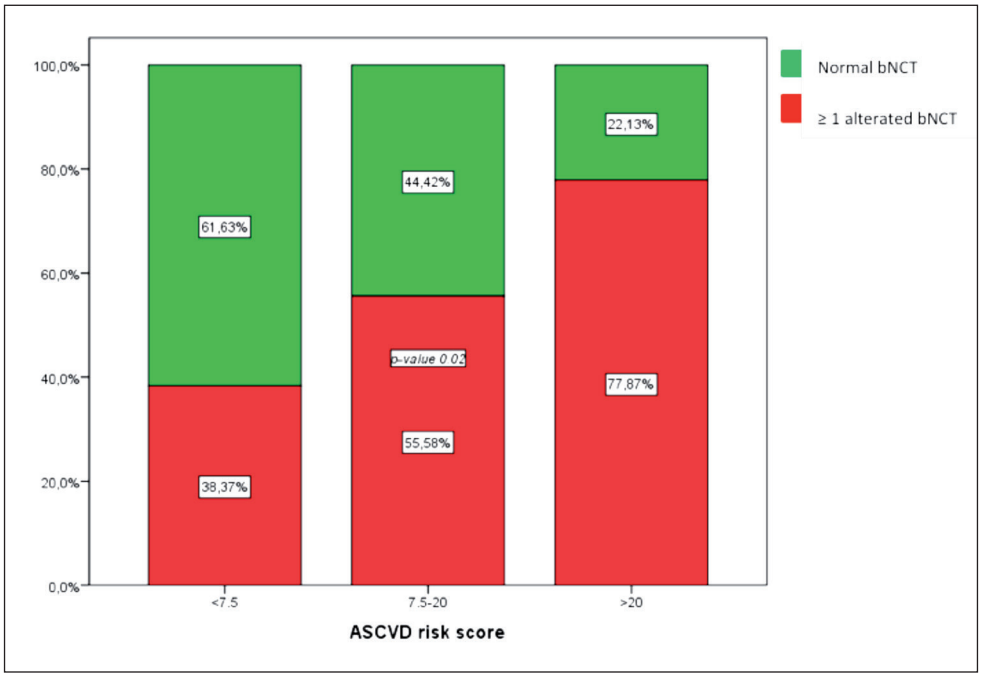

Figure 1. Patients with at least one altered bNCT split for 10 yyASCVD score, showing how patients with intermediate/high cardiovascular risk had a worse test performance (p=0.02).

According to HIV infection, mean CD4 cell count nadir is lower in the population with worse performances at all bNCT but without significant difference in two groups (3Qs p=0.7, IHDS p=0.4, aFAB p=0.2 and CDT p=0.1). Suppressed HIV RNA load is more represented in the group with normal bNCT except for CDT test (3Qs p=0.002, IHDS p=0.01, aFAB p=0.002), without significant difference in duration of suppression. About cART, patients with previous exposure to old NRTIs, as didanosine, stavudine or indinavir, or with current NNRTIs based regimen got a low IHDS score (p=0.007), while PIs and INI based regimes seemed to be over-represented in patients with normal performances.

DISCUSSION

In the context of multimorbidities and HAND, assessing and treating a HIV-infected patient is truly challenging, in particular, the diagnosis and cure of cofactors for HAND[32].

The social comorbidities that affect HAND and other neurocognitive disorders will continue to be a particularly difficult factor to modify, as HIV infection predominates in under resourced and economically marginalized communities. Translational research approaches for neurocognitive disorders will need to focus on these intersections of multiple physical and social comorbidities. On the basis of these premises, we screened for neuropsychological and cardio-metabolic diseases, as a primary prevention intervention, 420 HIV-positive patients over four years.

Brief NCT screening tests were abnormal in 107 (32%), 109 (42.4%), 56 (13.3%) and 38 (9%) patients, according to 3Qs, IHDS, CDT and aFAB, respectively. One fifth of the total received full NCT and HAND was diagnosed in 44 patients (51.7%). Old age and education level determined alteration of the result of at least one bNCT. Metabolic syndrome and pathological IMT levels had been most often observed in the group of patients with the IHDS score <10. In particular, higher cardiovascular risk score corresponds to lower bNCT score, especially for IHDS. Furthermore, patients with higher CD4 count nadir and HIV RNA undetectability performed better bNCT score, except for CDT. Previous exposure to old NRTIs regimen and current NNRTIs based regimen could reduce the IHDS performance although this might be a proxy for longer treatment duration (and potentially toxicities) and selection of drug-resistant variants (and therefore potential incomplete antiviral efficacy).

CONCLUSIONS

Our work confirms the need for an early neuropsychological and cardiovascular assessment for HIV-1 subjects to guarantee a prompt risk-factor identification. The NCT screening test represents a valid, rapid and inexpensive method that all clinicians without specific skills can easily perform for deciding which patients need a full NCT evaluation. Patients with known cardiovascular risk factors, HCV co-infection and a long history of HIV infection should perform neurocognitive assessment even in the absence of changes in memory, mood, attention or any neurological symptoms. Studies assessing the impact of cardiovascular risk reduction on cognition in HIV-positive subjects are urgently needed.

Table 3. bNCT performances according to cardio-metabolic history diseases, cardiovascular risk scores , HIV immunovirological features and HAART history.

	3QS < 1	3Qs ≥ 1	*p*-value	IHDS >10	IHDS ≤10	*p*-value	aFAB>13.4	aFAB≤13.4	*p*-value	CDT<3	CDT≥3	*p*-value
Mean age (Mean, SD)	48 (±13.6)	56 (±12.7)	0.01	44.5±12	55.4±12.7	0.002	50.9±15	49.7±12	0.5	49.9±13	54.8±12	0.4
Education (years)	8.65 (±6)	8 (±5.3)	0.4	9.8±6.8	7.4±5	0.001	8.7±6	7.2±5	0.1	8.5±6.3	7.5±5.2	0.2
History of HTN (%)	60 (53.6)	52 (46.4)	<0.001	34 (48.6)	36 (51.4)	0.05	50 (80.6)	12 (19.4)	0.4	101 (78.9)	27 (21.1)	0.005
Anti-hypertensive therapy yy (Mean, SD)	1.4 (±4.4)	3.6 (±7.1)	0.6	0.9±2.9	1.2±3.4	0.6	2.1±5	2.3±6	0.1	1.7±4.7	3.2±6.7	0.3
History of dysplipidemia n (%)	65 (61.9)	40 (38.1)	0.07	33 (44.6)	41 (55.4)	0.006	17 (89.5)	2 (10.5)	0.01	105 (88.2)	14 (11.8)	0.2
Lipid lowering therapy yy (Mean, SD)	0.6 (±2.8)	1.2 (±4)	0.4	0.33±1.4	0.86±2.5	0.6	1±3.9	0.7±2.6	0.3	0.7±2.8	0.4±1.9	0.02
Known mellitus diabetes n (%)	15 (50)	15 (50)	0.02	8 (36)	14 (63.6)	0.03	61 (87.1)	9 (12.9)	0.1	24 (75)	8 (25)	0.06
Antidiabetic therapy yy (Mean, SD)	0.4 ±3	0.7±2.8	0.3	0.1±8	0.89±3.5	0.7	0.4±2.6	0.2±6	0.9	0.4±2.6	0.8±3	0.1
Metabolic syndrome n (%)	41 (63)	24 (36.9)	0.3	26 (57.8)	19 (42.2)	1	27 (77.1)	8 (22.9)	0.4	70 (88.6)	9 (11.4)	0.5
IMT > 0.9 mm N (%)	37 (59.7)	25 (40.3)	0.2	19 (42.2)	26 (57.8)	0.05	60 (78.9)	16 (21.1)	0.5	69 (88.5)	9 (11.5)	1
10yyASCVD>7.5	90 (63.4)	52 (36.6)	0.1	46 (46)	54 (54)	0.003	85 (75.2)	28 (24.8)	0.01	151 (87.8)	21 (12.2)	0.4
10yyFramigham>10 (n, %)	199 (65.2)	106 (34.8)	0.003	123 (53.2)	108 (46.8)	<0.0001	153 (81.4)	35 (18.6)	0.7	312 (85)	55 (15)	0.03
10yy Cuore >10 n (%)	51 (60.7)	33 (39.3)	0.1	13 (25)	39 (75)	<0.0001	39 (79.6)	10 (20.4)	0.6	81 (86.2)	13 (13.8)	1
5yyDAD>5 (n, %)	60 (55.6)	48 (44.4)	0.001	22 (29.3)	53 (70.7)	<0.001	54 (80.6)	13 (19.4)	0.6	104 (81.9)	23 (18.1)	0.1
Nadir CD4 count (Mean, SD)	230 ±181	207 ±139	0.7	245.8±188	206±144	0.4	235±244	172±161	0.2	236±172	160±163	0.1
Current CD4 count (Mean, SD)	514 ±262	584 ±309	0.4	502.7±251	560±302	0.2	529±289	566±336	0.3	544±265	506±275	0.4
HIV RNA <20 cp/ml (n, %)	147 (62.8)	87 (37.2)	0.002	94 (52.5)	85 (47.5)	0.01	122 (84.1)	23 (15.9)	0.02	24.7 (86.1)	40 (13.9)	1
HIV RNA<20 yy (mean, SD)	7.3±19	8.3±15	0.7	6.5±18	9.9±21	0.3	8.4±19	4.2±5	0.3	7.2±16	10.9±25	0.1
cART duration yy (mean, SD)	11±19	13.4±15	0.3	10.5±20	14.6±21	0.3	12.2±17	7.3±6	0.1	11.4±16	17.2±28	0.1
Anxiety (n, %)	52 (57.1)	39 (42.9)	0.01	38 (53.5)	33 (46.5)	0.4	50 (83.3)	10 (16.7)	0.4	92 (80.7)	22 (19.3)	0.04
Depression (n, %)	36 (49)	37 (50)	<0.001	25 (49)	26 (51)	0.2	39 (81)	9 (18)	0.5	73 (82)	16 (18%)	0.2
NNRTIs (n, %)	79 (66.9)	39 (33.1)	0.8	38 (45.2)	46 (54.8)	0.007	67 (80.7)	16 (19.3)	0.8	127 (87)	19 (13)	0.7
PIs (n, %)	97 (66.4)	49 (33.6)	0.6	63 (55.3)	51 (44.7)	0.5	65 (81.3)	15 (18.8)	0.8	146 (85)	26 (15)	0.5
INI (n, %)	51 (56)	40 (44)	0.006	46 (61.3)	29 (38.7)	0.4	60 (92.3)	5 (7.7)	0.007	97 (84.7)	14 (15.3)	0.6
DDI/IDV/LPV Previous exposure	41 (63)	36 (46.8)	0.002	23 (39)	36 (61)	<0.001	48 (88.9)	6 (11.1)	0.1	89 (84)	17 (16)	0.5

Conflicts of Interest:
The Authors declare that they have no conflict of interests.

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