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Cognitive and Fine Motor Performance in People Above 65 years of Age with and without HIV

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Abstract

Background: Cognitive and motor performances decline with ageing, and this may be exacerbated in people with HIV (PWH) due to several factors. The study aimed to compare cognitive and fine motor performance between older adults with and without HIV.

Methods: We conducted a cross-sectional study of participants ≥65 years in the GEPPO cohort using Mini-Addenbrooke's Cognitive Examination (MACE) and Grooved Pegboard Test (GPT). Quality of life, depression, anxiety, and sleep quality were also measured.

Results: PWH (n=239) were younger (73.7 vs. 80.6 years) and more commonly males at birth (85 vs. 25%) than PWoH (n=52). No significant differences in MACE scores were observed between groups (24 vs. 23, p>0.900). Time to complete GPT was longer in PWoH (140 vs. 106 seconds, p=0.004), with 56% exceeding normative GPT values vs. 24% in PWH (p<0.001). In multivariate models, older age and lower education predicted worse MACE and GPT scores, whereas benzodiazepine/Z drug use predicted poorer fine motor skills. PWH reported lower quality of life but similar or better depression, anxiety, and sleep scores compared to PWoH.

Conclusions: Older PWH show comparable cognitive but better fine motor performance than PWoH. Education and benzodiazepine use emerged as key modifiable or protective factors, underscoring the importance of targeted geriatric and mental health interventions.

Background

As global life expectancy increases, the number of elderly individuals (i.e. those above th age of 60 or 65 years) is steadily growing, highlighting the need for understanding the natural processes of aging and their effects on physical and cognitive health. Cognitive aging is characterized by declines in processing speed, working memory, executive function, and fine motor coordination, while some other abilities may remain stable for longer times.(1) The rate and pattern of decline vary considerably across individuals; they are influenced by genetics, education, lifestyle, comorbidities, concomitant treatments, and social environment.(2) It should also be noted that functional autonomy is often maintained through compensatory strategies and accumulated experience.(3)

In healthy aging, white matter alterations are linked to slower processing speed and reduced fine motor skills, and these impairments appear to be more pronounced in people with HIV (PWH).(4) This probably reflects poorer vascular health, and the association between HIV (but also latent herpesviridae such as CMV, EBV, and VZV) and brain vessel changes has been repeatedly reported.(5–7) Due to the success of combination antiretroviral therapy (cART), PWH are living into older age but with a significant burden of concomitant diseases.(8–10) Prospective data reports that cognitive trajectory in PWH is influenced by comorbidities (such as diabetes, cardiovascular disorders, and chronic obstructive pulmonary disease), mood and sleep disorders, and consequently drug consumption.(11) The observed high burden of comorbidities is a risk factor for polypharmacy (i.e., the simultaneous use of five or more medications), inappropriate prescriptions, drug-drug interactions, and a high anticholinergic burden.(10) These factors have all been associated with poorer cognitive performance and a higher incidence of geriatric syndromes such as falls. In this context, the concomitant presence of low cognitive performance and frailty, known as “cognitive frailty”, has been related to increased disability and reduced survival.(12)

This standard trajectory of cognitive aging can be modified also directly by HIV. HIV can invade the central nervous system early, causing chronic inflammation and neuronal damage.(13) While cART has drastically reduced the incidence of HIV-associated dementia (HAD), low cognitive performance is still prevalent despite the ongoing discussion on its diagnostic criteria and classification.(14) Several US cohorts suggest that PWH have a

significantly higher risk of clinically diagnosed dementia than people without HIV after 65 years of age.(15–17)

Older PWH confront unique additive or synergistic factors beyond typical aging. Chronic immune activation, vascular and metabolic comorbidities, possible neurotoxic effects of long-term cART, and social determinants like isolation and stigma may enhance neurocognitive vulnerability. Matched cohort studies adjusting for confounders indicate that HIV independently increases risk for neurocognitive impairment, suggesting that age-related and HIV-specific processes interact. (18,19)

Moreover, a decline in cognitive and fine motor performance may also impact health-related quality of life and lead to increased burden of depression, anxiety, and poor sleep. Several studies showed that cognitive impairment and reduced ability in activities of daily living are directly linked to higher rates of depressive symptoms and poorer sleep quality in older adults.(20) Impairments in daily living and fine motor skills further mediate this relationship, as reduced functional (motor) independence is associated with both lower quality of life and higher risk of depression. Mental health is a critical issue in PWH since depression, anxiety, post-traumatic stress disorder and sleep disturbances have been reported to be highly prevalent.(21)

Several critical research gaps exist, such as limited data on PWH over 60 and an incompletely understood interaction between treated HIV infection and aging processes.(22–24) In summary, aging is naturally associated with declines in cognition and motor abilities, influenced by diverse factors. In older PWH, these trajectories need to be better defined, given the burden of risk factors and the potential progression to dementia.

The primary objective of this study was to compare cognitive and fine motor performance between older adults with and without HIV and to examine the contribution of HIV-related factors to potential impairments. We also aimed to assess differences in patient-reported outcomes (PROs), including quality of life, depressive symptoms, anxiety, and sleep quality, in relation to cognitive and fine motor performance among older adults with and without HIV.

Material and methods

This was a cross-sectional observational study including older adults with and without HIV from the GEPPO cohort. GEPPO (GEriatricPatients living with HIV/AIDS: a Prospective multidimensional assessment of an ageing cOhort & community) primary objective is to

describe geriatric health domains in older people living with HIV (OPLWH, >=65 years of age) versus community dwelling HIV-negative individuals. Several infectious diseases and geriatric centers in Italy (https://www.dsm.unito.it/do/home.pl/View?doc=/Ricerca/Geppo.html) are participating: enrolled individuals are visited annually.

A GEPPO visit lasts approximately 1-1.5 hours, and it includes medical and treatment history, physical examination, physical function tests, and patients' reported outcomes (PROs). Participants in the GEPPO cohort were included in this study if they had completed the Mini-Addenbrooke's Cognitive Examination (MACE) and the Groover Pegboard test (GPT) tests. The protocol has been approved by the Coordinating Institution's (CET Lombardia 3, ID 712_2018 and 720_SA_01.09.2023) and by all participating centres' Ethics Committees; all participants signed a written informed consent before being enrolled. All methods and procedures were carried out according to Helsinki's declaration and international guidelines.

The MACE is a brief cognitive screening test that evaluates four main cognitive domains (orientation, memory, language, and visuospatial function) with an administration time of five minutes. It has been previously validated in PWH.(25) The GPT is a manipulative dexterity assessment tool designed to evaluate visual-motor coordination and fine motor skills: it features 25 holes with randomly positioned slots, and it requires individuals to manipulate pegs with a "key" along one side, rotating them to match the hole before insertion.

MACE was administered by a trained physician and scored 0-30 points; we used the 21-point cut-off given the older age of participants. The GPT was also administered by a trained physician, and the time was recorded for the dominant and non-dominant hand. We compared the results with normative data (age-adjusted values in healthy volunteers).(26) We considered abnormal those values above 2 standard deviations above the age-adjusted normative data. We evaluated the last observation if multiple ones were available.

PROs included the EuroQOL 5-domanin 5-level questionnaire ("EQ-5D-5L", used with permission) for quality of life, the Center for Epidemiologic Studies Depression Scale ("CES-D") for depressive symptoms, the Hamilton Anxiety Rating Scale ("HAM-A") for anxiety symptoms and the Pittsburgh Sleep Quality Index ("PSQI") for sleep quality. Probable depression was defined as CES-D ≥17 while anxiety symptoms were stratified according to HAM-A scores (<7 none, 8-14 mild, 15-23 moderate, ≥24 severe anxiety). A PSQI score ≥5 was considered abnormal.

Multimorbidity (MM) was defined as the presence of ≥3 concomitant diseases while polypharmacy (PP) as the use of ≥5 non-antiretroviral concomitant medications. The anticholinergic burden (ACB) was measured using the ACB score and categorized as 0, 1-2 or ≥3.[ref] The following ATC codes were used to identify benzodiazepine/Z drugs: N05BA01, N05BA03, N05BA04, N05BA06, N05BA08, N05BA09, N05BA12, N05BA13, N05BA15, N05CD02, N05CD03, N05CD04, N05CD05, N05CD06, N05CD07, N05CD08, N05CF01, N05CF02, N05CF03.

Statistical analysis

Data were summarised using median and IQR for quantitative variables, counts and percentages for categorical variables.

Comparison between PWH and PWoH was performed using the Wilcoxon-Mann-Whitney non-parametric test for quantitative variables, while categorical variables were evaluated using the Chi-square test with p-values computed via Montecarlo simulation (B=2000).

MACE values were modelled using multivariate beta regression with a log link, to account for high left skewness, after scaling in a 0-1 range. Therefore, the *beta* can be interpreted as an odds ratio. GPT values were modelled using multivariate linear models with GPT on a log scale. Hence, betas can be interpreted as ratios.

All tests were two-sided, and results were reported as estimates (betas) and corresponding 95% CI. All analyses were performed using R (version 4.5.1).

Results

Participants' characteristics

We enrolled 239 PWH and 52 PWoH aged ≥65 years. Table 1 shows the demographic, clinical and treatment characteristics of the two groups of participants; the vast majority of the participants were of European ancestry (99% of PWH and 100% of PWoH). Participants with HIV were younger and more commonly males at birth. HIV-specific features showed an excellent virological suppression and a current CD4 cell count associated with a good immunological recovery after many years of treatment (Table 1).

PWH were all on treatment with cART and virological control was observed in 221 participants (94%, 177 with non-detectable HIV RNA). Patients were receiving three-drug regimens (154, 64.7%), mostly based on integrase inhibitors (INSTI, 106, 68.8%) or non-nucleoside reverse transcriptase inhibitors (NNRTI, 38, 24.6% mostly rilpivirine with doravirine used by only 3 persons). Two-drug regimens (84, 35.3%) mainly consisted of combinations of INSTI plus lamivudine (37, 44%) or INSTI plus NNRTI (29, 34.5%). Additionally, 49 (20.6%) participants were on boosted regimens. Among those receiving a NNRTI-INSTI combination (n=33), most were treated with rilpivirine plus dolutegravir (n=23, 69.7%) or etravirine plus raltegravir (n=7, 21.2%).

Cognitive and fine motor performance and patient-reported outcomes

Table 2 reports the results of the MACE, dominant and non-dominant hand GPT and the PROs that were included in the GEPPO visit, according to participants' group.

As for the cognitive evaluation we observed no difference in MACE results between the two groups (24 vs. 23, p>0.900) while worse fine motor function was observed in participants without HIV (with 56% vs. 24% showing ndh-GPT values above 2 SD, p<0.001). Figure 1 depicts the distribution of MACE and ndh-GPT scores in the two groups. As for the PROs we observed worse, self-reported, depression and sleep quality in participants without HIV. Specifically, probable depression and abnormal sleep were reported by 38% and 75% of older participants without HIV as compared to 26% and 47% in those with HIV. Despite non-significant differences in HAM-A scores between the two groups, PWH reported more frequently severe anxiety symptoms (23 vs. 15%, p=0.048). Finally, quality of life was reported to be lower by participants with HIV (0.76 vs. 0.90, p<0.001).

Differences between groups with and without low cognitive and fine motor function

We then created 4 groups of participants according to the results of MACE/GPT test for assessing the factors associated with low cognitive performance, low fine motor performance or both. Supplementary Table 1 shows the characteristics of participants in each category.

Despite small numbers in subgroups, we observed that those with low cognitive and fine motor performance were more commonly older, had lower education years. In PWH female participants were more frequently represented in the low cognitive and fine motor function group.

We then explored the factors associated with low cognitive or fine motor performance in the whole study population (including HIV serostatus as a covariate) and then in PWH only. Supplementary Tables 2-5 include full multivariate models parameters.

In the entire study population, in multivariate analysis for MACE score (adjusted for age, sex, HIV status, presence of diabetes, hypertension, and cardiovascular disease, use of benzodiazepines/Z drugs), the only independent predictors were age (p=0.043, Beta 0.98, 95%CI 0.96-1.00) and the duration of education (p<0.001, Beta 1.10, 95%CI 1.07-1.13). Adjusting for the same variables, GPT scores were predicted by age (p<0.001, Beta 1.03, 95%CI 1.01-1.04), female sex at birth (p=0.029, Beta 1.25, 95%CI 1.02-1.53) and education years (p=0.011, Beta 0.98, 95%CI 0.96.- 0.99).

In PWH the multivariate analysis (adjusted for adjusted for age, sex, CD4 nadir, presence of diabetes, hypertension, and cardiovascular disease, use of benzodiazepines/Z drugs, use of NNRTI or boosted agents) the only independent predictor of higher MACE scores was the duration of education (p<0.001, Beta 1.08, 95%CI 1.05-1.12). Adjusting for the same variables GPT scores were predicted by age (p=0.026, Beta 1.02, 95%CI 1.00-1.04), benzodiazepine/Z drug use (p=0.038, Beta 1.30, 95%CI 1.02-1.567) and duration of education (p=0.004, Beta 0.97, 95%CI 0.95 - 0.99).

We observed no effect of specific HIV disease features on cognitive or fine motor function: specifically, current or nadir CD4 and virological suppression (including the difference between detectable and not detectable HIV RNA below 50 copies/mL) were not significantly associated with our outcomes of interest. Antiretroviral drugs (assessed as INSTI vs. NNRTI vs. PI use, 2- vs. 3-drugs and boosted vs. unboosted regimens) were also not associated with cognitive or fine motor function in PWH.

Patient reported outcomes

Finally, we explored whether participants with low cognitive and/or fine motor performance had significantly different scores on PROs related to quality of life, depressive or anxiety symptoms and sleep quality. Figure 2 depicts the scores in EQ-5D-5L, CES-D, HAM-A and PSQI scores according to MACE/ndhGPT categories. No statistically significant differences were observed among categories. Yet, those with abnormal MACE had a lower probability of self-reporting anxiety symptoms (p=0.024, OR 0.94, 95%CI 0.88-0.99); worse fine motor function was associated with increased odds of probable depression (p=0.016, OR 1.37, 95%CI 1.06-1.76).

Discussion

This study, aiming to evaluate the cognitive and fine motor performance of older PWH compared to older persons without HIV PWoH, reveals several important insights into the cognitive ageing and mental health of PWH, particularly concerning cognitive performance, fine motor function, quality of life, and comorbidities. It should be highlighted that PWoH showed significant demographic and clinical differences that may have influenced our results. PWoH were approximately 7 years older, presented more comorbidities, were less frequently treated with benzodiazepines; they were also more commonly female and had a different distribution of yearly income (less frequently in the poorer and richer strata).

We chose to include MACE and GPT in the GEPPO cohort evaluation because of its reported results as a screening test and in order to have a short test in a very long (1-1.5 hours) visit. Previous studies suggested a good predictive performance, a higher sensitivity and lower ceiling effect in comparison to mini mental state examination test and its utility in elderly with comorbidities such as chronic kidney disease and diabetes; a small validation study (with few elderly participants) validated MACE in PWH. (27–30)It should be highlighted that MACE is a screening test requiring confirmation through full cognitive tests and it may be affected by participants' education and cognitive reserve.

We observed no significant differences in the MACE scores between PWH and PWoH, suggesting that cognitive performance, as measured by MACE, is relatively comparable across both groups. When using the lower MACE cutoff (21 points out of 30), a sizeable

proportion of PWH and PWoH showed a lower cognitive performance (34 vs. 40%): this will require full neurocognitive test and brain imaging to confirm it and to understand its pathogenesis. Yet, this finding may be surprising, given the known cognitive vulnerabilities associated with HIV. The lack of observed differences may reflect the effect of virological control achieved with modern cART therapies; (24)) however, this interpretation is limited by the cross-sectional design and the presence of potential confounders not fully captured in our models. In the multivariate analysis, HIV serostatus was not associated with MACE scores when correcting for the other confounders and contributors; the length of education, as expected, was the only independent predictor of cognitive performance we found.(31) Apart from cognitive reserve, it is also an indirect measure of social and environmental features, with persons who attended more years of school showing socially advantaged environments.(32) When we focused on PWH, we – again - identified only the length of education as a protective factor for lower cognitive performance, while lower CD4 at nadir and specific antiretroviral class were not. This was not entirely expected since several studies identified CD4 nadir as a contributing factor to cognitive weakness in younger individuals with HIV; one possible explanation is that other contributing factors, apart from HIV-associated inflammation and damage, may be more relevant in older individuals receiving fully effective ART.(33) We may not have completely captured these contributing factors, and a potential survival and performance bias (with severely cognitively impaired participants having died or not available for on-site visits).

A notable difference between PWH and PWoH was observed in fine motor performance, with PWoH exhibiting significantly worse scores on the non-dominant hand Grooved Pegboard Test (ndh-GPT). Specifically, 56% of PWoH scored more than 2 standard deviations above the normative data, indicating poorer fine motor performance, compared to just 24% in PWH ($p < 0.001$). This divergence in fine motor function may be partially attributable to the substantial age difference between the two groups, since the age-related decline in motor function (along with slower processing speeds and fine motor coordination) has been reported in the general population.(34,35) Although we controlled for age in our analysis, the higher average age of PWoH could explain part of the observed differences in fine motor performance.(36) It is essential to acknowledge that the presence of HIV may exacerbate vascular changes and white matter lesions, both of which have been linked to poor motor function. Studies have indicated that white matter abnormalities in PWH can lead to slower processing speeds and impaired motor performance.(23) Yet, this apparent better

motor performance in older PWH should be interpreted with caution, as it may be influenced by differences in baseline characteristics between groups. While we lack a clear explanation for this observation, several hypotheses could be considered (e.g., adaptive or compensatory mechanisms, differences in healthcare engagement, learning effect or familiarity with testing environments), although these remain speculative and cannot be tested within the current study design (37–40) In addition, fine motor measures may be more sensitive than brief cognitive screening tools in detecting subtle functional differences in older populations (not entirely reflected in global cognitive scores) or that they capture a different patients' phenotype whose trajectory need to be studied prospectively.(41,42) Overall, these findings should be considered exploratory and hypothesis-generating rather than indicative of a true protective effect of HIV status on motor performance.

Importantly, by analyzing cognitive and fine motor performance together, we were able to identify distinct phenotypes—individuals with isolated cognitive impairment, isolated motor impairment, and those with both. This combined impairment, often referred to as 'dual decline,' is particularly significant: prior studies have linked it to increased risk of disability, functional dependency, institutionalization, and mortality in older adults. Understanding these phenotypes in the context of HIV is critical, as dual decline may reflect a compounded vulnerability from both HIV-related and age-related mechanisms.(42) This approach reinforces the importance of integrated geriatric assessment in older PWH and suggests that targeted interventions may be needed for those with dual impairments. Participants both cognitively and motorly impaired were a minority (9.2% and 17.3%), but this limited our ability to analyze this particularly vulnerable group of patients.

The results of this study further confirm the complex interplay between aging, multimorbidity, polypharmacy, and cognitive health in older PWH. Multimorbidity was more prevalent in PWoH, which could contribute to their higher average age, but PWH also exhibited a high rate of polypharmacy (29% vs. 35% in PWoH), which is a known risk factor for cognitive decline and frailty in older populations. Available literature suggest that polypharmacy is particularly concerning because it often involves drugs with anticholinergic properties, which have been linked to cognitive impairment.(43) The anticholinergic burden observed in this cohort was not significantly different between PWH and PWoH and it was not a major determinants of the cognitive/fine motor performance in this study. (44) Specifically, our analysis revealed that benzodiazepine/Z drug use in PWH was associated with poorer fine

motor performance, underscoring the importance of careful pharmacological management in this population.(45)

The comparison of patient-reported outcomes (PROs) revealed significantly lower quality of life in PWH compared to PWoH. The mean EQ-5D-5L score for PWH was 0.76 compared to 0.90 for PWoH ($p < 0.001$). This discrepancy underscores the ongoing challenges PWH face, even in the context of long-term virological suppression. Several factors may contribute to this diminished quality of life in PWH, including the burden of multimorbidity, polypharmacy, the loneliness of dealing with both chronic infection and aging, and ongoing social stigma.(46) Older PWH often live with multiple comorbidities (such as diabetes, cardiovascular disease, and COPD), all of which are known to impact quality of life. Furthermore, the psychological effects of living with HIV—such as anxiety and depression—may also exacerbate the perceived quality of life. Indeed, our results indicated that PWoH showed higher scores in the depression domain as well as poor self-reported sleep quality; the anxiety scale did not substantially differ between the two groups, albeit a higher prevalence of severe anxiety emerged in PWH (23% vs. 15%, $p=0.048$). The contradictory results confirm, once again, the complex interplay between mood, cognition, and social determinants of health. Unfortunately, we did not measure both stigma and loneliness: it may contribute to poor quality of life and cognition and further studies need to include such domains in the evaluation of older PWH.(47)

Several limitations must be considered. First, the cross-sectional nature of the study prevents us from drawing causal relationship between HIV status and aging outcomes. Future longitudinal studies are needed to better understand the trajectory of cognitive and motor decline in PWH over time. Additionally, while we controlled for a range of potential confounders, there may be other unmeasured factors (e.g., diet, exercise, or genetic predispositions) that contribute to the differences observed and education and socio-economic status were sel-reported and not assessd in depth. Finally, although we used a large sample size, the number of PWoH participants was smaller, which may limit the generalizability of our findings. Additionally, the tests we used have been developed for screening purposes, and a more detailed assessment using complete neuropsychological evaluation, imaging, or biomarkers may increase our ability to identify clinically relevant conditions.(48,49)

In conclusion, we observed no worse cognitive and fine motor performances in older PWH in this cohort; however, these findings should be interpreted cautiously and should not be taken as evidence of preserved cognitive aging, given the cross-sectional design and the potential impact of selection and survival biases. Yet this study highlights the complex interplay between HIV, aging, and cognitive and motor function in older adults suggesting the need of a comprehensive geriatric assessment in HIV care bundles. While PWH did not show significant differences in cognitive performance compared to PWoH, they exhibited better fine motor performance. When assessing patient-reported outcomes, we observed that older PWH had better or equal scores in anxiety, depression, and sleep quality, but self-reported quality of life was markedly lower than in persons without HIV. These findings underscore the importance of considering both age-related processes and HIV-specific factors when addressing the health needs of older PWH. Apart from non-modifiable factors (such as age and duration of education), we identified modifiable variables (such us benzodiazepine use) that may prompt interventions (such as medication revision) to improve cognitive health and well-being in high-risk individuals. Overall, our results should be interpreted as hypothesis-generating and warrant confirmation in longitudinal and better-matched studies

Authors' contribution

AC, EF, and GG conceived the study. SC and FRC performed the statistical analyses and drew the graphics. All other authors enrolled participants and actively contributed to study design and manuscript preparation. AC wrote the first draft of the manuscript, and all authors participated in the preparation of its final version.

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Disclosure of potential conflict of interest

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Data availability

Data are available upon reasonable request.

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Confounders and Neurocognition. Viruses. 2022 Apr 4;14(4):753. doi:10.3390/v14040753 PubMed PMID: 35458483; PubMed Central PMCID: PMC9031633.

Tables

	PWH	**PWoH**	**P values**
Age (years): median (IQR)	73.3 (7.7)	80.6 (8.3)	<0.001
Male sex at birth: n (%)	203 (85%)	13 (25%)	<0.001
Comorbidities: n (%) Diabetes Hypertension Cardiovascular Disease COPD	 56 (23%) 165 (69%) 78 (33%) 15 (6.3%)	 7 (13%) 41 (79%) 14 (27%) 2 (3.8%)	 0.110 0.200 0.500 0.600
Comorbidities: n (%)	4.0 (3.0)	6.0 (3.0)	<0.001
Multimorbidity (>3); n (%)	134 (56%)	30 (58%)	0.900
Polypharmacy	70 (29%)	18 (35%)	0.500
Anticholinergic burden score: n (%) 0 1-2 ≥3	 143 (60%) 83 (35%) 13 (5.4%)	 31 (60%) 21 (40%) 0 (0%)	0.200
Benzodiazepine/Z drugs use n (%)	25 (11%)	1 (2.0%)	0.058
Current CD4 cell count: cell/mm^3	592 (383)	-	-
Current CD4/CD8 ratio	0.88 (0.71)	-	-
Nadir CD4 cell count: cell/mm^3	181 (230)	-	-
HIV RNA <50 copies/mL	221 (94%)	-	-
Duration of HIV infection: years	17 (12)	-	-
Yearly income (euro): n (%) <10000	 51 (23%)	 5 (9.6%)	<0.001

10-30000	116 (53%)	35 (67%)	
30-70000	47 (21%)	7 (13%)	
>70000	6 (2.7%)	0 (0%)	
Education, highest degree: n (%)			0.300
None	3 (1.3%)	2 (3.8%	
Primary School (5 yy)	66 (29%)	9 (17%)	
Lower Secondary School (8 yy)	68 (30%)	17 (33%)	
Secondary School (13 yy)	61 (27%)	19 (37%)	
University	29 (13%)	5 (9.6%)	

Table 1. Demographic, clinical, and treatment characteristics of study participants. P values refer to bivariate comparisons between the two groups using Pearson's Chi-squared test, Wilcoxon rank sum test, or Fisher's exact test as appropriate. "PWH", people with HIV; "PWoH", people without HIV; "COPD", Chronic Obstructive Pulmonary Disease.

	PWH	**PWoH**	**P values**
MACE	24 (6.0)	23 (7.3)	>0.900
MACE ≤21	78 (34%)	21 (40%)	0.400
Non-dominant hand GPT: seconds	106 (48)	140 (66)	0.004
Non-dominant hand GPT ≥2SD	54 (24%)	24 (56%)	<0.001
EQ-5D-5L	0.80 (0.20)	0.91 (0.10)	<0.001
CES-D	11 (12)	14 (14)	0.001
CES-D ≥17	30 (26%)	20 (38%)	0.140
HAM-A	8 (12)	9 (8)	0.600
HAM-A based anxiety symptoms			0.048
None	57 (50%)	20 (38%)	
Mild	31 (27%)	24 (46%)	
Severe	27 (23%)	8 (15%)	
PSQI	4.0 (5.0)	7.0 (4.3)	0.001
PSQI ≥5	44 (47%)	39 (75%)	0.003

Table 2. Results of the neurocognitive and patient-reported outcomes tests according to participants' groups. P values refer to Wilcoxon rank sum test; Pearson's Chi-squared test with simulated p-value (based on 2000 replicates). "PWH", people with HIV; "PWoH", people without HIV; "MACE", Mini-Addenbrooke Cognitive Test; "GPT", Grooved Pegboard Test; "EQ-5D-5L", EuroQOL 5-domanin 5-level questionaire; "CES-D", Center for Epidemiologic Studies Depression Scale; "HAM-A", Hamilton Anxiety Rating Scale, "PSQI", Pittsburgh Sleep Quality Index.

Figures

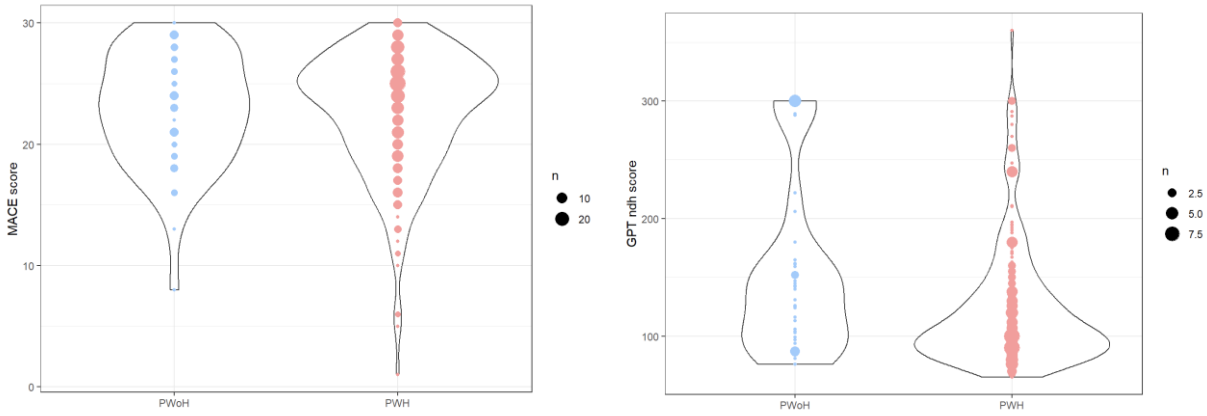

Figure 1. Violin plots showing the individual distribution of Mini-Addenbrooke Cognitive (MACE) and non-dominant hand Grooved Pegboard (ndh-GPT) Tests according to participants' group. Participants with HIV are shown in red, those without HIV in light blue.

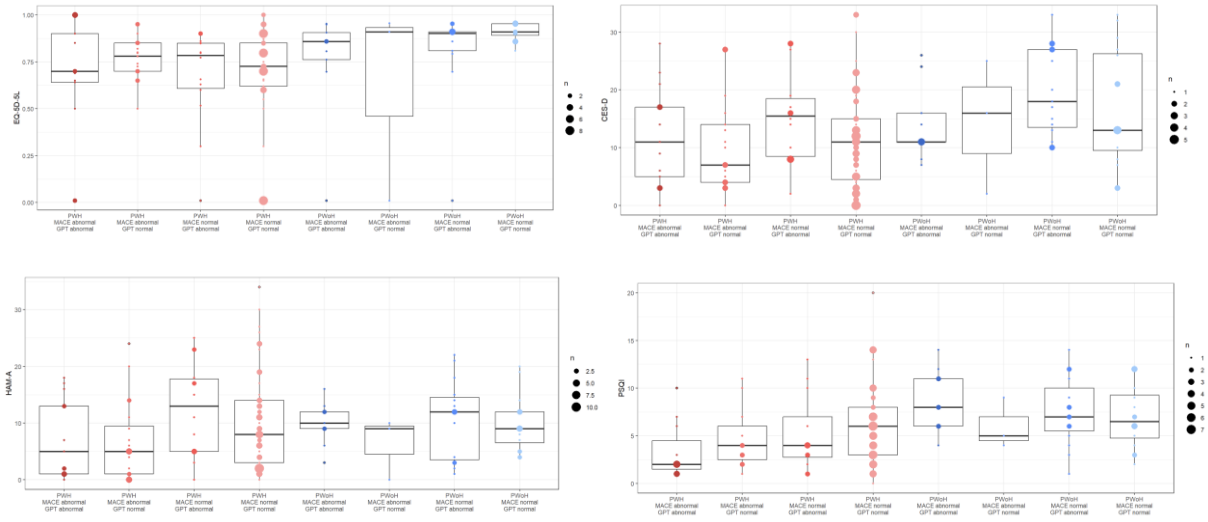

Figure 2. Boxplot reporting the scores in patient-reported outcomes according to mini-Addenbrooke Cognitive and non-dominant hand grooved pegboard tests. The scores of participants with HIV are shown in red, those of persons without HIV in light blue.