Associations between Cognitive Impairment and Patient-reported Measures of Physical/Mental Functioning in Older People Living with HIV

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Running title:
Cognitive impairment and patient-reported outcomes

Key words:
HIV, cognitive impairment, patient-reported outcomes, activities of daily living.

Abstract

Word count: 247 (max 250)

Objectives

Whilst cognitive impairment is frequently reported in HIV-positive individuals and has historically been associated with poorer functional outcomes, the associations between cognitive impairment and patient-reported outcome measures (PROMs) in contemporary cohorts are unclear.

Methods

We tested cognitive function using a computerised battery (CogState™) in 290 HIV-positive and 97 HIV-negative individuals aged ≥50 participating in the POPPY Study. Participants completed questionnaires detailing physical and mental health (SF-36), cognitive function (EACS questions), activities of daily living (Lawton IADL), depression (PHQ-9, CES-D), falls and sexual desire.

Cognitive impairment was defined using the Frascati criteria, global deficit score (GDS) and multivariate normative comparison (MNC). In the HIV-positive group, classification performance of the different definitions of cognitive impairment and dichotomised questionnaire results were calculated.

Results

Prevalence of cognitive impairment in the HIV-positive group was 34.5% (GDS), 30.0% (Frascati) and 22.1% (MNC) with only 2% diagnosed with HIV-associated dementia. In

general, the associations between cognitive impairment and PROMs were weak regardless of the definition used: mean c-statistics were 0.543 (GDS), 0.530 (MNC) and 0.519 (Frascati). Associations were similar using the global T-score to define cognitive impairment. Summary health scores (SF-36) were lower, but only significantly so for those with cognitive impairment identified using MNC, for both mental health (61.4 vs. 75.8, p=0.03) and physical health (60.9 vs. 75.0, p=0.03).

Conclusion

The associations between cognitive impairment and PROMs were weak, possibly because impairment was mild and therefore largely asymptomatic. Further work is needed to elucidate the clinical implications of cognitive impairment in HIV-disease.

Manuscript

Word count (1,987 max 2,000)

Introduction

Despite the development of virologically effective combination antiretroviral therapy (cART), cognitive impairment remains frequently reported in HIV-positive individuals with several different diagnostic classification systems currently in use (1). The implicit assumption is that those with cognitive impairment are more likely to have a higher frequency of mental and physical complaints as part of a general syndrome of ill health. Whilst severe cognitive impairment has previously been associated with impairment of objective measures of everyday functioning, such reports were derived in patient populations with lower CD4+ lymphocyte cell counts than is typically seen in the current era, and in whom cART regimens would now be considered suboptimal (2,3). Additionally, whilst associations with cognitive impairment and patient related outcomes may be statistically significant, the clinical significance of the associations seen are unclear. We aimed to test the hypothesis that cognitive impairment would be associated with other measures of mental and physical dysfunction in a contemporary cohort of HIV-positive individuals.

Methods

Participants

Participants were prospectively enrolled into the Pharmacokinetic and Clinical Observations in People Over Fifty (POPPY) study (ClinicalTrials.gov Identifier: NCT01737047). This multicentre cohort study aims to investigate the effects of ageing and comorbidities on HIV-

positive individuals in the UK and Ireland. Inclusion criteria were documented presence or absence of HIV-infection, self-defined white or Black-African ethnicity, age over 50 years at study entry and the ability to comprehend the study patient information leaflet. Additional inclusion criteria for the HIV-positive participants were probable route of HIV acquisition via sexual exposure (either by male-to-male exposure if white or by heterosexual exposure if white or Black-African). Considerable care was taken to recruit appropriate HIV-negative controls from sexual health clinics and using targeted community advertising and by frequency matching the controls to the HIV-positive participants by gender, ethnicity, sexual orientation and location (in or out London).

The study was approved by the UK National Research Ethics Service (NRES; Fulham, London, UK, reference number 12/LO/1409). All participants provided written informed consent.

Cognitive function testing

All participants underwent cognitive function testing using a computerised battery (CogState™) covering six cognitive domains including visual learning, psychomotor function, visual attention, executive function, verbal learning and working memory (supplementary table 1). This has been shown to be a sensitive diagnostic tool for the assessment of HIV-associated cognitive impairment and allows standardised assessment across sites to be completed in a reasonable amount of time (4).

Raw test scores were log-transformed or arcsine root–transformed where necessary (as per CogState analysis guidelines) and converted into demographically adjusted T-scores (mean: 50, standard deviation: 10) using the HIV-negative control group as the reference

population accounting for age, level of education, gender and ethnicity as appropriate. This method was used as the CogState norms do not account for the range of age of participants in our study. Within each cognitive domain individual T-scores were averaged to calculate the domain T-score and across domains to calculate the global T-score. For all T-scores, higher scores indicate better cognitive function.

Cognitive impairment was defined using published methods for HIV-associated neurocognitive disorder, commonly known as the 'Frascati' criteria (applied to domain T-scores to minimise multiple testing) (5), the global deficit score (GDS) (6) and multivariate normative comparison (MNC) (7). We subdivided those with Frascati-defined impairment, using Lawton Instrumental Activities of Daily Living (IADL) (3), for descriptive purposes only to avoid circularity in assessing the relationship between objective cognitive impairment and subjective symptomology. We also tested a more stringent, combined definition of cognitive impairment whereby participants had to meet the Frascati, GDS *and* MNC criteria to be defined as impaired as well as using a global T-score cut-off of <45. This is equivalent to a change in z-score of 0.5 which is thought to represent a clinically significant difference in cognitive function and has been used as a primary outcome in clinical trials assessing interventions for the management of cognitive impairment in HIV-disease (8).

Patient-reported outcome measures (PROMs)

All participants answered the previously recommended cognitive complaints screening questions (9): 'Do you experience frequent memory loss?'; 'Do you feel that you are slower when reasoning, planning activities, or solving problems?' and 'Do you have difficulties paying attention?'. Participants also completed validated questionnaires detailing: physical

& mental health with the Short Form Health Survey (SF-36) (10); activities of daily living with the IADL (11) and depression with the Patient Depression Questionnaire (PHQ-9) (12) and the Centres for Epidemiologic Studies Depression scale (CES-D) (13). Additionally, falls and sexual desire were assessed by asking 'over the past 28 days have you had any falls?' and 'how often have you worried about minimal sexual desire during the last 4 weeks?' respectively. Outcomes were then dichotomised for further analysis (see supplementary data for details).

Statistical analysis

Demographic differences and comparisons of the prevalence of cognitive impairment between groups were assessed using the Chi-squared test and Wilcoxon rank-sum tests as appropriate. In the HIV-positive group, classification performance of the different definitions of cognitive impairment with dichotomised questionnaire results was assessed using the concordance (or 'c') statistic (equivalent to the area under the receiver operating characteristic curve). This gives an indication of the ability of the different definitions of cognitive impairment to discriminate between those with and without symptoms based on the questionnaire data. Concordance is typically considered reasonable when the c-statistic is >0.7 and strong when >0.8 (14). In addition, sensitivity and specificity were calculated. Optimal global T-score cut-offs were calculated for each PROM by maximising the c-statistic. Differences in physical and mental health between those with and without cognitive impairment were calculated using the Wilcoxon rank-sum tests. All analyses were performed using SAS v9.4 and *R* v3.2.1. Only p-values (two-sided) <0.05 were considered statistically significant.

Results

Participants

Of 387 participants enrolled between January 2013 and September 2014, 290 were HIV-positive and 97 were matched HIV-negative controls (table 1). The HIV-positive group was typical of older patients in care in the UK with a median (IQR) age of 57 (53-62) years and CD4+ cell count of 610 (479-780) cells/μL; 80% of the HIV-positive group were receiving cART. HIV-positive and HIV-negative participants were well matched in terms of demographics such as age, ethnicity and level of educational attainment, however there was a slight preponderance of females in the HIV-negative control group. Recreational drug use was more frequent in the HIV-positive group.

Cognitive function

HIV-positive participants exhibited higher rates of cognitive impairment compared to the HIV-negative control group (table one). In general, cognitive impairment was mild with only 8 (2.8%) and 6 (2.1%) HIV-positive participants fulfilling the Frascati definitions of mild neurocognitive disorder or HIV-associated dementia respectively. Cognitive impairment was not associated with recreational drug use in the last 6 months ($p>0.2$ for cognitive impairment defined with Frascati, GDS or MNC) or duration of known HIV-infection ($p>0.4$). Using a global T-score cut-off of 45 to define cognitive impairment the prevalence was 31.0% vs. 16.5%, OR 2.28 (95% confidence interval 1.29 – 4.24, $p<0.01$) for the HIV-positive vs. HIV-negative groups respectively.

Patient-reported outcome measures (PROMs)

Of the HIV-positive participants with complete data 79 (28.6%) reported frequent memory loss, 105 (38.2%) reasoning difficulties and 79 (28.9%) attention problems, 40 (14.3%) were not fully independent, 76 (28.9%) and 102 (39.1%) were depressed by PHQ-9 and CES-D scoring respectively, 50 (17.9%) reported falls in the last 28 days, and 125 (45.1%) reported minimal sexual desire over the preceding 4 weeks.

In general, the associations between cognitive impairment and PROMs were weak regardless of the method of identification of cognitive impairment used (table 2): mean c-statistics were 0.543 (GDS), 0.530 (MNC) and 0.519 (Frascati). Sensitivity analyses, excluding those with nervous system disorders did not significantly change associations. Using an alternative definition of cognitive impairment, based on a global T-score cut-off of <45, associations with PROMS were not dramatically improved (mean c-statistic 0.560). Even using the combined measure of cognitive impairment (14.1% of HIV-positive and 6.2% of HIV-negative individuals), the associations were weak (mean c-statistic 0.534). Concordance was optimised (mean c-statistic of 0.582) by varying the global T-score threshold by which cognitive impairment was defined (range 41.3-47.6) to maximise both sensitivity and specificity (table 2). The strongest associations between cognitive impairment and symptoms were consistently seen with memory loss and in general the weakest were with sexual desire.

Summary health scores (SF-36) were lower in those with vs. without cognitive impairment, for both mental and physical health (supplementary figure 1) but only significantly so for cognitive impairment identified with MNC.

Discussion

HIV-positive individuals exhibited poorer cognitive function when compared to an appropriate HIV-negative control group. As has been shown previously, the prevalence of cognitive impairment is sensitive to the method used (1). This presents a problem when trying to assess associations with other outcomes which is why we chose to study three commonly used definitions of cognitive impairment, their combination and the global T-score with varying cut-offs.

Regardless of the definition used, cognitive impairment correlated poorly with symptomatology. There are several possible explanations for our observations. Firstly, a lack of a 'gold-standard' method of diagnosing cognitive impairment may have limited our ability to make such observations. To mitigate against this, we have utilised several methods to define cognitive impairment in addition to trying different global T-score thresholds. Secondly, over-reporting of symptoms, whereby patients both with and without cognitive impairment report high rates of symptomatology makes finding associations challenging. Thirdly, the subjectivity of some questions regarding mental state (e.g. memory) makes it difficult to establish a clear relationship between subjective experience and objective measures of cognitive function. Similar reasons may explain the weak associations between cognitive impairment and other PROMs. Our findings are in contrast to previous studies which reported poorer functional outcomes (2,3), which may be explained by differences in populations. Previously published studies tended to have low levels of suppressive cART use and more severe cognitive impairment. Due to the higher frequency of prior AIDS events, participants were more likely to have accumulated disability. Therefore, it is likely that an increased severity of both cognitive impairment and symptomatology resulted in a stronger

association between the two. In contrast, our study population was comparatively well and the vast majority of cognitive impairment was mild with only 2% of the total HIV-positive population meeting the criteria of HIV-associated dementia. However, even using a stringent, combined definition of cognitive impairment, which only captures the most impaired, the associations with PROMS remained weak. This highlights the potential dichotomy between cognitive impairment and other PROMs. Longitudinal study is needed to assess prospectively the clinical impact of mild cognitive impairment.

Limitations

Although great effort was made to recruit a comparable control population, differences between the groups unrelated to HIV-infection may exist. As such, not all the differences in cognitive impairment we report here may be secondary to HIV-disease. To maximise recruitment and generalisability of our findings, exclusion criteria were kept to a minimum. As such, cognitive impairment could have been caused by degenerative neurological diseases other than HIV-disease. However, rates of neurological diagnoses did not differ significantly between the groups therefore rates of cognitive impairment should not be biased towards one group.

Given our study is a 'real-world' sample and subjects were recruited prior to the publication of the INSIGHT START study not every HIV-positive individual was receiving suppressive antiretroviral therapy (15). cART prescribing was in line with national guidelines at the time of enrolment. Those not receiving cART in our study had a median CD4+ cell count of 664 cells/µL, which makes it unlikely that lack of suppression of HIV replication in a minority is skewing our findings. Additionally, given the poor concordance of cognitive impairment with

other PROMs it seems unlikely excluding a small percentage of our sample would dramatically change our results.

Conclusion

The associations between cognitive impairment and patient-reported measures of physical and mental health were weak regardless of the method used to identify those with cognitive impairment. However, the cognitive impairment observed was generally mild and asymptomatic. Further work is needed to understand the clinical implications of this common phenotype in the modern antiretroviral era.

Acknowledgements

POPPY Management Team:
Marta Boffito, Paddy Mallon, Frank Post, Caroline Sabin, Memory Sachikonye, Alan Winston

POPPY Scientific Steering Committee:
Jane Anderson, David Asboe, Marta Boffito, Lucy Garvey, Paddy Mallon, Frank Post, Anton Pozniak, Caroline Sabin, Memory Sachikonye, Jaime Vera, Ian Williams, Alan Winston

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Department of Infection and Population Health, University College London (Ian Williams, Damilola Otiko, Laura Phillips, Rosanna Laverick)

Elton John Centre, Brighton and Sussex University Hospital (Martin Fisher, Amanda Clarke, Jaime Vera, Andrew Bexley, Celia Richardson)

HIV Molecular Research Group, School of Medicine, University College Dublin (Paddy Mallon, Alan Macken, Bijan Ghavani-Kia, Joanne Maher, Maria Byrne, Ailbhe Flaherty)

Homerton Sexual Health Services, Homerton University Hospital (Jane Anderson, Sifiso Mguni, Rebecca Clark, Rhiannon Nevin-Dolan, Sambasivarao Pelluri)

Ian Charleson Day Centre, Royal Free Hospital (Margaret Johnson, Nnenna Ngwu, Nargis Hemat, Martin Jones, Anne Carroll)

Imperial Clinical Trials Unit, Imperial College London (Andrew Whitehouse, Laura Burgess, Daphne Babalis)

St. Mary's Hospital London, Imperial College Healthcare NHS Trust (Alan Winston, Lucy Garvey, Jonathan Underwood, Matthew Stott, Linda McDonald)

St Stephen's Centre, Chelsea and Westminster Hospital (Marta Boffito, David Asboe, Anton Pozniak, Chris Higgs, Elisha Seah, Stephen Fletcher, Michelle Anthonipillai, Ashley Moyes, Katie Deats, Irtiza Syed, Clive Matthews)

POPPY Funders:
The POPPY study is funded from investigator initiated grants from BMS, Gilead Sciences, Janssen, Merck and ViiV Healthcare.

Other acknowledgements:
We acknowledge the use of the NIHR/Wellcome Trust Clinical Research Facility at King's College Hospital.

The research is supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Imperial College Healthcare NHS Trust and Imperial College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the department of Health.

All the POPPY clinical sites in the UK are grateful for NIHR Clinical Research Network (CRN) support.

Funding

The POPPY study is funded from investigator initiated grants from BMS, Gilead Sciences,

Janssen, Merck and ViiV Healthcare.

Some of these data were presented at the 15th European AIDS Clinical Society Conference

2015 as a poster presentation (PE15/9, abstract 242).

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