Published in final edited form as:

J Neurovirol. 2017 October ; 23(5): 725–733. doi:10.1007/s13365-017-0557-5.

Effort and Neuropsychological Performance in HIV-Infected Individuals on Stable Combination Antiretroviral Therapy

Robert Paul^{1,2}, Gina Rhee³, Laurie M. Baker^{1,2}, Florin Vaida⁴, Sarah A. Cooley³, and Beau M. Ances³

¹Department of Psychological Sciences, University of Missouri- St. Louis

²Missouri Institute of Mental Health, St. Louis

³Department of Neurology, Washington University in St. Louis

⁴Department of Family Medicine and Public Health, Division of Biostatistics and Bio-informatics, University of California San Diego

Abstract

The expression of cognitive symptoms associated with HIV varies over time and across individuals. This pattern may reflect transient contextual factors, including the degree of effort exerted by individuals undergoing cognitive testing. The present study examined whether effort corresponds to the expression of persistent HIV-related cognitive impairment among individuals receiving combination antiretroviral therapy (cART). HIV+ individuals ($n = 111$) averaged 48.2 (14.9) years of age 13.0 (2.7) years of education and HIV– individuals ($n = 92$) averaged 34.9 (17.2) years of age and 13.5 (1.9) years of education. Participants completed a neuropsychological battery and a clinically validated measure of effort (Test of Memory Malingering, Trial 1). Results revealed that the vast majority of HIV+ (85%) and HIV– (89%) individuals performed above published guidelines for adequate effort. Furthermore, the expression of cognitive impairment in HIV was not related to effort performance. The results were unchanged when examining HIV+ individuals with and without viral suppression. Finally, disability and disability-seeking status, and a proxy measure of apathy did not correspond to effort levels in HIV+ individuals. These findings suggest that variability in the expression of cognitive impairment in the cART era is unlikely to represent overt effort failures or other confounds unrelated to the disease. Persistent cognitive impairment in HIV likely represents historical and/or ongoing disease mechanisms despite otherwise successful treatment.

Keywords

Test of Memory Malingering (TOMM); effort; HIV; neuropsychological performance; cognition

Introduction

Individuals infected with human immunodeficiency virus (HIV) continue to exhibit cognitive impairment despite suppressive combination antiretroviral therapy (cART; Antinori et al., 2007; Clifford & Ances, 2013; Zhou & Saksena, 2013). The frequency and severity of cognitive impairment related to HIV varies across individuals (Saylor et al., 2016), cohorts (De Francesco et al., 2016; Nightingale et al., 2014), and time (Heaton et al., 2015; Marcotte et al., 2003) among those on stable cART. Variable cognitive performance in HIV-infected (HIV+) individuals is consistent with the pattern of cognitive impairment associated with other chronic immunoregulatory diseases, such as multiple sclerosis (Amato et al., 2001; Lovera & Kovner, 2002; Rao et al., 1991) and systemic lupus erythematosus (Carbotte et al., 1986; Maneeton et al., 2010). However, individual and contextual factors, such as secondary gain, reduced drive, or engagement during completion of challenging cognitive tasks undermine the validity and reliability of testing. This may result in high variability in performance during formal cognitive assessments (Bush et al., 2005; Green et al., 2007; Vickery et al., 2001).

The potential for suboptimal effort to confound cognitive testing is particularly relevant in the assessment of HIV-related cognitive status. HIV+ individuals report reduced motivation to engage in goal-directed activities (Castellon et al., 1998; Hinkin et al., 2001; McIntosh et al., 2015; Kamat et al., 2012; Paul et al., 2005a; Paul et al., 2005b) and high rates of psychiatric comorbidities that could interfere with validity of cognitive assessment (Bing et al., 2001; Chander et al., 2006; Klinkenberg & Sacks, 2004). Early work by Slick and colleagues (2001) reported a correlation between feigned effort and memory impairment in HIV+ individuals with immune suppression (mean CD4 T-cell count = 259). However, the degree of feigned effort was derived from secondary measures intended to identify intentional cognitive failures due to secondary gain. Furthermore, only 60% of the sample was on treatment (zidovudine monotherapy) and 30% were diagnosed with acquired immunodeficiency syndrome (AIDS). Woods et al. (2003) reported adequate performance on an abbreviated measure of effort in mildly impaired HIV+ individuals (70% with AIDS), though the authors cautioned that the abbreviated measure may have lacked the requisite sensitivity to detect suboptimal effort. Further, the study focused on HIV+ individuals with defined cognitive impairment and the results may not generalize to the larger HIV+ population, in which cognitive impairment is not universal (De Francesco et al., 2016; Nightingale et al., 2014).

In contrast to the findings above, Levine et al. (2017) reported a strong link between subjective ratings of effort and neuropsychological performance in HIV+ individuals. In this study, effort was self-rated by HIV+ participants on an analogue scale, and the relationship between self-ratings and severity of neuropsychological impairment was defined using Frascati criteria (Antinori et al., 2007). Consistent with Woods et al. (2003), the vast majority of HIV+ individuals rated themselves as providing adequate effort when completing a demanding neuropsychological battery. However, HIV+ individuals with cognitive impairment were more likely to rate themselves as providing suboptimal effort. A change in HIV-Associated Neurocognitive Disorder (HAND) status correlated with a change in self-defined effort levels. These results suggest that while most HIV+ individuals endorse

optimal effort during testing, those with cognitive impairment perceive themselves as less engaged in the testing process. The study did not include a validated measure of effort as a cross reference, and therefore, it is unclear whether HIV+ cognitively impaired individuals exhibited objective evidence of suboptimal effort.

The purpose of the present study was to examine effort and cognitive performance in a large sample of HIV+ individuals ($n=111$) on stable cART using a common, standardized measure of effort (Test of Memory Malingering Trial 1; Tombaugh, 1996). Effort was compared between HIV+ individuals ($n=111$) and a sample of community-based HIV– individuals ($n=92$). All participants completed cognitive testing to determine whether frequencies of adequate versus suboptimal effort corresponded to cognitive status. We also examined whether effort performance was associated with predictors of secondary gain (e.g., disability-seeking status) or lack of interest in goal-oriented behavior (e.g., apathy).

Methods

Participants

HIV+ participants were recruited from the Washington University School of Medicine (WUSM) Infectious Disease Clinic in Saint Louis, the WUSM AIDS Clinical Trial Group (ACTG), and the Supporting Positive Opportunities with Teens (SPOT). HIV– controls were selected from a community sample that lived within the same general vicinity but were not at increased risk of acquiring HIV. HIV– individuals did not report high frequency of HIV-related risk behaviors (e.g., unprotected anal sex, injection drug use, etc.). Recent use of marijuana, opiates, stimulants (e.g., methamphetamine, cocaine) barbiturates, benzodiazepines, hallucinogens, and alcohol was recorded for all participants. HIV– controls were administered a rapid oral HIV buccal test to confirm seronegative status at the time of neuropsychological testing. Inclusion criteria were as follows: 18 years of age, 8 years of education, ability to read/write in English, and ability to provide informed written consent. Exclusionary criteria for all participants included: history of loss of consciousness > 30 min, seizures, developmental delay, severe psychiatric conditions, or significant depression defined by a score of ≥ 29 on the Beck Depression Inventory-II (BDI-II; Beck et al., 1996).

All HIV+ participants were infected for ≥ 3 months ($M=13.7$ years; $SD=8.6$ years). Lab values including current plasma CD4 T-cell count and plasma HIV RNA levels were collected within 3 months of evaluation. Nadir CD4 T-cell count was recorded as the lowest value from either self-report or review of medical records. All HIV+ individuals were on stable cART and most had an undetectable (< 20 copies/mL) plasma viral load (77%; Table 1). All individuals provided informed consent and were financially compensated for participation. The WUSM Institutional Review Board approved the study. Overall demographics are presented in Table 1.

The Test of Memory Malingering

The Test of Memory Malingering (TOMM; Tombaugh, 1996) is a forced-choice symptom validity measure utilized frequently in clinical practice (Ashendorf et al., 2004; Batt et al.,

2008; Merten et al., 2007; O'Bryant et al., 2007; Sharland & Gfeller, 2007; Teichner & Wagner, 2004; Tombaugh, 1997; Yanez et al., 2006). The test requires participants to discriminate between 50 visual targets from paired foils following two separate learning trials. After a 10-minute delay, participants are administered the recognition trial. Published guidelines identify a score of 45/50 correct on either the first or second learning trial as consistent with adequate effort (Gavett et al., 2005; Hilsabeck et al., 2011; O'Bryant et al., 2008), while a score < 45/50 is defined as suboptimal effort on the TOMM. Prior work suggests similar sensitivity between performance on Trial 1 alone or Trial 1 and Trial 2 (Bauer et al., 2007; Hilsabeck et al., 2011). For the present study, we administered only Trial 1 (T1) of the TOMM to reduce participant burden.

Neuropsychological Battery

A standardized neuropsychological battery was administered to all participants. The tests and the representative cognitive domains were as follows: Learning and Memory: Hopkins Verbal Learning Test-Revised-immediate and delayed recall (HVLT-R; Benedict et al., 1998; Brandt & Benedict, 2001). Psychomotor/Processing Speed: Grooved Pegboard dominant and non-dominant hand (Klove, 1963), Digit Symbol (DSMT; Wechsler, 1997), and Trail Making Test A (Reitan & Davison, 1974). Executive Function: Letter Number Sequencing (LNS; Wechsler, 1997), Trail Making Test B (Reitan & Davison, 1974), verb fluency (Piatt et al., 1999), and letter fluency (FAS; Borkowski et al., 1967). Raw scores were converted to standardized z-scores using published normative standards with adjustments for demographics where applicable (Supplemental Table 1; Benedict et al., 1998, Friedman et al., 2002; Gladsjo et al., 1999; Heaton et al., 2004; Lucas et al., 2005; Norman et al., 2011; Piatt et al., 2004; Wechsler, 1997; Woods et al., 2005; see Supplemental Table 1). Performances were aggregated by domain to create domain-specific Z-scores (Learning and Memory; Psychomotor/Processing Speed; Executive Function). A global measure of cognitive function (NPZ-Global) was determined by averaging the individual domain Z scores. Individuals were classified as cognitively impaired if they had a Z-score of < -1.0 in two or more cognitive domains or a Z-score of < -2.0 in at least one cognitive domain.

Beck Depression Inventory II

The BDI-II (Beck et al., 1996) is a 21-item self-report instrument of depression. The scale is generally consistent with symptoms of depression defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychological Association, 2000). A total score of 0–13 is considered minimal depression, 14–19 is mild, 20–28 is moderate, and 29–63 is severe (Beck et al., 1996). A proxy measure for apathy was determined based on three items from the BDI-II that reflect loss of interest in rewarding/motivated behavior: loss of pleasure, loss of interest, indecisiveness, and loss of interest in sex.

Disability and Disability-Seeking Status

Employment status (i.e., employed, unemployed, retired, or on disability) was collected via self-report for all participants. Disability-seeking status was operationalized as being under the age of 62 and self-reported unemployment in the absence of current disability benefits.

Statistical Analyses

Statistical analyses were conducted using IBM SPSS Statistics software (version 24). Each continuous variable was examined for normality using a Shapiro-Wilk test. TOMM T1 scores significantly deviated from normality (p 's < 0.001). Therefore, TOMM T1 variables were log-transformed for subsequent analyses. Differences in demographic variables (age, sex, education, and race) and BDI-II scores were examined between HIV+ and HIV– individuals using independent samples t tests for continuous variables and chi-square analyses for categorical variables. The duration of infection and immunological factors (nadir and recent CD4 T-cell count) were compared between cognitively impaired and cognitively normal HIV+ participants. These same variables were contrasted between individuals that performed below versus above the recommended cutoff for adequate effort. Variables that significantly differed between groups served as covariates in subsequent analyses.

An independent samples t test (or analysis of covariance [ANCOVA]) was used to determine differences in TOMM T1 scores between the HIV+ and HIV– groups. Differences in frequencies of individuals exhibiting adequate or suboptimal effort on the TOMM T1 were also examined between HIV serostatus groups using a chi-square analysis. Furthermore, differences in mean TOMM T1 as a function of cognitive status were assessed for the HIV+ group using an independent samples t test (or ANCOVA). Relationships between TOMM T1 scores and cognitive performance (NPZ-Global, Learning and Memory, Psychomotor/Processing Speed, and Executive Function) in HIV+ individuals were assessed using Pearson's correlation coefficients.

Additional analyses were conducted to determine whether disability/disability-seeking status or estimated apathy corresponded to suboptimal effort in HIV+ individuals. Differences in apathy scores were examined between groups using an independent samples t test (or ANCOVA). Lastly, a chi-square analysis examined employment status (currently employed [$n = 48$]), disability [$n = 23$], or disability-seeking [$n = 22$]) and TOMM T1 performance.

Results

Relationship between effort and HIV serostatus

Results revealed significant differences in age, sex, and race between HIV serostatus groups (p 's < 0.05), therefore these variables were used as covariates in subsequent analyses examining differences between the HIV+ and HIV– groups. There were no significant differences in recent substance misuse according to serostatus (all p 's > 0.05; Table 1). The HIV+ and HIV– groups did not differ significantly on TOMM T1 scores ($F(1, 201) = 0.08$, $p = 0.78$; *Cohen's d* = −0.04; raw mean difference = 0.15, 95% confidence interval (CI) [−0.94, 1.24]) after controlling for age, sex, and race. Additionally, there were no significant differences in the proportion of individuals who performed above the recommended cutoff for adequate performance between serostatus groups ($X^2(1, n = 203) = 0.86$, $p = 0.35$; HIV+ = 85%, HIV– = 89%; Table 1).

Relationships between effort and cognitive performance

Results comparing the HIV+ individuals that met criteria for cognitive impairment and HIV+ participants without cognitive impairment indicated no significant differences on demographic factors, BDI-II scores, duration of infection, immunological factors, or percent of individuals with undetectable plasma viral load (p 's > 0.05). The subset of HIV+ individuals who met criteria for cognitive impairment ($n = 31$) did not perform significantly worse on the TOMM T1 than HIV+ individuals without cognitive impairment ($n = 80$) ($t(109) = 1.73$, $p = 0.09$; *Cohen's d* = 0.32; Figure 1). Additionally, TOMM T1 scores did not correlate with the NPZ-Global ($r = 0.15$, 95% CI [-0.04, 0.33]; $R^2 = 0.02$; $p = 0.12$; Figure 2), or performance in the Learning and Memory ($r = 0.10$, 95% CI [-0.09, 0.28]; $R^2 = 0.01$; $p = 0.29$), Executive Function ($r = 0.12$, 95% CI [-0.07, 0.30]; $R^2 = 0.01$; $p = 0.20$) or Psychomotor/Processing Speed ($r = 0.10$, 95% CI [-0.09, 0.28]; $R^2 = 0.01$; $p = 0.28$) domains. Half of the HIV- controls who met criteria for suboptimal effort were cognitively impaired. However, only 5% of the HIV- cohort was cognitively impaired.

Relationships between effort, apathy, disability, disability-seeking status, and substance use

Results comparing HIV+ individuals who exhibited adequate performance on the TOMM T1 and HIV+ individuals exhibiting suboptimal performance indicated no significant differences on demographic factors, BDI-II scores, duration of infection, immunological factors, or percent of individuals with an undetectable plasma viral load (p 's > 0.05 ; Table 2). There were no significant differences in apathy scores in HIV+ individuals with adequate and suboptimal effort ($t(109) = -0.55$, $p = 0.58$, *Cohen's d* = -0.15; Table 2). The frequency of suboptimal effort on the TOMM T1 did not significantly differ between HIV+ individuals who were currently employed, on disability, or disability-seeking ($\chi^2(2, 93) = 0.51$, $p = 0.77$, *Cramer's V* = 0.07; Table 2).

Discussion

Results of the present study indicate that HIV+ individuals and HIV- controls provide adequate effort on neuropsychological assessment based on TOMM T1 performance. In both HIV+ and HIV- participants, the vast majority of individuals (85–89%, respectively) exhibited adequate performance on a common clinical measure of effort. The pattern of results did not change based on the severity of cognitive impairment, viral suppression, disability/disability-seeking status, history of substance use, or score on an estimated measure of apathy derived from the BDI-II scale. Considering that most of the HIV+ individuals had an undetectable viral load, the findings suggest that objectively poor effort is an unlikely explanation for persistent cognitive impairment in the cART era.

Our outcomes bolster results reported by Woods et al. (2003) describing a low frequency of poor effort in HIV when examined using an abbreviated effort measure. Importantly, Woods et al. (2003) focused on individuals with at least some degree of cognitive impairment, many of whom were immunosuppressed. The current results provide compelling new data that HIV+ individuals receiving cART exhibit adequate effort on the TOMM T1 during demanding neuropsychological testing, independent of cognitive status, prior or current level

of immunosuppression, or AIDS diagnosis. It is important to note that these results may not generalize to a clinical setting. As such, clinicians are encouraged to consider effort testing, particularly when concerns of secondary gain exist.

Further, while our results appear on the surface to differ from the findings recently reported by Levine et al. (2017), it is important to point out that the overwhelming majority of HIV+ individuals in the latter study defined themselves as providing sufficient effort. It is noteworthy that change in HAND status corresponded to a different level of perceived effort as rated by the HIV+ individuals. The temporal correspondence between these outcomes implies that fluctuations in effort account for within person differences in cognitive impairment over time. However, perceived effort vs. true effort exerted during cognitive testing is difficult to differentiate. That individuals with the greatest degree of cognitive impairment rated themselves as having adequate effort suggests that the relationships between these constructs is complicated and not a linear function. Future studies are needed that examine both perceived and objectively defined effort to help disentangle these dimensions. Relatedly, it is possible that other symptom validity tests (e.g., The Word Memory Test; Green, 2005), use of both trials of the TOMM, and/or use of multiple symptom validity tests, would have greater sensitivity in identifying differences in effort between groups.

The rate of cognitive impairment in our HIV+ sample (28%) is generally consistent with other studies in the cART-era (Heaton et al., 2010; McCutchan et al., 2007; Sacktor et al., 2016). In our HIV- sample, the elevated rate of cognitive impairment (27%) likely reflects our recruitment strategy aimed at matching HIV+ and HIV- groups on demographic and historical factors that could impact cognition (e.g., recruiting from community samples within the same general vicinity). Our groups were well matched on most variables, and when present, differences in demographics were adjusted in the analyses and application of appropriate norms.

A few limitations warrant discussion. Relatively few HIV+ individuals exhibited major cognitive impairment and therefore, the opportunity to examine relationships between more severe cognitive impairment and effort was restricted. Since the introduction of cART, severe cognitive impairment (HIV associated dementia) is rare (Clifford & Ances, 2013; Heaton et al., 2010; Heaton et al., 2011; McArthur et al., 2010). As such, our HIV+ sample adequately reflects the cognitive phenotype in the cART era. Finally, the study was not designed to model an exhaustive list of predictors of poor effort (e.g., fatigue, pain) and the measure of apathy utilized in the current study was derived from a small subset of questions on the BDI-II. It is possible that a formal apathy measure would have detected more severe levels of apathy and a stronger link between apathy and effort. However, the low frequency of poor effort observed in the study suggests that the pattern of results would not have changed with the inclusion of these additional measures.

In summary, results of the present study suggest that the majority of HIV+ individuals provide adequate effort, as assessed by the TOMM T1. This finding is important, as it suggests that persistent cognitive difficulty in the modern era of HIV patient care does not reflect overt or clear alterations in motivated engagement during neuropsychological

assessment. However, vigilance to the integrity of the testing process remains a high priority. Management of internal distractors (e.g., nicotine withdrawal), external distractors (e.g., noises and interruptions), and drift from the test protocol are required to facilitate a valid assessment process. Results from the present study, combined with strong fidelity to the testing process, provides additional support for the application of neuropsychological assessment to delineate the historical and/or ongoing disease mechanisms and functional consequences of HIV-related neurocognitive disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

There are no actual or potential conflicts of interest for any of the authors on this manuscript. Research reported in this publication was supported by the Washington University Institute of Clinical and Translational Sciences grant UL1 TR000448 from the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health (NIH). Funding was also supported by the National Institute of Nursing Research (NR012907, NR014449, and NR012657). The content is solely the responsibility of the authors and does not necessarily represent the official view of the NIH.

References

1. Amato MP, Ponziani G, Siracusa G, Sorbi S. Cognitive dysfunction in early-onset multiple sclerosis: a reappraisal after 10 years. *Archives of Neurology*. 2001; 58(10):1602–1606. [PubMed: 11594918]
2. American Psychological Association. Diagnostic and statistical manual of mental disorders: DSM-IV. Washington, DC: American Psychological Association; 2000.
3. Antinori A, Arendt G, Becker JK, Brew BJ, Byrd DA, Cherner M, Clifford DB, Cinque P, Epstein LG, Goodkin K, Gisslen M, Grant I, Heaton RK, Joseph J, Marder K, Marra CM, McArthur JC, Nunn M, Price RW, Pulliam L, Robertson KR, Sacktor N, Valcour V, Wojna VE. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*. 2007; 69(18):1789–99. [PubMed: 17914061]
4. Ashendorf L, Constantinos M, McCaffrey RJ. The effect of depression and anxiety on the TOMM in community-dwelling older adults. *Archives of Clinical Neuropsychology*. 2004; 19:125–130. [PubMed: 14670385]
5. Batt K, Shores EA, Chekaluk E. The effect of distraction on the Word Memory Test and Test of Memory Malingering performance in patients with a severe brain injury. *Journal of International Neuropsychological Society*. 2008; 14(6):1074–80.
6. Bauer L, O'Bryant SE, Lynch JK, McCaffrey RJ, Fisher JM. Examining the Test of Memory Malingering Trial 1 and Word Memory Test Immediate Recognition as screening tools for insufficient effort. *Assessment*. 2007; 14(3):215–222. [PubMed: 17690378]
7. Beck, AT., Steer, RA., Brown, GK. Manual for the Beck Depression Inventory-II. San Antonio, Texas: Psychological Corporation; 1996.
8. Benedict RHB, Schretlen D, Groninger L, Brandt L. Hopkins Verbal Learning Test–Revised: Normative data and analysis of inter-form and test-retest reliability. *The Clinical Neuropsychologist*. 1998; 12:43–55.
9. Bing EG, Burnam MA, Longshore D, Fleishman JA, Sherbourne CD, London AS, Turner BJ, Eggan F, Beckman R, Vitiello B, Morton SC, Orlando M, Bozzette SA, Ortiz-Barron L, Shapiro M. Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States. *Archives of General Psychiatry*. 2001; 58:721–728. [PubMed: 11483137]
10. Borkowski JG, Benton AL, Spreen O. Word fluency and brain damage. *Neuropsychologia*. 1967; 5:135–140.

11. Brandt, J., Benedict, RHB. Hopkins Verbal Learning Test–Revised: professional manual. Lutz, FL: Psychological Assessment Resources, Inc; 2001.
12. Bush SS, Ruff RM, Tröster AI, Barth JT, Koffler SP, Pliskin NH, Reynolds CR, Silver CH. Symptom validity assessment: practice issues and medical necessity. *Archives of Clinical Neuropsychology*. 2005; 20:419–426. [PubMed: 15896556]
13. Carbotte RM, Denburg SD, Denburg JA. Prevalence of cognitive impairment in systemic lupus erythematosus. *Journal of Nervous and Mental Disease*. 1986; 174(6):357–364. [PubMed: 3711879]
14. Castellon SA, Hinkin CH, Wood S, Yarema KT. Apathy, depression, and cognitive performance in HIV-1 infection. *Journal of Neuropsychiatry*. 1998; 10(3):320–329.
15. Chander G, Himelhoch S, Moore RD. Substance abuse and psychiatric disorders in HIV-positive patients: epidemiology and impact on antiretroviral therapy. *Drugs*. 2006; 66(6):769–789. [PubMed: 16706551]
16. Clifford DB, Ances BM. HIV-associated neurocognitive disorder. *Lancet Infect Dis*. 2013; 13(11): 976–86. [PubMed: 24156898]
17. De Francesco D, Underwood J, Post FA, Vera JH, Williams I, Boffito M, Sachikonye M, Anderson J, Mallon PWG, Winston A, Sabin CA. on behalf of the POPPY study group. Defining cognitive impairment in people-living-with-HIV: the POPPY study. *BMC Infectious Diseases*. 2016; 16:617–625. [PubMed: 27793128]
18. Friedman MA, Schinka JA, Mortimer JA, Borenstein-Graves A. Hopkins Verbal Learning Test – Revised: Norms for elderly African Americans. *The Clinical Neuropsychologist*. 2002; 16(3):356–372. [PubMed: 12607148]
19. Gavett BE, O’Bryant SE, Fisher JM, McCaffrey RJ. Hit rates of adequate performance based on the Test of Memory Malingering (TOMM) Trial 1. *Applied Neuropsychology*. 2005; 12(1):1–4. [PubMed: 15788216]
20. Gladsjo JA, Schuman CC, Evans JD, Peavy GM, Miller SW, Heaton RK. Norms for letter and category fluency: demographic corrections for age, education, and ethnicity. *Assessment*. 1999; 6(2):147–178. [PubMed: 10335019]
21. Green P, Rohling ML, Lees-Haley PR, Allen LM III. Effort has a greater effect on test scores than severe brain injury in compensation claims. *Brain Injury*. 2007; 15(12):1045–1060.
22. Green, P. User’s manual and program (revised 2005). Edmonton, Alberta: Green Publishing; 2005. Word Memory Test for windows.
23. Heaton RK, Clifford DB, Franklin DR Jr, Woods SP, Ake C, Vaida F, Ellis RJ, Letendre SL, Marcotte TD, Atkinson JH, Rivera-Mindt M, Vigil OR, Taylor MJ, Collier AC, Marra CM, Gelman BB, McArthur JC, Morgello S, Simpson DM, McCutchan JA, Abramson I, Gamst A, Fennema-Notestine C, Jernigan TL, Wong J, Grant I. CHARTER Group. HIV– associated neurocognitive disorders persist in the era of potent antiretroviral therapy. *Neurology*. 2010; 75:2087–2096. [PubMed: 21135382]
24. Heaton RK, Franklin DR, Ellis RJ, McCutchan JA, Letendre SL, LeBlanc S, Corkran SH, Duarte NA, Clifford DB, Woods SP, Collier AC, Marra CM, Morgello S, Rivera-Mindt M, Taylor MJ, Marcotte TD, Atkinson JH, Wolfson T, Gelman BB, McArthur JC, Simpson DM, Abramson I, Gamst A, Fennema-Notestine C, Jernigan TL, Wong J, Grant I. CHARTER HNRC Groups. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *Journal of Neurovirology*. 2011; 17:3–16. [PubMed: 21174240]
25. Heaton RK, Franklin DR Jr, Deutsch R, Letendre S, Ellis RJ, Casaletto K, Marquine MJ, Woods SP, Vaida F, Atkinson JH, Marcotte TD, McCutchan JA, Collier AC, Marra CM, Clifford DB, Gelman BB, Sacktor N, Morgello S, Simpson DM, Abramson I, Gamst AC, Fennema-Notestine C, Smith DM, Grant I. CHARTER Group. Neurocognitive change in the era of HIV combination antiretroviral therapy: the longitudinal CHARTER study. *HIV/AIDS*. 2015; 60:473–480.
26. Heaton, RK., Miller, SW., Taylor, MJ., Grant, I. Revised comprehensive norms for an expanded Halstead-Reitan Battery: Demographically adjusted neuropsychological norms for African American and Caucasian adults. Lutz, FL: PAR; 2004.

27. Hilsabeck RC, Gordon SN, Hietpas-Wilson T, Zartman AL. Use of Trial 1 of the Test of Memory Malingering (TOMM) as a screening measure of effort: suggested discontinuation rules. 2011; 25(7):1228–1238.
28. Hinkin CH, Castellon SA, Atkinson JK, Goodkin K. Neuropsychiatric aspects of HIV infection among older adults. *Journal of Clinical Epidemiology*. 2001; 54:S44–S52. [PubMed: 11750209]
29. Kamat R, Woods SP, Marcotte TD, Ellis RJ, Grant I. HIV Neurobehavioral Research Program (HNRP) Group. Implications of apathy for everyday functioning outcomes in persons living with HIV infection. *Archives of Clinical Neuropsychology*. 2012; 27(5):520–531. [PubMed: 22705481]
30. Klinkenberg WD, Sacks S. Mental disorders and drug abuse in persons living with HIV/AIDS. *AIDS Care*. 2004; 16(1):22–42.
31. Klove, H. Clinical neuropsychology. In: Forster, FM., editor. *Medical Clinics of North America*. New York: Saunders; 1963.
32. Levine AJ, Martin E, Sacktor N, Munro C, Becker J. Multicenter AIDS Cohort Study-Neuropsychology Working Group. Predictors and Impact of Self-Reported Suboptimal Effort on Estimates of Prevalence of HIV-Associated Neurocognitive Disorders. *JAIDS Journal of Acquired Immune Deficiency Syndromes*. 2017 Jun 1; 75(2):203–10. [PubMed: 28328547]
33. Lovera J, Kovner B. Cognitive impairment in multiple sclerosis. *Current Neurology and Neuroscience Reports*. 2012; 12(5):618–627. [PubMed: 22791241]
34. Lucas JA, Ivnik RJ, Smith GE, Ferman TJ, Willis FB, Petersen RC, Graff-Ranford NR. Mayo's older African American normative studies: Norms for Boston Naming Test, Controlled Oral Word Association, Category Fluency, Animal Naming, Token Test, WRAT-3 Reading, Trail Making Test, Stroop Test, and Judgment of Line Orientation. *The Clinical Neuropsychologist*. 2005; 19:243–269.
35. Maneeton B, Maneeton N, Louthrenoo W. Cognitive deficit in patients with systemic lupus erythematosus. *Asian Pacific Journal of Allergy and Immunology*. 2010; 28:77–83. [PubMed: 20527520]
36. Marcotte TD, Deutsch R, McCutchan JA, Moore DJ, Letendre S, Ellis RJ, Wallace MR, Heaton RK, Grant I. Prediction of incident neurocognitive impairment by plasma HIV RNA and CD4 levels early after HIV seroconversion. *Archives of Neurology*. 2003; 60:1406–1412. [PubMed: 14568811]
37. McArthur JC, Steiner J, Sacktor N, Nath A. Human immunodeficiency virus-associated neurocognitive disorders: mind the gap. *Annals of Neurology*. 2010; 67:699–714. [PubMed: 20517932]
38. McCutchan JA, Wu JW, Robertson K, Koletar SL, Ellis RJ, Cohn S, Taylor M, Woods S, Heaton R, Currier J, Williams PL. HIV suppression by HAART preserves cognitive function in advanced, immune-reconstituted AIDS patients. *AIDS*. 2007; 21(9):1109–1117. [PubMed: 17502721]
39. McIntosh RC, Rosselli M, Uddin LQ, Antoni M. Neuropathological sequelae of human immunodeficiency virus and apathy: a review of neuropsychological and neuroimaging studies. *Neuroscience and Biobehavioral Reviews*. 2015; 55:147–164. [PubMed: 25944459]
40. Merten T, Bossink L, Schmand B. On the limits of effort testing: symptom validity tests and severity of neurocognitive symptoms in non-litigant patients. *Journal of Clinical and Experimental Neuropsychology*. 2007; 29(3):308–18. [PubMed: 17454351]
41. Nightingale S, Winston A, Letendre S, Michael BD, McArthur JC, Khoo S, Solomon T. Controversies in HIV-associated neurocognitive disorders. *Lancet Neurol*. 2014; 13(11):1139–1151. [PubMed: 25316020]
42. Norman MA, Moore DJ, Taylor M, Franklin D Jr, Cysique L, Ake C, Lazarretto D, Vaida F, Heaton RK. HNRC Group. Demographically corrected norms for African Americans and Caucasians on the Hopkins Verbal Learning Test–Revised, Brief Visuospatial Memory Test–Revised, Stroop Color and Word Test, and Wisconsin Card Sorting Test 64-card version. *Journal of Clinical and Experimental Neuropsychology*. 2011; 33(7):793–804. [PubMed: 21547817]
43. O'Bryant SE, Finlay C, O'Jile JR. TOMM performance and self-reported symptoms of depression and anxiety. *Journal of Psychopathology and Behavioral Assessment*. 2007; 29(2):111–114.

44. O'Bryant SE, Gavett BE, McCaffrey RJ, O'Jile JR, Huerkamp JK, Smitherman TA, Humphreys JD. Clinical utility of Trial 1 of the Test of Memory Malingering (TOMM). *Applied Neuropsychology*. 2008; 15:113–116. [PubMed: 18568603]
45. Paul R, Brickman AM, Navia B, Hinkin C, Malloy PF, Jefferson AL, Cohen RA, Tate DF, Flanigan TP. Apathy is associated with volume of the nucleus accumbens in patients infected with HIV. *Journal of Neuropsychiatry and Clinical Neuroscience*. 2005a; 17(2):167–171.
46. Paul R, Flanigan TP, Tashima K, Cohen R, Lawrence J, Alt E, Tate D, Ritchie C, Hinkin C. Apathy correlates with cognitive function but not CD4 status in patients with human immunodeficiency virus. *Journal of Neuropsychiatry and Clinical Neuroscience*. 2005b; 17(1):114–8.
47. Piatt AL, Fields JA, Paolo AM, Tröster AI. Action (verb naming) fluency as an executive function measure: convergent and divergent evidence of validity. *Neuropsychologia*. 1999; 37:1499–1503. [PubMed: 10617270]
48. Piatt AL, Fields JA, Paolo AM, Tröster AI. Action verbal fluency normative data for the elderly. *Brain and Language*. 2004; 89:580–583. [PubMed: 15120548]
49. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology*. 1991; 41(5):685–691. [PubMed: 2027484]
50. Reitan, RM., Davison, LA. *Clinical Neuropsychology: current status and applications*. New York: John Wiley; 1974.
51. Sacktor N, Skolasky RL, Seaberg E, Munro C, Becker JT, Martin E, Ragin A, Levine A, Miller E. Prevalence of HIV-associated neurocognitive disorders in the Multicenter AIDS Cohort Study. *Neurology*. 2016; 86(4):334–340. [PubMed: 26718568]
52. Saylor D, Dickens AM, Sacktor N, Haughey N, Slusher B, Pletnikov M, Mankowski JL, Brown A, Volsky DJ, McArthur JC. HIV-associated neurocognitive disorder – pathogenesis and prospects for treatment. *Nat Rev Neurol*. 2016; 12(4):234–248. [PubMed: 26965674]
53. Sharland MJ, Gfeller JD. A survey of neuropsychologists' beliefs and practices with respect to the assessment of effort. *Archives of Clinical Neuropsychology*. 2007; 22:213–223. [PubMed: 17284353]
54. Slick DJ, Hinkin CH, van Gorp WG, Satz P. Base rate of a WMS-R malingering index in a sample of non-compensation-seeking men infected with HIV-1. *Applied Neuropsychology*. 2001; 8(3):185–189. [PubMed: 11686655]
55. Teichner G, Wagner MT. The Test of Memory Malingering (TOMM): normative data from cognitively intact, cognitively impaired, and elderly patients with dementia. *Archives of Clinical Neuropsychology*. 2004; 19(3):455–464. [PubMed: 15033228]
56. Tombaugh, TN. *Test of Memory Malingering (TOMM)*. New York: Multi-Health Systems, Inc; 1996.
57. Tombaugh TN. The Test of Memory Malingering (TOMM): normative data from cognitively intact and cognitively impaired individuals. *Psychological Assessment*. 1997; 9:260–268.
58. Vickery CD, Berry DTR, Inman TH, Harris MJ, Orey SA. Detection of inadequate effort on neuropsychological testing: a meta-analytic review of selected procedures. *Archives of Clinical Neuropsychology*. 2001; 16:45–73. [PubMed: 14590192]
59. Wechsler, D. *WAIS-III administration and scoring manual*. San Antonio, TX: Psychological Corporation; 1997.
60. Woods SP, Conover E, Weinborn M, Rippeth JD, Brill RM, Heaton RK, Grant I. HIV Neurobehavioral Research Center (HNRC) Group. Base rate of Hiscock Digit Memory Test failure in HIV-associated neurocognitive disorders. *The Clinical Neuropsychologist*. 2003; 17(3):383–389. [PubMed: 14704888]
61. Woods SP, Scott JC, Sires DA, Grant I, Heaton RK, Tröster AI. HIV Neurobehavioral Research Center Group. Action (verb) fluency: Test-retest reliability, normative standards, and construct validity. *Journal of the International Neuropsychological Society*. 2005; 11(4):408–415. [PubMed: 16209421]
62. Yanez YT, Fremouw W, Tennant J, Strunk J, Coker K. Effects of severe depression on TOMM performance and disability-seeking outpatients. *Archives of Clinical Neuropsychology*. 2006; 21:161–165. [PubMed: 16226428]

63. Zhou L, Saksena NK. HIV associated neurocognitive disorders. Infect Dis Rep. 2013; 5(Suppl 1):e8.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 1.

Raw TOMM T1 score for HIV- individuals, cognitively normal HIV+ individuals, and cognitively impaired HIV+ individuals. Cognitive impairment was defined as a Z-score < -1.0 in two or more cognitive domains, or a Z-score of < -2.0 in at least cognitive domain. No significant differences existed between the three groups.

Figure 2.

Relationship between TOMM T1 and NPZ-Global in HIV+ Individuals. A majority of HIV+ participants provided optimal effort. No significant relationship was seen between cognition and effort for HIV+ individual

Table 1**HIV+ and HIV– Group Characteristics**

	HIV+ (n = 111)	HIV– (n = 92)	p value
Mean age (years) (SD) **	48.15 (14.87)	34.87 (17.20)	0.00
Male sex, n (%) **	80 (72%)	43 (47%)	0.00
African American race, n (%) *	79 (71%)	52 (57%)	0.03
Mean education ^a (years) (SD)	13.00 (2.71)	13.50 (1.87)	0.12
Mean BDI-II (SD) (n = 201)	8.61 (6.74)	7.48 (6.77)	0.27
Mean duration of infection (years) (SD)	13.68 (8.64)		
Median CD4-T cell count (cells/μl) (IQR)	602 (424–884)	-	-
Median nadir CD4 T-cell count (cells/μl) (IQR)	188 (59–322)	-	-
Undetectable plasma viral load, n (%)	85 (77%)	-	-
Mean NPZ-Global score (SD)	–0.36 (0.58)	–0.40 (0.63)	0.65
Mean Psychomotor/Processing Speed Z score (SD)	–0.11 (0.76)	–0.28 (0.79)	0.12
Mean Executive Function Z score (SD)	–0.30 (0.69)	–0.14 (0.77)	0.12
Mean Learning and Memory Z score (SD)	–0.98 (1.01)	–1.16 (0.99)	0.21
Raw Mean TOMM T1 score (SD)	47.4 (3.1)	47.4 (3.9)	0.91
TOMM T1 score <45, n (%)	17 (15%)	10 (11%)	0.35
Substance use past six months, n (%)			
Marijuana	36 (32%)	38 (41%)	0.19
Cocaine	6 (5%)	9 (10%)	0.24
Methamphetamine	4 (4%)	2 (2%)	0.55
Barbiturates	2 (2%)	0 (0%)	0.20
Opiates	3 (3%)	6 (7%)	0.19
Benzodiazepines	6 (5%)	4 (4%)	0.73
Alcohol	64 (58%)	50 (54%)	0.64
Hallucinogens	2 (2%)	0 (0%)	0.20
Cognitively Normal	80 (72%)	67 (73%)	
Cognitively Impaired	31 (28%)	25 (27%)	

* $p < 0.05$;** $p < 0.01$

SD = Standard Deviation; IQR = Interquartile Range; NPZ-Global = composite neuropsychological summary Z-score; BDI-II = Beck Depression Inventory-II

Table 2

Characteristics of Individuals Based on TOMM T1 Performance

	HIV +			HIV – controls		
	Adequate Effort (n = 94, 85%)	Suboptimal Effort (n = 17, 15%)	p value	Adequate Effort (n = 82, 89%)	Suboptimal Effort (n = 10, 11%)	p value
Age; mean (SD)	48.40 (14.88)	46.76 (15.21)	0.68	35.24 (17.63)	31.80 (13.32)	0.55
Male sex (%)	67 (71%)	13 (76%)	0.66	38 (46%)	5 (50%)	0.88
African American (%)	65 (69%)	14 (82%)	0.27	44 (54%)	8 (80%)	0.11
Education; mean (SD)	13.12 (2.83)	12.28 (1.80)	0.25	13.56 (1.91)	12.90 (1.37)	0.29
BDI-II (n =201)	8.70 (6.69)	8.12 (7.18)	0.74	7.31 (6.56)	8.80 (8.52)	0.52
Duration of infection	14.14 (8.70)	11.09 (8.10)	0.18	-	-	-
CD4-T cell count (cells/ μ l); median (IQR)	635 (459, 896)	438 (331, 745)	0.21	-	-	-
Nadir CD4 (cells/ μ l); median (IQR)	193 66, 333)	112 (28, 245)	0.30	-	-	-
Undetectable plasma viral load (%)	73 (80)	12 (71)	0.70	-	-	-
BDI-II apathy score	1.91 (1.86)	1.65 (1.69)	0.58	1.44 (1.67)	1.40 (1.26)	0.95
NPZ-Global score	-0.33 (0.57)	-0.54 (0.61)	0.16	-0.35 (0.63)	-0.71 (0.45)	0.12
Employed (%)	42 (44.7)	6 (35.3)		55 (67.1%)	6 (60.0%)	
On disability (%)	19 (20.2)	4 (23.5)		2 (2.4%)	0 (0.0%)	
Disability seeking (%)	18 (19.1)	4 (23.5)		16 (19.5%)	4 (40.0%)	
Cognitively Normal (%)	69 (73)	11 (65)		69 (84%)	5 (50%)	
Cognitively Impaired (%)	25 (27)	6 (35)		13 (16%)	5 (50%)	