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Planning Deficits in HIV-Associated Neurocognitive Disorders: Component Processes, Cognitive Correlates, and Implications for Everyday Functioning

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Abstract

Executive dysfunction remains among the most prevalent cognitive domains impaired in persons with HIV-associated neurocognitive disorders (HAND). However, little is known specifically about the cognitive architecture or everyday functioning implications of planning, which is an aspect of executive functions involving the identification, organization, and completion of sequential behaviors toward the accomplishment of a goal. The current study examined these issues using the Tower of London^{DX} in 53 individuals with HAND, 109 HIV-infected persons without HAND, and 82 seronegative participants. The HAND+ group performed significantly more poorly than HIV-infected individuals without HAND on number of correct moves, total moves, execution time, time violations, and rule violations. Within the HIV+ group as a whole, greater total move scores and rule violations were most strongly associated with executive dysfunction. Of clinical relevance, elevated total moves and rule violations were significant, independent predictors of self-reported declines in instrumental activities of daily living and unemployment status in HIV. These results suggest that planning accuracy, efficiency, and rule-bound control are impaired in HAND, and may meaningfully affect more cognitively complex aspects of everyday living.

Keywords

Planned behavior; executive functioning; employment status; activities of daily living; higher order processes

Although severe forms of HIV-associated Neurocognitive Disorders (HAND) have decreased since the widespread use of combination antiretroviral therapies (cART) in the mid-1990's (Ances & Clifford, 2008), executive dysfunction remains highly prevalent in HAND (Heaton et al., 2011; Reger, Welsh, Razani, Martin, & Boone, 2002). In fact, among individuals with well-managed HIV disease, rates of impairment in executive functions may have actually increased relative to other cognitive domains, such as information processing speed, in the cART era (Heaton et al., 2011). All told, impaired executive functions are detected in approximately 50% of HIV+ individuals with neurocognitive impairment (Heaton et al., 2011). Executive dysfunction can emerge early in the course of infection

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(Moore et al., 2011), and the severity of impairment tends to increase with advancing HIV disease (Reger et al., 2002). Although there is no single prototypical pattern of neurocognitive impairment in HIV, it has been argued that executive dysfunction may be a cardinal feature of HAND in the cART era (Dawes et al., 2008). Executive functions rely heavily on the integrity of frontostriatal circuits (Mega & Cummings, 1994), which are commonly affected by HIV-associated neuropathologies (Everall et al., 2005). In HIV-infected populations, deficits have been observed on a variety of different executive functions, including measures of abstraction (Heaton et al., 1995), response inhibition (Tozzi et al., 1999), cognitive flexibility (Carter et al., 2003), and decision-making (Martin et al., 2004). These deficits are clinically meaningful in that executive dysfunction is among the strongest predictors of a wide range of everyday functioning complications, including laboratory functional skills (e.g., medication management; Heaton et al., 2004), medication non-adherence (e.g., Hinkin et al., 2004), automobile driving (Marcotte et al., 2004), and vocational status (e.g., van Gorp et al., 1999; Rabkin et al., 2004).

Despite significant advances in our knowledge about the prevalence, clinical correlates, and functional impact of HIV-associated executive dysfunction over the past 20 years, we still know very little about the construct of *planning*. Planning is a fundamental subcomponent of executive functions that describes the complex and multifaceted process involving the identification, organization and integration of the steps required to meet a particular goal (Cohen, Bronson, & Casey, 1995). In addition to these core requirements, successful planning also depends on a variety of related capacities such as generating and selecting between alternatives, understanding sequential ideas, and exercising impulse control. Memory functions, psychomotor speed, and sustained attention may also be required (Lezak, 2004). Failure of any of these subcomponents could result in impairments on laboratory or naturalistic planning tasks. While several planning paradigms exist, the oft-used "tower-transfer" tasks, in which a participant must replicate target structures by sequentially moving balls between three pegs, have been shown to sensitively identify differences in planning and problem solving (e.g., Unterrainer & Owen, 2006). These planning tasks (e.g., Tower of London – Drexel version or TOL^{DX}; Culbertson & Zilmer, 2001) are based upon Shallice's (1982) information-processing model of prefrontal functioning. This model includes a higher-order Supervisory Attentional System (SAS) that is used to select and monitor behavior in problem-solving tasks when automatic processes (e.g., schema) are inadequate to meet task demands. In contrast with more naturalistic planning paradigms (e.g., Multiple Errands Test; MET; Alderman et al., 2003), tower-transfer tasks specifically assess a participant's ability to solve *novel* problems that require advance planning of sequences of progressively higher numbers of moves in order to replicate the target structure. Although the nomenclature and operationalization of "planning" varies somewhat across studies, common metrics include the number of moves that a participant makes to solve a problem, initial planning speed (i.e., before a move is made), solution execution speed (i.e., time from the first move until the last move), and solution efficiency (e.g., a ratio of planning speed to accuracy). At the neural level, planning processes recruit the prefrontal regions bilaterally (particularly the anterior medial and dorsolateral systems), as well as the basal ganglia and posterior parietal cortex (Koechlin et al., 2002; Newman et al., 2003; Stuss et al., 2002). Planning processes underlie the successful completion of a variety of important everyday functioning outcomes relevant to the management of HIV infection, including compliance with complex medication regimens (Waldrop-Valverde et al., 2010). Planning has also been implicated in high-risk HIV transmission-related behaviors, such as sharing injection drug use materials (Severtson et al., 2009).

Only a few studies have investigated planning abilities in HIV, and even within the tower-transfer paradigm, existing studies have defined and measured planning differently. Across

studies, large disparities exist between the measures examined (e.g., problem complexity vs. solution efficiency) and the level of demand placed on related abilities (e.g., working memory) in order to solve each problem. Two papers in the pre-cART era provided evidence that HIV+ individuals (particularly those with symptomatic illness) have poorer planning abilities versus seronegative comparison subjects, and that these differences may be moderated by the cognitive demands of the planning task. Sahakian and colleagues (1995) found that HIV+ individuals were both less accurate and less efficient than healthy participants when planning and executing a sequence of cognitive or motor actions. Planning deficits were more pronounced when the minimum sequence required to complete the task was extended beyond five moves. In the other pre-cART study, Bartok and colleagues (1997) intensified the working memory demands of their planning task by requiring participants to memorize the target configuration before beginning each trial. Symptomatic HIV+ substance users solved significantly fewer problems relative to HIV+ asymptomatic and HIV- substance users, though the groups did not significantly differ from each other in the total number of moves (Bartok et al., 1997). The two studies in the cART-era reported planning deficits in a single sample of HIV+ individuals as measured by the computerized Cambridge Neuropsychological Test Automated Battery (CANTAB). Relative to a normative standard, individuals with HIV were impaired on indices of planning accuracy and pre-trial planning time, although task completion time fell within normal limits (Judd et al., 2005). At two-year follow-up, significant improvement was noted particularly in individuals who were not depressed, though whether this reflects improvement beyond the expected effects of practice is not clear (Gibbie et al., 2006). Correlational analyses in HIV-infected samples in the cART era show that planning is associated with other aspects of executive functions (Gupta et al., 2010), and executively demanding aspects of episodic memory, including prospective (Woods et al., 2007) and source (Morgan et al., 2009) memory. HIV-associated deficits in planning might also be associated with important everyday functioning outcomes, including vocational functioning, medication management, and household activities (Waldrop-Valverde et al., 2010). Notably, individuals with HAND may fail social and activity planning tasks at higher rates than a variety of other everyday living tasks (e.g., financial management; Benedict et al., 2000).

The present study extends this relatively small and heterogeneous literature by examining the component processes, cognitive correlates, and everyday functioning implications of planning in a large, well-characterized sample of HIV-infected individuals using a standardized clinical task. As noted above, planning is a multifaceted construct containing multiple subcomponents at which failure can impair performance (Berg et al., 2010). However, several key component processes of planning (e.g., impulsivity, rule-bound control) have not yet been examined in detail in the cART era. The current study investigated the relationship between these component processes of planning in HIV-infected persons with and without HAND as compared to seronegative individuals using a standardized test of higher-order problem solving ability (i.e., the Tower of London^{DX}) administered within a larger neuropsychological battery containing measures of attention, memory, motor, and executive abilities, along with assessments of important everyday functioning outcomes (e.g., employment). An array of clinical studies have indicated that the TOL^{DX} is sensitive to a complex set of cognitive processes, including planning, working memory, mental flexibility, attention allocation, and response inhibition (Culbertson & Zillmer, 2001). We hypothesized that HAND would be associated with lower scores on planning indices of efficiency, speed, and impulsivity, which in turn would be associated with executive dysfunction, more severe HIV disease, and poorer everyday functioning.

Method

Participants

The current study was approved by the institution's human research protections program and all participants provided written, informed consent. A total of 244 volunteers were recruited from the San Diego community and local HIV clinics for this study. Participants' serostatus was determined by enzyme-linked immunosorbent assays and confirmed by a Western Blot test, resulting in a sample of 162 persons infected with HIV and 82 seronegative comparison participants. Within the HIV+ group, participants were classified as either HAND– (N = 109) or HAND+ (N = 53) in accordance with Frascati research guidelines (see Antinori et al., 2007) based on a diagnosis derived from a comprehensive neuromedical, psychiatric, and standardized neurocognitive assessment. A diagnosis of HAND required evidence of impairment (i.e., 1+*SD* below the normative mean) in ≥ 2 neurocognitive domains as determined by blinded clinical ratings (Woods et al., 2004). Scores on the planning task were not used in the determination of HAND. Domains and associated measures contributing to the determination of HAND included executive functions (Trail Making – Test Part B [TMT; Reitan & Wolfson, 1985]; Action Fluency Test [Woods et al., 2005]), learning (California Verbal Learning Test – Second Edition [CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000] Trials 1–5; Logical Memory I subtest of the Weschler Memory Scale-III [WMS-III; Psychological Corporation, 1997]), memory (CVLT-II Recognition Discriminability; WMS-III Logical Memory II), motor (Grooved Pegboard; Kløve,1963), attention (CVLT-II Trial 1 total; Digit Span subtest of the Wechsler Adult Intelligence Scale [WAIS-III; Psychological Corporation, 1997]), and processing speed (Trail Making Test – Part A [TMT; Reitan & Wolfson, 1985]). Individuals with histories of severe psychiatric illness (e.g., schizophrenia or bipolar disorder), neurological disease (e.g., seizure disorders, closed head injuries with loss of consciousness greater than 15 minutes, CNS opportunistic infection), or verbal IQ estimates < 70 (based on the Wechsler Test of Adult Reading; Psychological Corporation, 2001) were excluded from the analysis. Additionally, substance-related exclusion criteria included meeting *Diagnostic and Statistical Manual-IV* (DSM-IV) criteria for current (i.e., within the last 30 days) substance abuse or dependence as determined by Composite International Diagnostic Interview (Version 2.1; World Health Organization, 1998), a urine toxicology screen positive for illicit substances (aside from marijuana), or a Breathalyzer test positive for alcohol on the day of evaluation. Hepatitis C (HCV) serostatus was determined using standard clinical antibody detection.

All groups were comparable on demographic factors and rates of current major depressive disorder (ps > 0.10; see Table 1). However, the HIV- sample had lower rates of lifetime major depressive disorder (p < .01) as measured by the CIDI and lower self-reported mood disturbance on the Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1981) questionnaire (p = .03). Rates of lifetime alcohol, cannabis, methamphetamine, cocaine, and other illicit substances were comparable between the groups, though opioid dependence was *lower* in HAND+ participants (p < .05). Rates of HCV infection significantly differed between the three groups (p < .05), and were highest in the HAND+ group. However, rates did not significantly differ between the HIV+ samples (HAND+ and HAND-; ps > .10) or between the HIV- and HAND- samples (p > .10). The HIV+ samples did not differ in estimated duration of infection, AIDS diagnoses, cART status, current or nadir CD4 count, or viral load (ps > .10).

Materials and Procedure

Tower of London - Drexel Version—All participants completed the Tower of London – Drexel Version (TOL^{DX}; Culbertson & Zillmer, 2001). Though similar to the original Tower of London test developed by Shallice (1982), the TOL^{DX} offers several modifications

in both administration and scoring, including the addition of more difficult items, the elimination of repeated trials for failed problems (to decrease possible practice effects), and 6- and 7-move test problem configurations (for more detailed information, see Culbertson & Zillmer, 2001). Test administration, recording, and scoring procedures for this study followed guidelines outlined by the TOL^{DX} Technical Manual (Culbertson & Zillmer, 2001). The TOL^{DX} provides scores for seven different variables which represent different aspects of an individual's planning performance, including: total correct, total moves, total problem solving time, initiation time and execution time, time violations, and rule violations. Per the authors of the task (Culbertson & Zillmer, 2001), these represent different but overlapping aspects of executive planning and problem-solving. For the purposes of the current study, five indices reflecting accuracy, efficiency, flexibility, and speed were selected for analysis (Total Correct, Total Moves, Initiation Time, Execution Time, and Rule Violations), as these were considered to be meaningful and somewhat distinct aspects of performance. Raw scores for each variable were used in data analyses in order to keep all cognitive variables on the same metric when examining their intercorrelations. Additionally, some recent studies have suggested that raw scores (uncorrected by demographics) may be more strongly associated with measures of functional status (Silverberg & Millis, 2009), which was a major aim of this investigation.

General Neuropsychological Assessment—The neuropsychological battery was comprised of standardized clinical and research tests. The tests delineated above (see *Participants* section) were used to make the determination of HAND in individuals with HIV. The following measures were used to investigate potential relationships between planning abilities and neurocognitive performance across domains. These domains and their associated tests included the following: (a) retrospective learning and memory (CVLT-II; WMS-III Logical Memory subtest); (b) speed of information processing (TMT Part A; (c) executive functions (TMT Part B; action fluency test); (d) attention/working memory (Digit Span subtest of the WAIS-III; trial 1 total on the CVLT-II); (e) motor skills (Grooved Pegboard Test). Raw scores were converted into population-based *z*-scores derived from the HIV+ ($N = 162$) sample, then averaged across tests in each domain to create composite *z*-scores for each neurocognitive domain.

Everyday Functioning Assessment—Participants also completed a modified version of the Lawton and Brody Activities of Daily Living Scale (Lawton & Brody, 1969). This instrument is designed to assess participants' current functioning and identify declines relative to their best ever level of functioning in areas related to routine daily tasks. Participants rated each item on a three (0–2) or four (0–3) point scale, with higher scores indicating poorer functioning. Modified from the procedure cited in Vigil et al. (2008), activities were classified as either instrumental (i.e., medication management, finance management, social and activity planning, childcare, transportation, telephone, groceries, cooking, shopping) or physical (i.e., bathing, dressing, home repairs, housekeeping, laundry) activities of daily living. Those who reported declines in two or more domains were classified as impaired in either instrumental (25% of the HIV+ sample) or physical activities of daily living (22% of the HIV+ sample). Current occupational status was determined as part of a semi-structured neurobehavioral interview. Each participant was classified as either 'employed' (n= 50) or 'unemployed' (n=95, which included 50 persons on disability). Students ($n = 6$), part-time workers ($n = 7$), and retired ($n = 13$) individuals were excluded from employment-related analysis.

Data Analysis—Due to the non-normality of the TOL^{DX} raw scores (Shapiro-Wilk test ps < 0.01), all primary between-group analyses were conducted using nonparametric tests. Between-group post-hoc analyses were restricted to the HAND+ group to minimize the

probability of committing a Type I error. First, a series of omnibus and follow-up pairwise Wilcoxon Ranked Sum tests and Cohen's *d* statistics were used to compare TOL^{DX} variables across HIV-, HAND-, and HAND+ groups. Next, a planned series of regressions were conducted to examine the unique effects of study group on TOL^{DX} variables, accounting for the effects of potentially confounding factors on which any of the groups differed (i.e., lifetime MDD, Hepatitis C status). A separate series of planned regressions were conducted in the HIV+ group in order to determine the relationships between planning component processes and population-based Z-scores across cognitive domains. Finally, logistic regressions were used to determine whether planning abilities significantly and independently predicted dependence in activities of daily living and employment status, taking into account current major depressive disorder, AIDS diagnoses, and global cognitive status. As a post-hoc analysis, Spearman's nonparametric correlations (ρ) were used to examine interrelationships between TOL^{DX} variables within the HIV+ sample, as well as associations between TOL^{DX} performance and medical (e.g., nadir and current CD4 count) and psychiatric variables (e.g., affective distress). A critical value of .01 was chosen to correct for multiple comparisons for these exploratory analyses, while the critical alpha was set to 0.05 for all hypothesis-driven analyses.

Results

Between-Group Effects on TOL^{DX}

Table 2 presents the means, standard deviations, and Hedge's *g* effect sizes for the TOL^{DX} variables across the three study groups. Significant omnibus group differences were observed on TOL^{DX} performance indices, including number of problems solved within the allotted moves, total moves minus minimum moves, execution time, total time, time violations, and rule violations (all *p*s < .05). Planned follow-up multiple regression analyses indicated that the group effect remained significant (ps < .05) even when HCV status and lifetime MDD were included in the models. Relative to the HAND- group, the HAND+ group had significantly fewer problems solved correctly, more total moves, took more time to complete the task, and had more time and rule violations (*p*s < .05). Relative to the HIV- group, the HAND+ group had significantly fewer correct moves, took more time to complete the task, and had more rule violations (ps < .05).

Cognitive Correlates of TOL^{DX} in HIV

A correlation matrix between ToL indices and cognitive domain performance is presented in Table 4. Executive domain performance was significantly associated with TOL^{DX} total correct ($\rho = .34$; $p < .05$), total moves ($\rho = -0.38$, $p < .05$), and execution time ($\rho = -0.46$; $p < .01$). Memory domain performance was significantly associated with execution time ($\rho = .27$, $p < .05$), and motor domain performance was significantly associated with initiation time ($\rho = .28$, $p < .05$) and execution time ($\rho = .49$, $p < .01$). Attention/working memory domain performance was not significantly associated with any TOL^{DX} index (*p*s > .10). Regression analyses showed that executive ($B = 0.51$, $p = .001$) and motor ($B = -0.55$, $p = .020$) domain z-scores significantly predicted TOL^{DX} total correct in the HIV+ group as a whole ($N = 162$, overall model adjusted $R^2 = .14$, $p = .021$). Executive ($B = -0.47$, p = .003) domain performance also significantly predicted TOL^{DX} total moves (overall model adjusted $R^2 = .10$, $p = .044$). Though the model predicting rule violations did not reach statistical significance (adjusted $R^2 = .08$, $p = .109$), executive domain *z*-score emerged as a significant predictor ($B = -0.40$, $p = .016$). Models predicting execution time and initiation time were not statistically significant (both *p*s > .10).

Intercorrelations of TOL^{DX} Variables in HIV

As a post-hoc analysis, Spearman's nonparametric correlations (ρ) between planning component processes were conducted in order to determine the interrelatedness of component processes in HIV+ individuals. Results are displayed in Table 4. Notably, total moves and total correct were strongly related (ρ = −.90, $p < .01$), but total moves demonstrated negative associations with initiation time (ρ = −0.35) and positive association with execution time (ρ= 0.80). Total correct was positively associated with initiation time (ρ = .44) and negatively associated with execution time (ρ = −0.66). Rule violations were moderately and positively correlated with total moves and execution time (ρ = 0.48 and 0.43, respectively; ps < .01). Initiation time and execution time, however, were not significantly correlated ($p > .10$).

Clinical Correlates of TOL^{DX} in HIV

TOL^{DX} performance indices were not associated with biomarkers of HIV disease severity (e.g., current or nadir CD4 counts). Similarly, TOL^{DX} performance was not associated with global affective distress as measured by the POMS or histories of substance use disorders (all $ps > .10$).

Everyday Functioning and TOL^{DX} in HIV

Table 3 displays results of three sets logistic regressions predicting declines in 1) instrumental activities of daily living, 2) physical activities of daily living, and 3) employment status. One representative variable from each component of planning (total moves, rule violations, and execution time) was included in these logistic regressions along with AIDS status, current MDD, and global cognitive performance (mean z-score). Total moves, rule violations, and execution time were all significant independent predictors of impairment in instrumental activities of daily living in HIV+ individuals (ps < .05). However, these models and TOL^{DX} variables were not significantly predictive of impaired physical activities of daily living (overall and TOL^{DX} ps > .19). A final set of logistic regressions indicated that total moves ($p < .02$) and rule violations ($p < .02$) were significant independent predictors of employment status, while execution time approached significance ($p < .09$).

Discussion

Although executive dysfunction is prevalent in HIV, few studies in the cART era have focused specifically on planning. Additionally, the existing studies have defined and measured planning differently, as well as required varying levels of related abilities (e.g., working memory) even within the same experimental paradigms. All of these factors limit the generalizability of findings across this relatively small body of work. The current study carefully defined and investigated the dissociable component processes, cognitive correlates, and everyday functioning implications of sequential planning and problem-solving using a standardized clinical task in a large, well-characterized cohort of persons infected with HIV. As we had hypothesized, HAND+ individuals evidenced difficulties in multiple aspects of planning. As measured by the TOL^{DX}, individuals with HAND were less accurate (solved fewer problems), efficient (excess moves), and flexible (rule violations), as well as generally slower (reflected by task execution time) in solving complex visuomotor problems. These differences in planning were not attributable to demographic factors, substance use characteristics, HIV disease severity, or factors that differed between the groups including HCV status and major depressive disorder. Therefore, it is reasonable to attribute the differences observed to HAND.

Overall, our data suggest that planning deficits in HAND are characterized by decreased efficiency and accuracy in problem-solving, as well as deficient rule-bound control. Interestingly, all groups spent approximately equivalent amounts of time devoted to initial planning. Nevertheless, the HAND group took much longer to complete the task, made significantly more total moves, and solved fewer problems. This pattern of performance suggests that the HAND cohort may have initiated problem solving somewhat impulsively and prior to having formed an effective plan. Consistent with this interpretation, longer initial planning time was negatively correlated with task execution time. Moreover, HAND+ individuals also demonstrated a substantially greater propensity to commit rule violations relative to the other groups. Specifically, HAND+ individuals are approximately three times more likely to commit more than one rule violation relative to HIV- individuals (OR = 2.83, 95% CI = 1.38, 5.93). These rule violation errors are atypical in healthy individuals, and suggest that HAND+ individuals may demonstrate increased difficulty with self-monitoring and inhibiting incorrect responses. The rules imposed by this particular task necessitate accurate performance monitoring, so attending to the qualitative aspects of task performance (e.g., specific error types indicating impaired rule-guided behavior) may help in distinguishing between clinical groups with overall planning performance deficits. Typically, rule violation errors tend to be elevated in populations with compromised frontal lobe integrity, such as those with lateral prefrontal cortex lesions (e.g., Yochim et al., 2009) and frontotemporal dementias (e.g., Carey et al., 2008). It has been suggested that the frontal lobes may play a special role in error monitoring, so the preferential frontostriatal pathology in HIV may represent increased risk of acquiring these particular deficits in addition to overall deficits in planning abilities. However, these observed group deficits should be interpreted in the context of our separation of (and focus on) HAND, which is the neurobehavioral hallmark of neuroAIDS. Given that only one-third to one-half of individuals with HIV demonstrate cognitive impairment, the clinical relevance of neurocognitive research in HIV can be enhanced by honing in on particulary at-risk subcohorts such as persons with HAND. Although one might argue that this decreases the specificity of observed findings to HIV factors, it simultaneously increases sensitivity to the condition of interest. Indeed, this approach is similar to research in many other conditions that are defined by the presence of neurocognitive impairment (e.g., Alzheimer’s disease, Mild Cognitive Impairment).

Deficits in planning accuracy and efficiency were most strongly related to executive dysfunction, and to a lesser extent, impairment in fine-motor skills and memory. While executive performance also significantly predicted rule violations (overall model approached significance), executive dysfunction was not predictive of initial planning time. Task execution time was significantly associated with executive domain performance. These findings suggest that planning impairments coincide with deficits in other important higher-order functions subserved by the frontal regions and basal ganglia (the regions that are preferentially affected by HIV infection). This is consistent with existing studies (e.g., Gupta et al., 2010, Sahakian et al., 1995) that have demonstrated associations between planning performance and other executive tasks, including spatial working memory and attentional set shifting using visual discrimination paradigms. The current study expands this literature by identifying robust relationships between planning and measures of cognitive flexibility and verbal fluency, which requires rapid, rule-guided retrieval from semantic memory stores. This is also the first study to show associations between motor ability and planning performance, which may be less surprising due to the speed and coordination aspects of the TOL^{DX} in general. Interestingly, in addition to the intuitive association between motor domain performance and execution time, a relationship emerged between motor performance and a non-speeded factor. Specifically, motor performance predicted the number of problems solved correctly on the first try, and did not significantly predict how

quickly the task was completed. Impaired motor performance, then, may slow task progress, thereby increasing the cognitive load and the difficulty of the task (Sahakian et al., 1995).

We were somewhat surprised that the memory and working memory/attention domains did not significantly predict planning component processes, especially since others (e.g., Cohen et al., 1996) have emphasized the potential role of memory in Tower of London performance. However, this lack of association may be attributable to the current study's omission of spatial (vs. verbal) episodic and working memory tasks. It may also be that our population represents individuals with more well-managed HIV disease, as our findings of null associations between memory and planning are more consistent with recent studies in healthy adult populations (e.g., Unterrainer et al., 2004). Finally, other studies (e.g., Bartok et al., 1997) may also have observed a more substantial contribution of memory due to the specific spatial memory demands of the planning task (e.g., recall of the target configuration during trials).

Results of the current study suggest that impaired planning performance has important implications for the day-to-day lives of individuals with HIV. Specifically, less accurate and efficient planners were more likely to be unemployed and to report declines in other instrumental activities of daily living (e.g., financial and medication management). These robust associations reflect the relevance of planning performance to the specific demands of complex tasks of daily living, which often require the resolution of novel multifaceted problems and the organization and execution of multiple steps. Importantly, we observed relationships between everyday functioning, planning efficiency and rule-bound control, while speed was not implicated. This suggests that the diminished capacity to successfully and efficiently navigate these situations, more so than the speed with which this takes place, may threaten an individual's ability to live and work independently. The specificity of these relationships with higher-level processes is supported by the lack of association between planning and declines in basic ADL tasks (e.g., bathing and dressing). Of note, these planning indices were *uniquely* predictive of instrumental activities of daily living as well as employment, adding predictive value above and beyond the influence of HIV disease severity, current depressive symptoms, and even global cognitive performance. Taken together, these results suggest that planning impairments may be useful predictors of everyday tasks relevant to independent living in persons infected with HIV.

Several limitations of the current study may be addressed prospectively in the future. For instance, future designs might also incorporate additional neuropsychological measures, as our analyses of planning correlates were hampered by the limitations of our executive battery (e.g., we did not include other executive tasks requiring abstraction). This particular planning task is also relatively difficult, suggesting that the analysis of planning in combination with more demanding naturalistic and performance-based everyday functioning correlates (e.g., employment performance reviews; driving simulator performance or infractions) may be more of interest than with simpler tasks. The inclusion of other-report and/or performance-based measures may also help to address the inherent limitations of self-report measures of everyday functioning. However, recent data suggests that self-report measures reasonably (albeit still imperfectly) approximate objective indicators of everyday functioning, as demonstrated by a 76% classification concordance rate in a large HIV-infected sample (Blackstone et al., 2012). Additionally, this study included only a single, clinical planning task: the TOL^{DX}. While this task yields measures of accuracy, efficiency, flexibility, and speed, several of these indices are significantly intercorrelated and undoubtedly reflect related processes. Whereas we believe the selected indices to be meaningful and somewhat distinct indicators, future studies may choose to replicate the procedures of Berg, Byrd, McNamara, & Case (2010) to determine whether their observed multi-factor structure is consistent in HIV samples. Moreover, the use of a clinical task

based on older theoretical models of planning limits our ability to test novel conceptual hypotheses regarding planning in HIV. Although this measurement caveat limits the theoretical impact of our work, it arguably increases the clinical applicability of our findings, particularly with regard to the prediction of everyday functioning outcomes. Future studies may also benefit from using this task to inform theory-driven hypothesis generation and testing using modern models of planning (e.g., neural network models of complex problem solving; Polk et al., 2002). They might also incorporate mazes or measures of social and activity planning in order to determine the impact of HIV on other laboratory and naturalistic measures of planning. Finally, while the current study includes a high proportion of men, this is nevertheless reflective of the current HIV epidemic in the United States. Future studies might recruit more gender-balanced samples in order to examine possible gender differences (or interactions) in planning in HIV.

Identifying the mechanisms of planning impairments in HIV and relationships with everyday functioning outcomes represent initial steps. Future work may also incorporate possible associations between planning and neurobehavioral symptoms (e.g., impulsivity), HIV-related pathology in prefrontal regions, and the temporal course after infection. The nature of HIV disease itself exacerbates the risks associated with some of the previously identified correlates of impaired planning (e.g., difficulty managing complex medication regimens [Waldrop-Valverde et al., 2010] and increased engagement in risky behaviors that increase chances of transmission [Severtson et al., 2009]). Medication nonadherence may contribute to higher viral loads, thereby increasing the transmission risk in individuals who may be concurrently engaging in more high-risk behaviors. However, future work may address these risks through intervention. Planning interventions have already been effectively utilized in community and clinical samples in order to improve adherence in cardiac and orthopedic rehabilitation patients (e.g., Schwarzer et al., 2008), enhance diabetes management (e.g., Griffin et al., 2011) and improve compliance with physical activity interventions (Dishman, Sallis, & Orenstein, 1985). As planning has been found to be independent of medication-related literacy and numeracy in predicting medication management abilities, perhaps efforts to reduce the pill burden and facilitate user-friendly labeling in HIV could occur in combination with brief, targeted planning interventions. Physicians might initiate the opportunity for individuals with HIV to problem-solve in areas that may affect their medication adherence (e.g., determine the best time of day or event-related cue for taking medications, plan pharmacy trips for refills in advance, and incorporate them into calendars or other assistive devices). Though planning impairments may confer risks to health status, adherence, and independent functioning, neuropsychologists and physicians may well be able to further explicate these relationships and implement interventions to improve outcomes.

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Table 1

Demographic, Psychiatric, and Medical Characteristics of the Study Participants (n = 244)

		HIV+		
Variable	**HIV− (n = 82)**	**HAND− (n = 109)**	**HAND+ (n = 53)**	***p***
Demographics				
Age (years)	45.5 (13.2)	45.7 (10.0)	45.4 (10.9)	.823
Education (years)	13.2 (1.9)	12.8 (2.0)	12.9 (2.8)	.413
Sex (% female)	25.6	13.8	17.0	.107
Ethnicity (% Caucasian)	52.4	56.9	56.6	.811
Psychiatric				
Current major depressive disorder (%)	3.7	13.0	11.5	.086
Major depressive disorder (%) [a]	30.9	51.9	57.7	.003
Generalized anxiety disorder (%)[a]	3.7	9.3	11.5	.203
Substance dependence (%) [a]	51.2	56.0	54.7	.805
POMS total[b]	38 (23, 60)	46 (23, 67)	53 (34, 84)	.025
Medical				
Hepatitis C (%)	11.0	15.2	26.9	.048
HIV Disease				
HIV duration (years)	–	13.3 (7.9)	12.6 (7.5)	.640
AIDS (%)	–	54.1	50.9	.703
HAART (%)	–	88.1	88.5	.915
Nadir CD4[b] (cells/μl)	–	200 (52, 312)	200 (67, 363)	.569
Current CD4[b] (cells/μl)	–	501 (330, 725)	527 (372, 802)	.269
plasma HIV RNA $\log_{10}$ (% detectable)	–	29.3	23.1	.413

Note. WTAR = Wechsler Test of Adult Reading. POMS = Profile of Mood States. HAART = highly-active antiretroviral therapy. HAND = HIV-associated neurocognitive disorder.

[a]Denotes any lifetime diagnosis.

[b]Median (interquartile range)

Table 2

Tower of London^{DX} Performance in the Study Samples (n = 244)

TOL^{DX} Variable	HIV− (n = 82)	HIV+		p	Hedge's g	
		HAND− (n = 109)	HAND+ (n = 53)		HIV− vs. HAND+	HAND− vs. HAND+
Total Correct	4 (2, 6)	5 (3, 7)	4 (2, 6)	.002	−0.18	−0.53*
Total Moves	34 (23, 43)	23 (11, 43)	36 (18, 51)	.011	0.32	0.49*
Total Problem Solving Time	316 (221, 386)	305 (225, 367)	349 (297, 466)	.003	0.51*	0.58*
Total Initiation Time	73 (51, 119)	80 (57, 129)	78 (52, 126)	.658	−0.04	−0.06
Total Execution Time	212 (164, 276)	201 (145, 269)	271 (200, 373)	<.001	0.53*	0.70*
Time Violations	1 (0, 2)	1 (0, 2)	1 (1, 3)	.008	0.29	0.50*
Rule Violations[a]	0.6 (1.2)	0.6 (1.6)	1.7 (3.0)	.001	−0.49*	−0.47*

Note. TOL^{DX} = Tower of London^{DX}. Data are presented as median values with the interquartile range in parentheses unless otherwise indicated.

[a]Data are presented as means and standard deviations.

*p <.05.

Table 3

Predictors of Employment Status and Everyday Living Impairment in HIV (n =143)

Outcome	Variable	χ^2	Unit odds ratio	95% CI	p
Employment	Full Model	13.985			0.007
	TOL^{DX} Total Moves		**1.020**	**1.004 – 1.039**	**0.015**
	AIDS status		2.324	1.127 – 4.896	0.022
	Cognitive Z		0.626	0.067 – 5.832	0.679
	Current MDD		2.630	0.781 – 12.067	0.124
Employment	Full Model	11.093			0.020
	TOL^{DX} Execution Time		**1.003**	**0.753 – 186.310**	**0.084**
	AIDS status		2.172	1.063 – 4.516	0.033
	Cognitive Z		0.773	0.057 – 4.721	0.562
	Current MDD		2.57	0.774 – 11.900	0.131
Employment	Full Model	14.117			0.007
	TOL^{DX} Rule violations		**1.322**	**1.046 – 1.864**	**0.014**
	AIDS status		2.270	1.104 – 4.743	0.025
	Cognitive Z		0.812	0.334 – 1.969	0.644
	Current MDD		3.024	0.090 – 13.898	0.076
IADL Impairment	Full Model	9.540			0.049
	TOL^{DX} Total Moves		**0.984**	**0.968 – 1.000**	**0.047**
	AIDS status		0.559	0.243 – 1.245	0.550
	Cognitive Z		1.333	0.520 – 3.510	0.550
	Current MDD		0.379	0.131 – 1.111	0.070
IADL Impairment	Full Model	10.158			0.049
	TOL^{DX} Execution Time		**0.997**	**0.994 – 1.000**	**0.034**
	AIDS status		0.574	0.249 – 1.278	0.175
	Cognitive Z		1.429	0.558 – 3.786	0.458
	Current MDD		0.383	0.133 – 1.119	0.078
IADL Impairment	Full Model	11.900			0.012
	TOL^{DX} Rule Violations		**0.815**	**0.672 – 0.957**	**0.012**
	AIDS status		0.562	0.165 – 0.241	0.165

Outcome	Variable	χ^2	Unit odds ratio	95% CI	*p*
	Cognitive Z		1.423	0.547 – 3.817	0.471
	Current MDD		0.333	0.114 – 0.986	0.043
PADL Impairment	Full Model	5.228			0.265
	TOL^{DX} Total Moves		0.995	0.979 – 1.013	0.596
	AIDS status		0.552	0.233 – 1.258	0.164
	Cognitive Z		0.831	0.319 – 2.167	0.704
	Current MDD		0.444	0.155 – 1.338	0.144
PADL Impairment	Full Model	5.235			0.264
	TOL^{DX} Execution Time		1.000	0.326 – 2.208	0.594
	AIDS status		0.557	0.236 – 1.265	0.163
	Cognitive Z		0.848	0.326 – 2.208	0.733
	Current MDD		0.444	0.156 – 1.337	0.144
PADL Impairment	Full Model	6.184			0.186
	TOL^{DX} Rule Violations		0.913	0.775 – 1.080	0.267
	AIDS status		0.552	0.232 – 1.259	0.159
	Cognitive Z		0.854	0.326 – 2.242	0.747
	Current MDD		0.417	0.144 – 1.267	0.119

Note. $p < .05$. ADLs = Activities of Daily Living. Unit odds ratio = effect for every unit increase in the predictor.

Table 4

Spearman's ρ Correlations between ToL^{DX} Planning Indices and Neurocognitive Domains in HIV (n = 162)

ToL^{DX} Variable	Executive Z	Memory Z	Attention/Working Memory Z	Motor Z
Total Correct	0.34*	0.05	0.06	−0.06
Total Moves	−0.38*	0.10	0.01	−0.05
Total Initiation Time	−0.07	0.22	0.12	0.28*
Total Execution Time	−0.46**	0.27*	−0.10	−0.49**
Rule Violations	−0.26	0.11	−0.08	−0.23

Note.

*$p < .05$.

**$p < .01$.

Table 5

Spearman's ρ Correlations among ToL^{DX} Planning Indices in HIV (n = 162)

	[1]	[2]	[3]	[4]	[5]
Total Correct [1]	--				
Total Moves [2]	−.90***	--			
Total Initiation Time [3]	.44***	−.36***	--		
Total Execution Time [4]	−.66***	.80***	−.04	--	
Rule Violations [5]	−.46***	.48***	−.25**	.43***	--

Note.

* $p < .05$.

** $p < .01$.

*** $p < .001$.