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Relationships Among Neurocognitive Status, Medication Adherence Measured by Pharmacy Refill Records, and Virologic Suppression in HIV-infected Persons

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Abstract

Background—Optimal antiretroviral therapy (ART) effectiveness depends upon medication adherence, which is a complex behavior with many contributing factors including neurocognitive function. Pharmacy refill records offer a promising and practical tool to assess adherence.

Methods—A substudy of the CHARTER (CNS HIV Anti-Retroviral Therapy Effects Research) study was conducted at the Johns Hopkins University (JHU) and the University of Washington (UW). Pharmacy refill records were the primary method to measure ART adherence, indexed to a “sentinel” drug with the highest central nervous system penetration effectiveness score.

Standardized neuromedical, neuropsychological, psychiatric and substance use assessments were performed at enrollment and at 6 months. Regression models were used to determine factors associated with adherence and the relationships between adherence and change in plasma and cerebrospinal fluid HIV RNA concentrations between visits.

Results—Among 80 (33 JHU, 47 UW) participants, the mean adherence score was 86.4% with no difference by site. In the final multivariable model, better neurocognitive function was associated with better adherence, especially among participants who were at JHU, male, and HIV-infected for a longer time-period. Worse performance on working memory tests was associated with worse adherence. Better adherence predicted greater decreases in cerebrospinal fluid HIV RNA between visits.

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Potential Conflicts of Interest

For the remaining authors, no potential conflicts of interest were reported.

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Conclusion—Poorer global neurocognitive functioning and deficits in working memory were associated with lower adherence defined by a pharmacy refill record measure, suggesting that assessments of cognitive function, and working memory in particular, may identify patients at risk for poor ART adherence who would benefit from adherence support.

Keywords

HIV; adherence; cognitive impairment; pharmacy refill records; HAND; CPE

INTRODUCTION

The introduction of combination antiretroviral therapy (ART) produced a marked decline in AIDS-associated opportunistic illnesses, incidence of HIV-associated dementia (HAD), and mortality [1–3]. However, lifelong ART will likely be needed. While more potent agents, simpler regimens, and combination formulations have improved ART, adherence remains important [4,5]. Suboptimal adherence is associated with incomplete HIV suppression, drug resistance, and treatment failure [6–8].

Many factors contribute to ART non-adherence, including regimen complexity, pill burden, side-effects, untreated depression, and substance abuse [4, 9–12]. Forgetfulness is the most frequently cited cause of suboptimal adherence, underscoring the potential impact of HIV-associated cognitive impairment on ART-taking behavior [4,13,14].

Incidence of HAD has declined, but reported prevalence of less severe forms of HIV-associated neurocognitive disorder (HAND) is reported to be 21–50% [15, 16]. HAND can affect multiple neuropsychological (NP) domains, including psychomotor skills, executive functioning, attention, information processing speed, and memory [15,17,18], and may decrease adherence [reviewed in 19]. Hinkin and his colleagues were first to describe a direct association between global NP impairment and ART non-adherence [20]. Subsequent studies have confirmed this observation, which appears to be driven by deficits in executive functions, attention/working memory, and prospective memory [20–23]. Risk of non-adherence associated with NP impairment is independent of other risk factors, including demographics, psychiatric illness, and substance abuse [22]. Importantly, NP impairment and non-adherence may be linked by a vicious cycle in which initial non-adherence results in ongoing HIV replication, which exacerbates NP impairment and results in worse adherence [24]. Studies evaluating NP impairment and adherence have rarely employed biologic endpoints like HIV RNA [18, reviewed in 19]. Despite the importance of lifelong adherence, few studies have reported more than one month of follow-up. The importance of extended follow-up is highlighted by one study where global NP function decline over six months was associated with decreased ART adherence [25]. We postulated that a longitudinal study which assessed performance on a comprehensive NP test battery, psychiatric illness, and substance abuse could better assess the impact of cognitive impairment on adherence and virologic suppression.

There is no universal standard for assessing adherence [26]. Medication self-report and pill counts are convenient and low-cost but may overestimate adherence. NP impairment may affect accuracy of self-reported adherence. A recent review identified only 11 publications that used standardized NP tests and a direct measure of ART adherence [19]. Medication Events Monitoring System (MEMS) caps provide detailed information about medication use but are costly and complicated. Using pharmacy refill records is relatively inexpensive and straightforward; their effectiveness is based on consistent use of the same pharmacy and the assumption that prescription-filling and adherence are correlated [27, 28]. Pharmacy refill

records have predicted plasma HIV RNA and immunologic responses in HIV-infected patients [28–30].

We conducted a longitudinal analysis of research participants with well-characterized cognitive function at two academic HIV clinics, using pharmacy refill records as the primary measure of adherence. We hypothesized that NP deficits and mood and substance use would predict subsequent ART adherence, and that adherence would be associated with virologic responses in plasma and cerebrospinal fluid.

METHODS

CHARTER (CNS HIV Anti-Retroviral Therapy Effects Research) is a prospective, observational study conducted at six U.S. academic medical centers that enrolled 1597 participants from 2003–2007 and followed 600 longitudinally [15].

Two CHARTER sites (Johns Hopkins University [JHU] and University of Washington [UW]) with access to pharmacy refill records conducted this sub-study. Eligible participants had CHARTER baseline and six month visits that were no more than 9 months apart. Each site's Institutional Review Board approved this research; all participants gave written informed consent.

Neuromedical and Laboratory Assessments

Participants underwent comprehensive, standardized evaluations of neuromedical, neuropsychological, and psychiatric status; substance use; and adherence at each visit [15]. HIV infection was diagnosed by enzyme linked immunosorbent assay with Western Blot confirmation. Plasma and cerebrospinal fluid (CSF) HIV RNA were measured centrally by reverse transcriptase-polymerase chain reaction (Roche Amplicor, version 1.5, lower limit of quantification, 50 copies/mL, Roche Diagnostic Systems, Indianapolis, IN). Estimated duration of HIV infection and nadir CD4+ T-count were obtained by self-report.

Neuropsychological Assessments

Participants completed a comprehensive NP test battery assessing seven cognitive domains: Verbal Fluency, Executive Functioning, Speed of Information Processing, Learning, Memory, Attention/Working Memory, and Motor performance (Appendix) [15]. Raw scores were converted to demographically corrected standard scores (T-scores) using best available normative standards that adjust for age, education, gender and ethnicity. We then applied an automated approach that yields a continuous estimate of functioning (Global Deficit Score [GDS]). GDS emphasizes number and severity of deficits, giving less weight to average and above average performances [31]. GDS of ≥ 0.5 classifies individuals as NP impaired. This approach was also used to generate deficit scores for each cognitive domain. An objective clinical rating algorithm was used to diagnose overall NP impairment (global impairment) [32]. Comorbidities that could contribute to NP impairment were classified as incidental (non-contributory), contributing, or confounding as previously described [15, 33]. We used Hollings head Two-Factor Index to assess social status [34]. The reading subset score of the Wide Range Achievement Test, 3rd Edition (WRAT), was used as an estimate of premorbid intellectual functioning.

Psychiatric and Substance Use Assessments

The Composite International Diagnostic Interview [35] examined current (within the last 30 days) and lifetime (more than 30 days ago) DSM-IV diagnoses of major depression and substance abuse and dependence for alcohol and illicit substances. Depressive symptoms

were collected using the Beck Depression Inventory-II [36]. A semi-structured interview examined quantity and frequency of alcohol and recreational drug use.

Adherence Assessments

Investigators (AA, ACC) reviewed ART regimens for irregularities in doses and regimens. Four participants who were prescribed ART for < 30 days and one participant prescribed one agent not intended as monotherapy were excluded. For each regimen, a sentinel drug was identified according to an Algorithm (Figure 1). Sentinel drugs were selected based on their central nervous system (CNS) penetration effectiveness scores (CPE) [37] with the assumption that drugs with higher CPE would have greater suppressive impact on CSF (brain) viral levels, and potentially improve cognitive status and adherence. If a regimen contained two drugs with identical CPE scores, the sentinel drug was selected by higher dosing frequency/pill burden and drug class. We assumed the sentinel drug was started the day after it was dispensed; if pills remained from a previous prescription, the new prescription was assumed to start after the current supply ran out. An injection/liquid dose was considered one "pill." Doses less frequent than daily were calculated as fractions. Sentinel drugs prescribed as part of co-formulated drugs were analyzed as individual agents. Pharmacy records were used to estimate ART adherence from 60 days before the baseline visit to the first follow-up visit (the six-month visit). Adherence was computed as number of days a participant had sufficient supply to take prescribed doses, divided by total number of days the sentinel drug was prescribed. Non-sentinel drugs were not analyzed.

Self-reported adherence was determined by 4-day report (proportion of prescribed doses taken) of the AIDS Clinical Trials Group Adherence Questionnaire [38].

Statistical Analysis

Transformations and nonparametric techniques were performed as needed. Parametric assumptions were verified. To stabilize variance, an arcsin transformation was applied to the pharmacy records-derived adherence measure, resulting in estimates weighted slightly more for longer exposure to ART (e.g., 100% adherence over eight months counted more than 100% adherence for two months) [39]. Two-sided testing, no multiple comparison adjustments, and a 5% significance level were used unless otherwise indicated. Site differences in baseline characteristics were tested using t-tests, Wilcoxon Rank Sum, Chi-square, or Fisher Exact tests, depending on parametric test assumption validity. Baseline variables were screened individually for their association with adherence using linear regression, first unadjusted, then including terms for site and the variable's interaction with site. Terms with $p < 0.10$ were retained as candidates for multivariable modeling. Main effects were always included with interactions.

Multivariable linear regression models, all including a term for site, were constructed after omitting all but one of the mutually correlated candidate variables based on removal of the minimal number of variables while retaining the least mutually correlated variables according to p-value (WRAT, age, Duration of ARVs removed). Since identifying the relationship of NP deficits to ART adherence was a primary aim, GDS, and its interaction with site if significant, were included in all models. Subsequent models included all terms from the previous model except for the one with the largest p-value > 0.05 ; this process was repeated until only significant variables remained. After this model was produced, GDS was replaced with each NP domain deficit score separately and that domain was tested for its association with adherence; non-significant interactions were excluded in the final models. To assess relationships between adherence and changes in log-transformed viral load in subjects who had detectable baseline HIV RNA, linear regression was used, after examining scatterplots of baseline versus change for evidence of regression to the mean [40]. If

warrented, adjustment for baseline level and its interactions with adherence were included in the regression model. The associations between adherence and HIV RNA changes are described separately for subjects with detectable and undetectable baseline viral loads with median (interquartile range). For descriptive purposes, we dichotomized self-reported adherence at 95%, as has been done by others [6]. For inferential analysis of self-reported adherence, we arcsine-transformed adherence and used the lowest self-report at either visit and analysed the data the same way as for pharmacy refill data on subjects with detectable baseline viral loads, except that adherence was dichotomized (100% versus <100%) and plasma HIV RNA change was compared between the two adherence levels using a Wilcoxon Rank Sum test.

RESULTS

Characteristics of the Study Population

The majority of participants were African-American (56%) and male (79%) (Table 1). Median estimated minimum duration of HIV infection was 10.6 years. Median nadir and current CD4+ T-counts were 72 and 383 cells/mm³, respectively. At baseline, participants reported taking their current ART regimen for median of 8 months. Lifetime major depression (49%) and substance abuse/dependence (83%) were common. Half of participants were globally NP impaired. JHU participants were more likely to be African-American, slightly older, and less likely to be male than UW subjects. The proportion of participants with baseline plasma HIV RNA <50 copies/mL was higher at JHU than at UW. The groups were similar in most other characteristics but mean WRAT scores, used to estimate pre-morbid intellectual functioning, were higher at UW.

Antiretroviral Adherence by Pharmacy Refill Records

The mean (SD) adherence rate to the sentinel drug was 86.4% (18.5%); rates were similar at JHU (85.7% [16.9]) and UW (86.9% [19.6]).

Factors Associated with ART Adherence

Table 2 shows baseline characteristics (both unadjusted and controlling for site and interactions with site) and their association with adherence. Of note, current ART regimen duration and depression or substance use diagnoses were not associated with adherence. Table 3 shows the final multivariable model that indicates male sex, longer estimated duration of HIV, and better baseline global NP performance were significantly associated with better ART adherence. Relationships between GDS and adherence differed by site; at JHU but not UW, worse global neurocognitive performance (higher GDS) was associated with worse adherence.

Relationship Between Neurocognitive Domains and Adherence

After replacing GDS with each of the 7 NP domains, only one, working memory, showed a significant effect on adherence ($p=0.026$, Table 3). Worse working memory was associated with poorer adherence. Duration of HIV infection was still associated with adherence in the model that included working memory, but sex was no longer a significant factor and was removed from the final model.

Relationship Between Adherence By Pharmacy Refill Data and Changes in Plasma and Cerebrospinal Fluid HIV RNA

The relationships between adherence and changes in plasma and in CSF HIV RNA were nonlinear. An examination of scatterplots of baseline HIV RNA levels versus change in RNA showed evidence of regression to the mean for viral load in plasma but not in CSF.

Only 12 of 74 subjects with RNA measurements in CSF had detectable baseline levels. Among these participants, better adherence was associated with greater declines in CSF HIV RNA, especially in those with higher baseline viral load (adherence $p=0.058$, RNA $p=0.013$, interaction $p=0.08$, Table 4). For example, mean (standard error[SE]) reduction in CSF HIV RNA ($\log_{10}$ copies/mL) was estimated to be -0.4 (0.7) for baseline RNA of $2 \log_{10}$ and -1.1 (0.9) in subjects with baseline RNA of $4 \log_{10}$ and approximately 75% adherence, whereas the mean (SE) changes estimated were -0.2 (0.8) and -2.4 (0.8) $\log_{10}$, respectively, with 100% adherence. Among the 58 subjects for which baseline CSF RNA results were available and undetectable, 52 (90%) had viral loads that remained undetectable at month six and had median (IQR) adherence of 96% (85%, 100%); the remaining 6, with median (IQR) adherence of 93% (58%, 100%), had increases of less than 1 $\log_{10}$ ($N=4$), and between 1 and 2 $\log_{10}$ ($N=2$) at month six.

Evidence of regression to the mean precluded any adjustment for baseline plasma RNA levels [41]. For the 46 subjects with detectable baseline plasma HIV RNA, adherence alone, estimated by pharmacy refill data was not associated with plasma viral load change ($p=0.719$); 17 (37%) of these subjects had undetectable plasma viral load at the six-month visit and median (IQR) adherence of 95% (67%, 99%); the remaining 29 who had detectable plasma HIV RNA at six months had median (IQR) of 92% (78%, 100%) adherence. Among the 34 subjects with undetectable plasma RNA at baseline, 29 (85%) had viral loads that remained undetectable at six months and had median (IQR) adherence of 95% (85%, 99%); the remaining 5 had plasma RNA increases ranging from 0.05 and 3.2 $\log_{10}$ and median (IQR) adherence of 98% (52%, 100%).

Antiretroviral Adherence By Self-Report

At baseline, the mean (SD) self-reported 4-day adherence for the 74 subjects for whom these data were available was 98.2% (5.7), with no site differences. When adherence was defined by this metric as 95%, 65(88%) and 69(94.5%) of subjects reported being adherent at baseline and the 6-month visits, respectively with no site differences.

Relationship Between Self-Reported Adherence and Changes in Plasma and Cerebrospinal Fluid HIV RNA

With the lowest self-reported adherence at either the baseline or six month visit dichotomized as 100% ($n=39$) vs. $<100\%$ ($N=7$) for the 46 subjects with detectable baseline plasma HIV RNA, there was no difference in plasma HIV RNA change between the two adherence groups ($p=0.748$).

Among the 12 subjects with detectable CSF HIV at baseline, there was a significant effect of self-reported adherence on change in CSF HIV RNA ($p=0.0055$) as well as significant effects of baseline CSF levels and the interaction of these two variables ($p<0.0001$ and $p=0.0024$, respectively). Those with higher baseline CSF HIV RNA and higher adherence had greater decreases estimated in their CSF HIV RNA over six months than those with lower baseline CSF viral load regardless of adherence.

DISCUSSION

The study utilized a novel metric to assess adherence and evaluated longitudinal plasma and CSF RNA changes. Data from these two U.S. sites in the CHARTER study suggest that HIV-infected participants with greater overall NP deficits and specific deficits in working memory have lower ART adherence, as defined by our pharmacy refill record review. This adherence measure was focused on the drug with the maximal CNS ART penetration-

effectiveness score [37]. Notably, better adherence based upon this metric was associated with decreasing levels of CSF HIV RNA over a six month time-period.

Global NP impairment has been independently associated with ART non-adherence in studies incorporating multivariable analyses to account for other confounding factors. After controlling for age, current psychiatric disorders, neurologic conditions, and regimen complexity, global NP impairment correlated with ART non-adherence measured by MEMS caps over a 4-week period [22]. In a different study, decreased NP function in adults over 50 years of age was the sole predictor of ART non-adherence [21]. Many studies relating cognition and adherence have been cross-sectional and unable to address causal associations. Does NP impairment result in suboptimal adherence, is poor adherence and consequent ongoing HIV replication causing NP impairment, or are both pathways contributing to a vicious cycle [24]? Relatively few longitudinal studies have addressed this issue. Older age is often associated with better adherence. However, Hinken et al. reported that 83% of subjects over 50 years with poor adherence were cognitively impaired [41]. Over four weeks, non-adherence (by MEMS caps) was associated with poor baseline global NP functioning in a subset of 23 subjects with consistently poor adherence [42]. Retrospective analyses of HIV-infected adults in Los Angeles showed that those with decline in global NP function over six months had a greater drop in ART adherence than those with stable function [25]. Controlling for baseline factors, our findings suggest that global cognitive deficits were associated with poor ART adherence over the subsequent six months.

Some prospective studies have reported that specific cognitive domains are associated with ART adherence. Levine et al. noted working memory and attention deficits in 27 subjects with poor weekend adherence in a four-week study [42]. A study of New York City men who have sex with men found worse performance on Trail Making Test Part B (which has a working memory component as well as flexibility of thinking and speed of information processing) was associated with worse adherence over 10 months [43]. Prospective memory, the ability to “remember to remember” something in the future correlated with adherence in a clinical trial [44]. Deficits in time-based prospective memory were independently predictive of poor ART adherence over one month [22]. Thus, our finding that worse working memory, in combination with other factors, was associated with lower subsequent ART adherence is generally consistent with these reports and suggests that our results may be generalized to other U.S. adults. Successful antiretroviral adherence is a complex task, requiring intention to take medication at specific time(s) per day, retaining this plan during daily activities, remembering dosing time and any associated instructions (e.g. take with food or on an empty stomach), and executing the plan by taking the medication [22]. Since others have described that working memory deficits can negatively affect higher level cognition, such as decision making [45] and everyday functioning [46], it is not surprising that such deficits can negatively impact ART adherence.

In our study, better adherence was seen in men and those with longer estimated duration of HIV infection. Data on the relationship between sex and ART adherence have been inconsistent, although a recent review suggested that women have worse adherence than men, similar to our findings [47]. In that report, depression and lack of support systems were associated with poorer adherence in women. While some reports link depression to non-adherence, this relationship was not found in other studies or in ours [21, 47]. We did not collect information on support systems, although our subjects may have benefitted from contact with CHARTER staff. In our multivariable model of specific NP domains, working memory moderated the significant association between sex and adherence (Table 3). Our observation that longer duration of estimated HIV infection was associated with better

adherence may reflect survivorship bias [48]. It is also possible that this association is confounded by age (i.e., better adherence in older subjects, after correcting for NP function).

We found that worse NP functioning led to poorer adherence in JHU patients, but had a negligible effect in UW participants. While our multivariable analyses contained likely confounding factors, these analyses may not have adequately adjusted for all potential differences between sites. For example, UW subjects were more likely to be male, younger, and less likely to be African-American. Although older patients usually have better adherence, age-related cognitive decline (i.e., normal cognitive aging) might have exacerbated the impact of disease-related NP deficits on adherence at JHU [21]. Higher level of premorbid intellectual function at UW, as indicated by higher WRAT scores, may also have moderated the impact of NP impairment. Finally, possible differences in adherence support services at the sites might also explain the greater impact of NP impairment on adherence at JHU.

We evaluated pharmacy refill records as an alternative monitoring tool because of concerns about the accuracy of self-reported adherence in NP-impaired patients. Like our pharmacy refill-based adherence data, self-reported adherence was significantly correlated with virologic suppression in CSF, even among the participants who had detectable CSF HIV RNA at baseline. Although pharmacy refill records have previously been correlated with plasma viral load suppression, we were not able to confirm such an association in our study. However, the four-day self-report has recognized limitations, including over-estimating adherence [5]. We did *a priori* identify our pharmacy refill metric as the primary adherence metric for this study and our refill records-based adherence metric was associated with reduction of CSF HIV RNA values in all subjects studied. Since CPE score was the primary criterion for identifying a sentinel drug in our study, the relationship between better adherence and reduction in CSF HIV suggests that the protection afforded by better CNS-penetrating drugs may have preserved cognition and consequently adherence. This possibility is supported by Cysique et al. who reported that CPE score was an independent predictor of NP improvement in study participants with HAND who started ART [49].

Our results are limited by a relatively small sample size. In addition, these findings are most generalizable to patients obtaining medications at a single pharmacy. Filling prescriptions does not guarantee that medications are taken. Finally, factors such as stockpiling doses or obtaining medications from other pharmacies could have affected our refill metric. In spite of these limitations, we believe this is the first prospective study with virologic outcomes using pharmacy refill records to quantify adherence to ART in HIV-infected patients who have undergone rigorous NP, psychiatric, and substance use assessments.

In conclusion, poor adherence to ART in our study population was correlated with working memory and global NP deficits. Careful assessment of working memory and cognition prior to ART initiation and in patients with suboptimal virologic responses to ART may help identify persons in need of adherence support. Working memory training for stimulant addicts and strategies for rehabilitation of working memory deficits in persons with HIV infection have been described [50, 51]. Such strategies should be further investigated in persons with HAND to determine whether they can improve adherence and optimize benefits of ART.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Algorithm for Identification of the Sentinel Drug in Each Antiretroviral Regimen*

* CPE = antiretroviral central nervous system penetration effectiveness score [37]

Table 1

Baseline Characteristics and Site Comparisons*

Characteristics	Total N=80	Johns Hopkins N=33	U Washington N=47	P-value
Demographics				
Ethnicity				<0.001 ^f
African-American	45 (56%)	31 (94%)	14 (30%)	
Caucasian	4 (5%)	2 (6%)	24 (51%)	
Hispanic	26 (33%)	0 (0%)	4 (9%)	
Other	5 (6%)	0 (0%)	5 (11%)	
Male sex	63 (79%)	22 (67%)	41 (87%)	0.028 ^c
Age (years)	45 (7.5)	47 (6)	43 (8)	0.024 ^t
Education (years)	12.6 (2.2)	12 (2)	13 (2)	0.161 ^t
Hollingshead index ^{**}	41 (11.3), n=76	43 (11), n=32	39 (11), n=44	0.178 ^t
Medical				
Estimated minimum HIV duration (months)	127 (73–179)	131 (95–187)	118 (67–174)	0.475 ^t
Nadir CD4+ T-cells/mm ³	72 (16–188)	56 (7–179)	91 (30–193)	0.451 ^t
CD4+ T-cells/mm ³	383 (206–519)	406 (214–524)	343 (202–516)	0.697 ^t
Plasma HIV RNA <50 copies/mL	34 (43%)	21 (64%)	13 (28%)	0.001 ^c
CSF HIV RNA, <50 copies/mL)	62 (84%), n=74	25 (89%), n=28	37 (80%), n=46	0.517 ^f
Comorbidity status ^{***}				0.733 ^c
Incidental	36 (45%)	14 (42%)	22 (47%)	
Contributing	30 (38%)	14 (42%)	16 (34%)	
Confounding	14 (18%)	5 (15%)	9 (19%)	
Duration of ARVs (months)	58 (21–82), n=76	57 (21–82), n=31	58 (19–85), n=45	0.695 ^t
Duration of current regimen (months)	8 (2–17), n=73	11 (1–19), n=31	6 (2–14), n=42	0.257 ^t
Psychiatric/Substance Use				
Current major depressive disorder [#]	6 (8%)	3 (9%)	3 (6%)	0.687 ^f
Lifetime major depressive disorder ^{##}	39 (49%)	14 (42%)	25 (53%)	0.342 ^c
Beck depression inventory (total score)	12 (10)	11.7 (9.7)	12.2 (9.7)	0.841 ^t
Current substance use diagnosis ^{###}	0 (0%)	0 (0%)	0 (0%)	na

Characteristics	Total N=80	Johns Hopkins N=33	U Washington N=47	P-value
Lifetime substance use diagnosis ⁺	66 (83%)	29 (88%)	37(79%)	0.280 ^c
Number of substances used within 30 days	0.48 (0.67)	0.27 (0.57)	0.62 (0.71)	0.015 ^w
Alcohol use within 30 days	32 (40%)	8 (24%)	24 (51%)	0.009 ^w
Alcohol, units ⁺⁺ (users only)	5.3 (12.3)	2.8 (11.3)	7.1 (12.7)	
Marijuana use within 30 days	16 (20%)	4 (12%)	12 (25%)	0.268 ^t
Marijuana, grams (users only)	2.7 (13.2)	0.76 (2.8)	4.1 (17.0)	
Cocaine use within 30 days	8 (10%)	3 (9%)	5 (11%)	0.697 ^t
Cocaine, grams (users only)	0.15 (0.62)	0.11 (0.41)	0.17 (0.74)	
<i>Neuropsychological</i>				
Wide Range Achievement Test	87 (16)	78 (14)	93 (14)	<0.001 ^t
Global neuropsychological status (impaired)	40 (50%)	17 (52%)	23 (49%)	0.820 ^c
Global Deficit Score	0.41 (0.34)	0.42 (0.30)	0.41 (0.37)	0.958 ^t

* Results are reported as N (%), Median (interquartile range), or Mean (standard deviation); na=not analyzable

** The Hollingshead Index is a measure of social position based on a person's education and occupation [34]. Hollingshead Index scores range from 11–69 with lower scores indicating higher social position. The mean score of 41 found in our participants indicates average socioeconomic class.

*** Comorbidity Status was determined as described previously using detailed guidelines for classifying commonly encountered comorbid conditions as incidental, contributing, or confounding. Classification is done using available information such as medical history, severity and time-course of symptoms, signs, and functional status [15, 33]. An example of an incidental condition would be a past cerebrovascular accident (CVA) with a return to normal cognition with a subsequent decline in the context of HIV. An example of a contributing condition would be a past CVA without a return to normal cognition, but with subsequent decline in the context of HIV. An example of a confounding condition would be a metastatic brain tumor.

Diagnostic and Statistical Manual (DSM)-IV major depressive disorder diagnosis within the past 30 days

DSM-IV major depressive disorder diagnosis ever

DSM-IV substance abuse or dependence diagnosis within the past 30 days

+ DSM-IV substance abuse or dependence diagnosis ever

++ One unit = one 12 ounce beer, one five ounce glass of wine, or one 1.5 ounce shot of liquor

^f Fisher exact test

^c Chi-square likelihood ratio test

^t t-test

^w Wilcoxon rank sum test

Association of Baseline Characteristics, Study Site, and Study Site x Characteristic Interactions with Antiretroviral Therapy Adherence as Assessed by Pharmacy Refill Records*

Table 2

Results from models that are adjusted for study site (and interactions when significant)						
Unadjusted						
Characteristic	P-value	β (SE) [95% CI]**	Effect***	P-value	Effect Size#	Effect on adherence
Site	0.639		Main	na		
Demographics						
Ethnicity	0.314		Main	0.266	---	
			Site	0.418	---	
Sex	0.058	7.7 (4.0) [-0.3, 15.6]	Main	0.068	7.7 (4.1) [-0.6, 15.9]	Better adherence in males.
			Site	0.996	---	
Age	0.384		Main	0.309	---	
			Site	0.478	---	
Education	0.089	1.3 (0.8) [-0.2, 2.8]	Main	0.102	---	
			Site	0.836	---	
Hollingshead index##	0.023	-0.3 (0.1) [-0.6, -0.05]	Main	0.024	-0.3 (0.2) [-0.7, -0.05]	Better adherence with higher socioeconomic status (low values of Hollingshead index).
			Site	0.859	---	
Medical						
Estimated minimum HIV duration	0.001	0.08 (0.02) [0.03, 0.12]	Main	0.001	0.08 (0.02) [0.03, 0.13]	Better adherence with longer duration of infection.
			Site	0.442	---	
Nadir CD4+ T-cells/mm ³	0.376		Main	0.356	---	
			Site	0.585	---	
CD4+ T-cells/mm ³ ###	0.840		Main	0.846	---	
			Site	0.643	---	
Plasma HIV RNA <50 copies/mL	0.509	1.1 (1.7) [-2.2, 4.5]	Main	0.039	5.6 (2.6) [0.3, 10.8]	Better adherence with undetectable HIV RNA.

Characteristic	Unadjusted			Results from models that are adjusted for study site (and interactions when significant)		
	P-value	β (SE) [95% CI]	Effect ***	P-value	Effect Size#	Effect on adherence
CSF HIV RNA < 50 copies/mL	0.475		Site	0.504	---	Better adherence for undetectable RNA at JHU and detectable RNA at UW than for detectable RNA at JHU.
			Interaction	0.048	JHU undet: 75 (3) [69, 81] UW det: 73 (3) [68, 78] JHU undet: 70 (4) [62, 78] JHU det: 64 (4) [55, 72]	
Comorbidity status	0.081		Main	0.461	---	Better adherence with contributing co-morbidities than with confounding co-morbidities.
			Site	0.780	---	
			Main	0.074		
			-Contr.		75 (3) [68, 81]	
			-Incid.		70 (3) [63, 76]	
Duration of ARVs, months	0.060	0.09 (0.05) [-0.00, 0.19]	-Conf.		64 (4) [55, 73]	
			Site	0.501	---	
Duration of current regimen, months	0.551		Main	0.060	0.09 (0.05) [-0.00, 0.19]	Better adherence with longer treatment.
			Site	0.683	---	
<i>Psychiatric/Substance Use</i>	0.751		Main	0.623	---	
			Site	0.466	---	
Current major depressive disorder ⁺	0.734		Main	0.734	---	
			Site	0.629	---	
Lifetime major depressive disorder ⁺⁺	0.270		Main	0.734	---	
			Site	0.629	---	
Beck depression inventory (total score)	0.478		Main	0.473	---	
			Site	0.629	---	
Lifetime substance use diagnosis ⁺⁺⁺	0.262		Main	0.242	---	Better adherence with no diagnosis at UW than with no diagnosis at JHU or with a diagnosis at UW.
			Site	0.083		
			Interaction	0.035	8.2 (4.7) [-1.1, 17.5] UW no dx: 81 (5) [72, 90]	

* ARVs=antiretroviral drugs; β =Beta regression coefficient; CI=confidence interval; CSF=cerebrospinal fluid; Conf=contributing; Contr=confounding; DSM-IV=Diagnostic and Statistical Manual-IV; GDS-global deficit score; HIV=human immunodeficiency virus; imp=impaired; JHU=Johns Hopkins University; Incid=incidental; na=not analyzable; nm=normal; SE=standard error; unde=undetectable; UW=University of Washington; "—"=absence of significant effect

** Unadjusted effect sizes are reported as β (standard error of β) [95% confidence interval] and are reported when unadjusted or adjusted main effect p-values are <0.10

*** Main—main effect for the baseline characteristic; Site—effect of study site (JHU or UW) on adherence; Interaction—characteristic and study site have an interaction (The interaction term was removed from the model if not significant at the 5% level)

For main effects: β regression coefficient (standard error of β) [95% confidence interval] are provided as the effect size except for Comorbidity status which has three category levels; For interaction effects and Comorbidity status, the least square means (standard error of the means) [95% confidence intervals] are reported as the effect size; units are in units of the transformed adherence proportion;

The Hollingshead Index is a measure of social position based on the person's education and occupation [34]. Hollingshead Index scores range from 11–69 with lower scores indicating higher social position. The mean score of 41 found in our sample indicates average socioeconomic class.

A square root transformation of CD4 was used in analyses.

+ DSM-IV major depressive disorder diagnosis within the past 30 days

++ DSM-IV major depressive disorder diagnosis ever

+++ DSM-IV substance abuse or dependence diagnosis ever

& 3rd Edition reading subset scores

Table 3

Predictors of Adherence in the Final Multivariable Models*

Global Deficit Score			Working Memory**	
Baseline Characteristic	Effect size***	P-value	Baseline Characteristic	P-value
Unadjusted				
GDS	-7.3 (4.9) [-17.1, 2.4]	0.140	DDS	0.083
Adjusted				
Site	0.5 (3.1) [-5.7, 6.6]	0.881	Site	0.772
Sex#	9.1 (3.7) [1.7, 16.5]	0.017	Sex	----
Estimated minimum HIV duration (months) ##	0.07 (0.02) [0.03, 0.12]	0.002	Estimated minimum HIV duration (months) ##	<0.001
GDS###	-23.8 (7.8) [-39.4, -8.1]	0.003	DDS###	0.026
GDS × Site+	Male, JHU	0.033	DDS × Site	----
	GDS=0: 83.4 (8.5)			
	GDS=1: 59.6 (10.3)			
	Male, UW			
	GDS=0: 75.2 (6.0)			
	GDS=1: 72.3 (7.3)			
	Female, JHU			
	GDS=0: 74.3 (9.2)			
	GDS=1: 50.5 (11.5)			
	Female, UW			
	GDS=0: 66.1 (8.3)			
	GDS=1: 63.2 (10.3)			
Overall model		<0.001		0.001

* DDS=Domain Deficit Score; GDS=Global Deficit Score; HIV=human immunodeficiency virus; JHU=Johns Hopkins University; UW=University of Washington;

“----” is used for terms that were removed from a model due to lack of significance (p 0.05)

** Unadjusted deficit scores for the other domains (verbal, executive functioning, speed of information processing, learning, memory, and motor) were not significant (p-values ranged from 0.06 to 0.88). After adjustment for site (p-values ranged from 0.66 to 0.89), sex (all p<0.044), and estimated minimum HIV duration (all p<0.002), domain deficit scores for these domains were not significant (p-values ranged from 0.07 to 0.87). Domain interactions with site were also not significant (all p 0.05) and were not included in the final models.

*** For main effects: β (beta) regression coefficient (standard error of β) [95% confidence interval] are reported as the effect size; For the interaction effect, the least square means (standard errors of the means) are reported as the effect size; units are in units of the transformed adherence proportion

Male sex is associated with better adherence.

Longer duration of HIV infection is associated with better adherence.

Worse performance (more deficits) is associated with worse adherence.

+ For JHU, worse performance (higher GDS) is associated with worse adherence. For UW, GDS was not associated with adherence.

Table 4

Relationship between Adherence Assessed by Pharmacy Refill Records and Change in Cerebrospinal Fluid (CSF) HIV RNA Between Visits for Subjects with Detectable Baseline CSF HIV RNA (N=12)^{*}

Effect ^{**}	P-value
Adherence	0.058
Baseline CSF HIV RNA	0.013
Adherence × baseline CSF HIV RNA	0.080

Effect sizes for selected (approximate) adherence and baseline RNA levels			
Adherence %	Baseline RNA (log ₁₀)	Mean RNA change (log ₁₀)	Standard Error
75%	2	-0.4	0.7
100%	2	-0.2	0.8
75%	3	-0.8	0.5
100%	3	-1.3	0.5
75%	4	-1.1	0.9
100%	4	-2.4	0.8

^{*} CSF=cerebrospinal fluid; HIV=human immunodeficiency virus; RNA=HIV RNA reported in log₁₀copies/mL

^{**} With better adherence, CSF HIV RNA is decreased, especially in those with higher baseline CSF HIV RNA