

Neuropsychological Impairment in Acute HIV and the Effect of Immediate Antiretroviral Therapy

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Objective: To investigate neuropsychological performance (NP) during acute HIV infection (AHI) before and after combination antiretroviral therapy (cART).

Design: Prospective study of Thai AHI participants examined at 3 and 6 months after initiation of cART.

Methods: Thirty-six AHI participants were evaluated pre-cART at median 19 days since HIV exposure and 3 and 6 months after cART with the Grooved Pegboard test, Color Trails 1 & 2 (CT1, CT2), and Trail Making Test A. Raw scores were standardized to 251 age- and education-matched HIV-uninfected Thais. To account for learning effects, change in NP performance was compared with that of controls at 6 months. Analyses included multivariable regression,

nonparametric repeated measures analysis of variance, and Mann–Whitney *U* test.

Results: Baseline NP scores for the AHI group were within normal range (z-scores range: -0.26 to -0.13). NP performance improved on CT1, CT2, and Trail Making Test A in the initial 3 months ($P < 0.01$) with no significant change during the last 3 months. Only improvement in CT1 was greater than that seen in controls at 6 months ($P = 0.018$). Participants who performed >1 SD below normative means on ≥ 2 tests ($n = 8$) exhibited higher baseline cerebrospinal fluid HIV RNA ($P = 0.047$) and had no improvement after cART.

Conclusions: Most AHI individuals had normal NP performance, and early cART slightly improved their psychomotor function. However, approximately 25% had impaired NP performance, which correlated with higher cerebrospinal fluid HIV RNA, and these abnormalities were not reversed by early cART possibly indicating limited reversibility of cognitive impairment in a subset of AHI individuals.

Key Words: HIV infection, HIV-associated neurocognitive disorder, neuropsychological tests, mild cognitive impairment, antiretroviral therapy

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INTRODUCTION

Despite access to combination antiretroviral therapy (cART), a large percentage of chronically infected HIV-positive individuals exhibit mild forms of cognitive impairment,^{1,2} known as HIV-associated neurocognitive disorders. Before widespread use of cART, 15%–20% of HIV patients developed HIV-associated dementia³ but that incidence is now greatly reduced. In contrast, the prevalence estimates of milder forms of cognitive impairment have not decreased, with up to 50% of chronically infected HIV-positive individuals still manifesting some degree of cognitive dysfunction.^{1,2,4,5} One possible explanation for persistent cognitive impairment in the cART era is that injury to the nervous system may be accrued during the very early stages of infection, before initiation of antiretroviral treatment. Limited information is available regarding the neuropsychological status among individuals during acute HIV infection (AHI, before antibody seroconversion) and whether cognitive function may be altered by very early initiation of cART.

We previously demonstrated detectable cerebrospinal fluid (CSF) HIV RNA as early as 8 days after estimated date of transmission,⁶ with concurrent evidence of central nervous system (CNS) inflammation, measured by magnetic resonance spectroscopy imaging and CSF markers of immune activation.^{6,7} There are limited data characterizing cognitive function in primary HIV infection, defined as the first year after HIV transmission, and these studies have not included individuals captured during the first month.^{8,9} Results from these studies have been mixed, with one study reporting impairments in processing speed, executive function, and learning among cART-naïve patients with primary infection,¹⁰ whereas others have not demonstrated statistically significant differences in neuropsychological (NP) performance between primary infection participants and HIV-uninfected controls.^{11,12} No studies have examined neurocognitive performance and HIV disease biomarkers during AHI or the impact of immediate antiretroviral therapy on cognitive performance during this acute stage.

The efficacy of cART in improving cognitive performance in individuals with advanced HIV disease is well understood.^{13–15} However, studies demonstrate that a considerable proportion of chronically infected persons continue to have neurocognitive deficits despite cART.¹⁶ Importantly, studies demonstrating chronic neurocognitive impairments despite treatment were focused on individuals who started cART at variable durations since exposure. As such, it is possible that neurological damage sustained during the early stages of HIV infection may have led to NP impairments that were refractory to later treatment. One study longitudinally examined the effect of cART on cognitive performance during early infection,¹⁰ identifying mild deficits in NP performance pre-cART and stabilization of cognitive function after cART. However, this observational study did not control for practice effects and assessed participants approximately 4 months after estimated HIV transmission, well after the acute phase of infection. Furthermore, in previous studies, neurocognitive assessments were conducted at variable times after infection.¹⁰

The current study evaluated Thai participants who were identified within days of estimated HIV exposure and before antibody seroconversion. We examined neuropsychological performance at 2 time points (3 and 6 months) after cART initiation and compared change in NP performance in the AHI cohort with that of Thai normative controls to account for practice effects. We hypothesized that neurocognitive impairment would be detected in AHI, and performance on the NP tests would improve significantly above and beyond practice effects after cART initiation.

METHODS

Study Design and Participants

Acute HIV study participants were recruited from the Thai Red Cross Anonymous Clinic in Bangkok, Thailand. AHI participants were identified through nucleic acid testing and were characterized according to the Fiebig stage defined by the sequential appearance of viral RNA, antigen, and antibodies, as previously described.^{17,18} The inclusion criteria for the AHI

group were confirmed acute HIV-1 infection, age ≥ 18 years, ART naïve, informed consent, and assent to initiating protocol-defined cART. Because the key defining feature of the unique study population was laboratory-defined AHI, we did not exclude any individuals eligible by the above criteria. However, mental health, substance use, and educational histories were obtained in all individuals, and no participants included in the analysis had major psychiatric diagnoses.

Participants completed baseline clinical, neurological, CSF sampling ($n = 21/36$), and NP testing before starting cART. Because of the nature of the parent study, individuals were randomized to either standard cART (efavirenz, tenofovir, and emtricitabine or lamivudine) or standard cART plus raltegravir and maraviroc (MVC). There were no significant differences in baseline characteristics (age, gender, days after HIV transmission, CD4 count, CD8 count, plasma HIV RNA, and CSF HIV RNA) between the 2 treatment arms using Mann–Whitney *U* test. Thus, for the purpose of this study, all participants were aggregated into one treatment group for analyses and the effect of MVC was evaluated in multivariable models. All were followed longitudinally with NP testing at 3 and 6 months after initial assessment.

Clinical Characterization

Psychiatric Assessment

Participants completed the Thai version of the Hospital Anxiety and Depression Scale (HADS), a 14-item scale with anxiety and depression subscales (7 items per subscale). Each item is scored from 0 to 3, with a total score range of 0–21 per subscale. HADS scores were correlated with baseline NP scores using Spearman correlation. Scores greater than 11 were considered positive cases.

Illicit Drug Use Quantification

Identification, duration, and frequency of drug use were elicited from participants through structured interviews.

Time of HIV Transmission

AHI was confirmed by serial laboratory testing at 2, 4, 8, 12, and 24 weeks after initial detection of positive HIV nucleic acid and negative HIV antibody. HIV transmission dates were estimated from the dates of HIV exposure within the past 30 days reported by the participants. When multiple possible dates were given, the mean time point was selected.

Neuropsychological Testing

The 4-test NP battery evaluated fine motor function/manual dexterity [Grooved Pegboard test (GP), nondominant hand], psychomotor speed [Color Trails 1 (CT1), Trail Making A (TM)], and executive function/set shifting [Color Trails 2 (CT2)].

We used an existing normative NP testing database of HIV-uninfected Thai control participants ($n = 449$).¹⁹ For the purpose of this study, we used only 251 HIV-uninfected controls in the similar age range as our AHI participants. The normative sample had a median [interquartile range (IQR)] age of 34 (27–42) years, 46% ($n = 115$) were males, and 30%

($n = 76$) had a bachelor's degree or higher. These control participants completed NP assessments at baseline and at 6 months follow-up. For baseline NP performance analysis, data of all 251 HIV-uninfected controls were used. In the longitudinal NP performance analyses, only 45 controls who had complete NP data for the 6-month study period were used.

The raw NP scores of the AHI participants were standardized using data from the HIV-uninfected control participants from equivalent age and education stratum to calculate z-scores. A composite score (NPZ-4), the arithmetic mean of individual z-scores, was calculated to provide an overall measure on NP performance.

Laboratory Measures

CSF protein and cell count were measured through lumbar puncture. CSF and plasma HIV RNA quantification (viral load) was completed using the Roche Amplicor HIV-1 Monitor Test V1.5 in most participants but by Roche COBAS TaqMan HIV-1 Test V2.0 for 3 participants because of testing platform change during the parent study. The lower limit of detection in CSF was 100 copies per milliliter because of dilution correction. CD4 and CD8 cell counts were determined by flow cytometry.

Statistical Analyses

Relationships between baseline demographic and clinical data and baseline NP performance were examined by Spearman correlation. A multivariable regression model was used to identify associations between clinical and laboratory parameters and NP performance at baseline (dependent variable = NPZ-4, independent variables = CD4, CSF HIV RNA, days after transmission). Data were assessed for normality before analysis. Data that were found not to be normally distributed were analyzed using the appropriate nonparametric tests. The nonparametric repeated measures analysis of variance, the Friedman test, was employed to compare baseline to follow-up NP values at the 3- and 6-month time points after treatment. The Mann-Whitney U test was used to compare the change in longitudinal NP performance of the AHI group to that of the matched controls at the 6-month time point.

RESULTS

Baseline Characteristics of AHI Participants

We enrolled 36 AHI participants with a median (IQR) age of 28 (24–33) years (Table 1). Most were young educated men (89% males, 58% with bachelor's degree or higher). The median estimated time since history of HIV exposure was 19 days (IQR 15–24 days). More than half (64%) were classified as Fiebig stages I (HIV RNA+, p24 antigen–, HIV IgM–) and II (HIV RNA+, p24 antigen+, HIV IgM–). Most (86%) were infected with circulating recombinant form 01_AE, the predominant subtype in Thailand, with the remaining being recombinant circulating recombinant form 01_AE and clade B. HIV-1 tropism data were available for 34 participants; all

TABLE 1. Baseline Characteristics of AHI Participants, $N = 36$

	Median (IQR) or Total (%)
Age	28 (24–33)
Male	32 (89%)
Bachelor's degree or higher	21 (58%)
Days post-HIV transmission	19 (15–24)
Fiebig I/II*	23 (64%)
Circulating recombinant form 01_AE	31 (86%)
CD4 count (cells per cubic millimeter)	411 (338–568)
CD8 count (cells per cubic millimeter)	578 (399–1013)
Plasma HIV RNA (\log_{10} copies per milliliter)	5.52 (4.56–5.87)
CSF HIV RNA (\log_{10} copies per milliliter)	3.37 (2.19–4.35)
No drug use†	26 (72%)

*Fiebig I: HIV RNA+, Fiebig II: HIV RNA+, p24 antigen+.

†Denies any lifetime drug use or any drug use in 4 months before enrollment.

were R5-tropic. The median (IQR) CD4 and CD8 counts were 411 (338–568) and 578 (399–1013) cells per cubic millimeter, respectively. Plasma and CSF HIV RNAs were 5.52 (4.56–5.87) and 3.37 (2.19–4.35) \log_{10} copies per milliliter, respectively. Almost three-quarters (72%) denied lifetime drug use or drug use in the 4 months before enrollment.

Baseline NP Performance and Correlates

The mean z-scores were close to zero for each NP test supportive of normal performance compared with controls (Fig. 1). Specifically, the mean z-scores on GP, CT1, CT2, and TM were -0.17 , -0.20 , -0.13 , and -0.26 , respectively. Mean NPZ-4 was -0.19 . However, 8 participants performed >1 SD below the mean performance of matched participants on at least 2 NP tests. A subset met threshold criteria for anxiety ($n = 16$, 44%) or depression ($n = 8$, 22%) on the

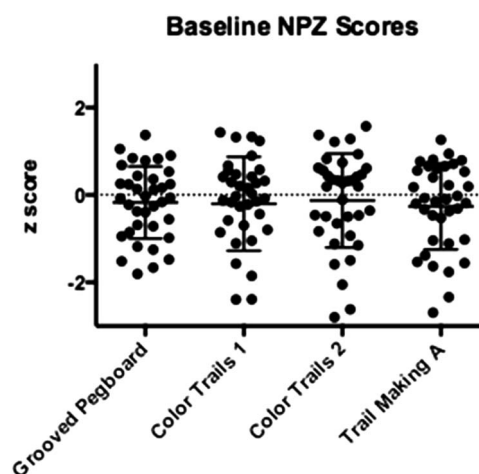


FIGURE 1. Baseline neuropsychological (NP) performance of AHI participants. Z-scores on Grooved Pegboard = -0.17 ; CT1 = -0.20 ; CT2 = -0.13 ; and Trail Making A = -0.26 . Eight participants performed >1 SD below normative means on ≥ 2 NP tests.

HADS. The composite NP score, NPZ-4, did not correlate with depression ($P = 0.336$) or anxiety scores ($P = 0.861$).

The baseline NP performance inversely correlated with CSF HIV RNA ($r = -0.493$, $P = 0.023$) and estimated days after transmission ($r = -0.389$, $P = 0.019$) (Fig. 2). There was no significant correlation seen with NP performance and plasma HIV RNA ($P = 0.203$), CD4 count ($P = 0.440$), CD8 count ($P = 0.468$), CSF white blood cell ($P = 0.073$), or CSF protein ($P = 0.995$). However, in multivariable modeling, CSF HIV RNA, CD4 count, and estimated duration of infection were found to explain 31% of the variance in NP performance at baseline (adjusted $R^2 = 0.310$, $P = 0.025$) with individual effects significant for CSF HIV RNA ($\beta = -0.725$, $P = 0.013$) and CD4 ($\beta = -0.882$, $P = 0.004$). Given the unexpected inverse relationship between CD4 count and NP performance, we included a CSF HIV RNA–CD4 count interaction term, which was significant ($\beta = 0.663$, $P < 0.001$) and resulted in an increase in the explained variance of the full model to 72%. The 21 participants with lumbar punctures were separated into 3 equal groups of low, moderate, and high CD4 count with ranges of 132–338, 339–555, and 565–970 cells per cubic millimeter, respectively. As CD4 count increased, the strength of the correlation between CSF HIV RNA and NPZ-4 decreased (low CD4 group, $R^2 = 0.37$; moderate CD4 group, $R^2 = 0.16$; high CD4 group, $R^2 = 0.02$).

Analysis of demographic differences between the subgroup of AHI participants ($n = 8$) that displayed NP testing impairment at baseline and the rest of the AHI participants ($n = 28$) revealed that the impaired subgroup had significantly higher levels of CSF HIV RNA ($U = 16$, $P = 0.047$) than the nonimpaired AHI participants [available CSF HIV RNA in impaired group ($n = 5/8$) vs. rest of AHI group ($n = 16/28$)].

Longitudinal NP Performance

Thirty-one of the 36 participants completed NP testing at both the 3- and 6-month follow-up periods. There were no baseline demographic differences between participants retained and those lost to follow-up using Mann–Whitney U test. We noted no change in motor performance over 6 months, $n = 31$ ($\chi^2(2) = 1.613$, $P = 0.446$). However, there was a significant improvement noted in CT1, $\chi^2(2) = 20.387$, $P = 0.000$; TM, $\chi^2(2) = 8.581$, $P = 0.014$; and CT2, $\chi^2(2) = 9.484$, $P = 0.009$, over the 6-month period. Post hoc analysis

with Wilcoxon signed rank tests identified significant improvement only in the initial 3 months after initial assessment ($P < 0.01$) with no significant change in performance during the last 3 months, Figure 3. Among the 8 participants who initially performed >1 SD below the mean of their matched controls on 2 or more NP tests, NP performance did not significantly change at either the 3- or the 6-month time point in any domain (CT1: $\chi^2(2) = 5.250$, $P = 0.072$; CT2: $\chi^2(2) = 4.750$, $P = 0.093$; TM: $\chi^2(2) = 1.750$, $P = 0.417$; GP: $\chi^2(2) = 1.750$, $P = 0.417$).

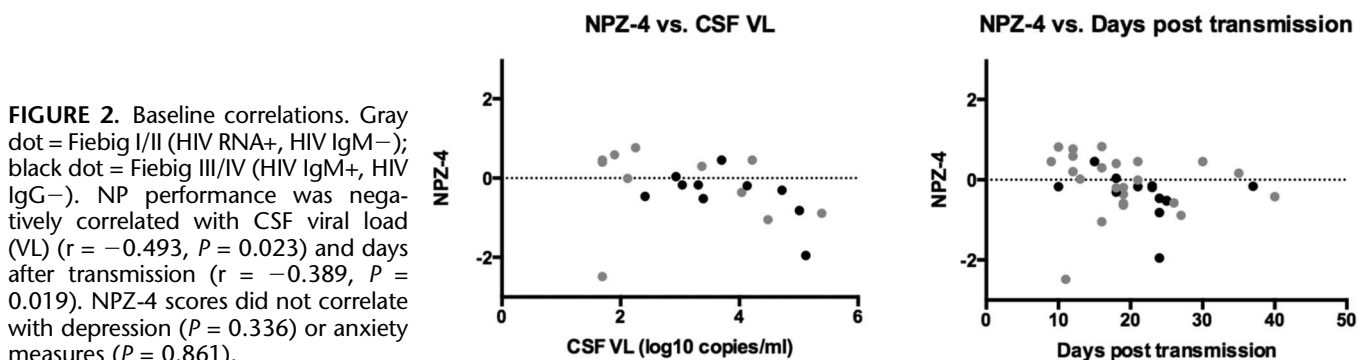
To determine how much improvement in the AHI group could be because of practice effects, we compared the change in longitudinal performance of the AHI group ($n = 31$) with that of the matched controls. Of the initial 251 HIV-uninfected controls used for baseline NP performance analysis, 45 control participants had complete NP data for the 6-month study duration and were used for the longitudinal NP performance analysis. This 45-participant subgroup had a median (IQR) age of 36 (25–45) years, 51% ($n = 23$) were males, and 13% ($n = 6$) had a bachelor's degree or higher. In comparison, the AHI group followed over time ($n = 31$) was younger [median (IQR) age of 29 (23–33) years], predominantly males (90%, $n = 28$), and more educated (52%, $n = 16$, with bachelor's degree or higher).

We found that the degree of NP improvement in the AHI group was greater than that seen in matched controls in one processing speed test, CT1 ($U = 473$, $P = 0.018$), Figure 4. The observed improvement in the AHI group was similar to that of controls on the other 3 NP tests (CT2: $U = 516$, $P = 0.055$; TM: $U = 612$, $P = 0.366$; GP: $U = 654$, $P = 0.646$).

In multivariable modeling (dependent variable = change in performance in each NP test, independent variables = MVC, CD4, CSF HIV RNA, days after transmission), MVC was not found to be a significant predictor of longitudinal NP performance in any NP test (CT1: $\beta = -0.129$, $P = 0.652$; CT2: $\beta = -0.042$, $P = 0.876$; GP: $\beta = 0.129$, $P = 0.642$; TM: $\beta = -0.418$, $P = 0.069$).

DISCUSSION

This prospective longitudinal study characterized NP performance in Thai participants during AHI, beginning at median estimated 19 days since history of HIV exposure and up to 6 months after cART. The baseline performance of the AHI group as a whole did not significantly differ from that of



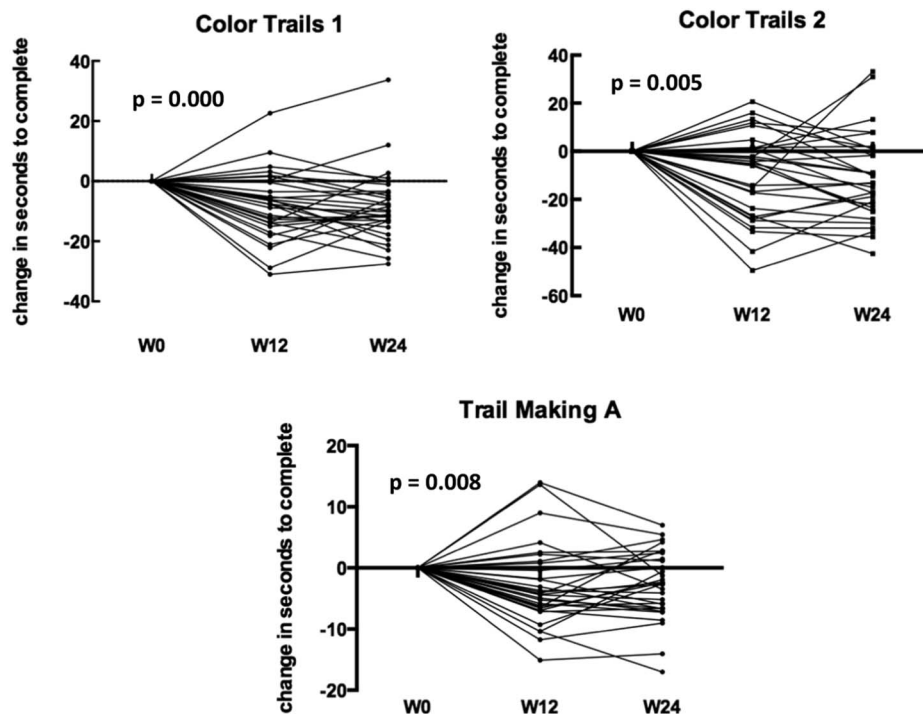


FIGURE 3. Longitudinal neuropsychological performance after ART initiation. Significant improvement was seen at weeks 0–12 in processing speed (CT1: $P = 0.000$; Trail Making A: $P = 0.008$) and executive functioning (CT2: $P = 0.005$) in the total cohort. No change in motor performance was observed.

an age- and education-matched group of HIV-uninfected controls in the domains of psychomotor speed, executive function, and fine motor performance. However, a subgroup of individuals exhibited cognitive impairment at baseline that correlated with higher CSF HIV RNA.

There are several possible explanations for the relatively normal performance of most AHI participants at baseline. First, given the very early timing after estimated

exposure, participants may have been at too early of a stage to have incurred processes such as neuronal injury that would underlie NP impairment. Neuronal injury can be measured by CSF neurofilament light chain, and we have shown that cART-naïve HIV participants have normal CSF neurofilament light chain levels and no evidence of axonal injury during very AHI.²⁰ Taking into consideration the finding of a notable subset of participants (~25%) who demonstrated

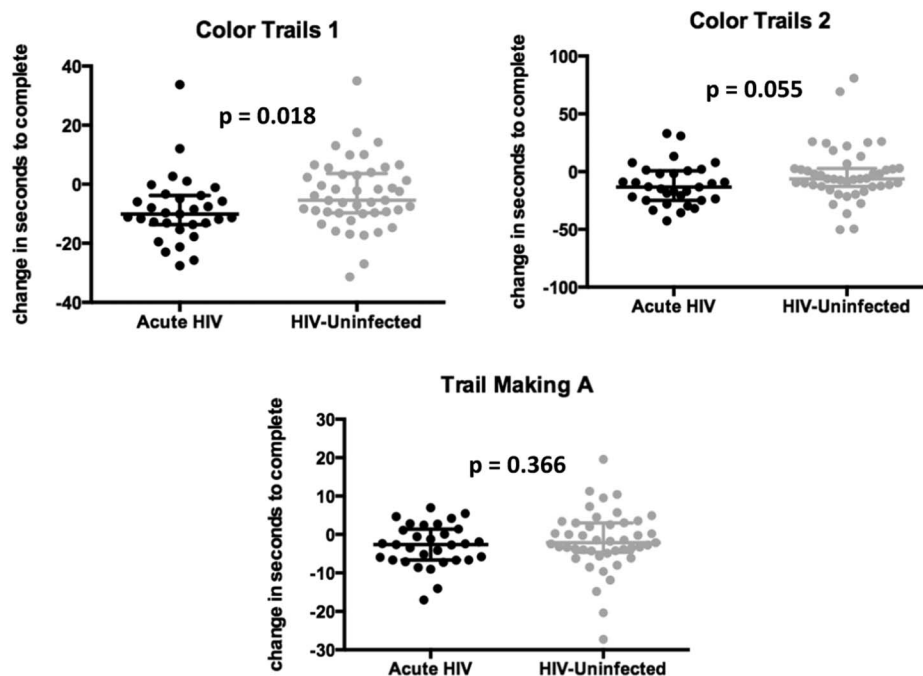


FIGURE 4. Comparison of neuropsychological performance improvement in AHI participants and HIV-uninfected controls. When compared with HIV-uninfected controls in NP performance at 6 months, AHI participants only had a greater improvement in one processing test (CT1: $P = 0.018$).

baseline neurocognitive impairment, it is most likely that there is a high level of heterogeneity in baseline NP performance in AHI with some performing above average and others exhibiting significant impairment. Second, small sample size could have limited our ability to identify very small differences in NP performance. And finally, it is possible that our neuropsychological battery was too brief to have sufficient sensitivity in identifying HIV-related neurocognitive impairment in acute HIV. Though some studies have successfully identified neurocognitive impairment with a short battery,¹³ these brief batteries may be more useful in chronic HIV rather than acute HIV.

Factors such as drug use, anxiety, and depression can affect NP performance.^{21–23} It is difficult to ascertain how much of an effect previous drug use and psychiatric symptoms have on neurocognitive performance, but the relatively low incidence of reported illicit drug use (28%) and the lack of correlation between anxiety/depressive symptoms and NP scores in this cohort reduce concern regarding the confounding nature of these premorbid factors.

We investigated clinical and biological markers that might render AHI participants at a higher risk for cognitive impairment. NP performance inversely correlated with CSF HIV RNA level and estimated days after HIV transmission, supporting the concept that NP impairment might be, in part, related to the level of viral burden in the CNS during this period. This was further supported by comparison analysis between the small subgroup of AHI participants who displayed cognitive impairment at baseline and the rest of the AHI participants, which demonstrated that those with baseline impairment had significantly higher levels of CSF HIV RNA than their fellow AHI counterparts. These correlations between NP performance and the selected clinical markers are preliminary evidence of associations and would require replication.

Interestingly, there was no significant association between CD4 count and NP performance in univariate modeling in this cohort. Previous work has shown that low CD4 count, especially a low CD4 nadir, is associated with neurocognitive impairment and that higher CD4 counts confer a lower risk of impairment.^{24,25} Our findings might be explained by differential effects of the CD4 count in AHI vs. chronic HIV infection. Unlike in chronic infection, low CD4 counts during AHI are less of a marker of sustained immunosuppression and related neurocognitive damage but instead reflect acute and potentially variable immunologic responses with unclear significance for the CNS.

Although we did not identify an association between CD4 count and NP performance in univariate analyses, a significant relationship was found in multivariable modeling between these 2 factors. In addition to CD4 count, CSF HIV RNA and days after transmission were also significant predictors of NP performance in a multivariable regression model. As expected, CSF HIV RNA and days after transmission had an inverse relationship with cognitive performance. However, there was an unexpected inverse relationship between CD4 count and NP performance evident from regression analyses. Because CD4 count drops and plasma viral load increases during the initial weeks of HIV infection,²⁶ it was hypothesized that higher CD4 would be

associated with better NP performance. Our finding is most likely related to the fact that CSF HIV RNA and CD4 are closely related; in fact, our correlational analysis showed a significant negative correlation of $r = -0.63$ between these 2 factors, thus suggesting multicollinearity and distortion of the relationship between CD4 and NP performance.

We found that CD4 level moderated the negative relationship between CSF HIV RNA and NP performance, suggesting that CD4 count may play a protective role in maintaining neurocognitive function despite high levels of CSF HIV RNA. This finding is important because it suggests that utilization of CD4 count alone as a clinical guidepost to facilitate treatment decisions to address neurocognitive performance may not be ideal. Furthermore, preventing advanced immune suppression and initiating cART at higher CD4 counts may result in better overall cognitive outcomes among HIV-infected individuals.

After immediate cART initiation, we observed improvement in most tests during the first 3 months but change in only one test (CT1) at 6 months exceeded that of change observed in controls, supportive of practice effects. This contrasts with some reports that have demonstrated deleterious effect of cART on cognition.^{27,28} The few participants ($n = 8$) who demonstrated NP impairment at baseline did not improve at 6 months. They had higher levels of CSF HIV RNA at baseline, which could support early unresolved cognitive deficits over 6 months. Premorbid factors may influence this outcome, but it is noteworthy that only 2 of the 8 individuals reported recent illicit drug use. As such, premorbid substance abuse is not a key driver of poor neuropsychological outcome after cART among individuals with impaired performance at baseline.

The most commonly described cognitive deficits in chronic HIV occur in the domains of motor and psychomotor functions, executive function, processing speed, and attention.^{29–31} Psychomotor performance and processing speed are regarded as more reliable markers of cognitive impairment longitudinally, given that they are less influenced by practice effects.¹⁰ In our cohort, there were no deficits detected on these tests at baseline. Given that our cohort was in the very early stages of HIV infection, the lack of deficit in motor performance is not surprising. It has been documented that impairment in this domain usually becomes evident in more advanced disease.³¹ The use of culturally matched longitudinal control data is a strength of our study; but because our study group was Thai and mostly infected with clade AE virus, broad generalizability may be limited.

In sum, we identify limited abnormalities on neuropsychological tests among individuals with AHI at baseline with improvement after treatment. We also identify approximately one-quarter of participants having performance in an impaired range during AHI with limited improvement after 6 months of cART. This study and future research should compare the long-term NP performance trajectory from AHI to chronic disease compared with those who initiate treatment later in disease. Such comparison may provide conclusive evidence to support the need for earlier initiation of cART to prevent the risk of developing HIV-associated neurocognitive impairment.

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