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Neuropsychological Testing Impairment in Acute HIV and the Effects of Immediate
Antiretroviral Therapy

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by

Idil Kore

2015

Abstract

Acute HIV infection (AHI) is accompanied by central nervous system infection and immune activation. We investigated baseline predictors of neuropsychological (NP) performance in Thai participants with AHI and the effect of antiretroviral therapy (ART) on domains of functioning known to be affected by HIV.

36 participants with AHI (89% male, median age of 28 years, median time since HIV exposure of 19 days) were evaluated at baseline and 3 and 6 months after ART.

Performance on the Grooved Pegboard test (GP), Color Trails 1 & 2 (CT1, CT2), and Trails Making Test A (TM) were standardized to 251 age and education matched HIV-uninfected Thais and summarized as a composite score (NPZ-4). Change in NP performance from baseline to 6 months was compared between AHI participants and matched Thai HIV- controls (n=45, 51% male, median age of 36 years) to account for practice effects. Analyses included Spearman correlation, multivariable regression, non-parametric repeated measures ANOVA, and Mann-Whitney U test.

Baseline NP scores for the AHI group were similar to controls on each test (z scores range: -0.26 to -0.13). NP performance was negatively correlated with cerebrospinal fluid (CSF) HIV RNA ($r = -0.493$, $p = 0.023$) and days post-transmission ($r = -0.389$, $p = 0.019$). NP performance improved on CT1, CT2, and TM 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 ($p = 0.018$). Eight participants performed

>1 standard deviation below normative means on ≥ 2 NP tests at baseline. This subgroup had higher cerebrospinal fluid (CSF) HIV RNA compared to the rest of the AHI group ($p=0.047$) and exhibited no improvement in NP performance across the follow-up periods.

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

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Table of Contents

I.	Introduction.....	1
II.	Statement of Purpose and Hypothesis.....	13
III.	Methods.....	14
IV.	Results.....	17
V.	Discussion.....	23
VI.	References.....	29

INTRODUCTION

Clinical features of HIV-associated neurocognitive disorders (HAND)

HIV infection is associated with a wide range of central and peripheral neurological complications. These include focal central nervous system (CNS) disorders such as cerebral toxoplasmosis, primary CNS lymphoma, and progressive multifocal leukoencephalopathy (PML), and non-focal disorders such as encephalitis, metabolic and toxic encephalopathies, peripheral neuropathy, and neurocognitive disease [1, 2]. The spectrum of neurocognitive disease currently documented in the HIV-infected population spans cognitive, motor, and behavioral impairments and is termed “HIV-associated neurocognitive disorders” (HAND) [3]. It ranges from asymptomatic neurocognitive impairment (ANI), to minor neurocognitive disorder (MND) and HIV-associated dementia (HAD) [3]. Patients with ANI have impairment in at least 2 cognitive areas, which do not interfere with daily functioning. The cognitive domains tested include attention/memory, learning, executive function, processing speed, and motor skills. Patients with MND similarly have cognitive impairment in 2 or more domains; but in addition, they suffer from mild functional impairment. Lastly, patients with HAD exhibit marked cognitive impairment in 2 or more domains, with marked functional impairment [4].

Despite access to antiretroviral therapy (ART), a large percentage of chronically infected HIV-positive individuals still exhibit mild forms of HAND [5, 6]. Prior to widespread use of ART, 15-20% of HIV patients developed HAD [4]; but that incidence is now greatly reduced. In contrast, the prevalence estimates of milder forms of cognitive

impairment (ANI and MND) have not decreased, with up to 50% of chronically infected HIV-positive individuals still manifesting some degree of cognitive dysfunction [5-8]. While the frequency and magnitude of cognitive deficits in HIV-infected individuals with established infection have been well documented, limited information is available regarding the neuropsychological status among individuals with acute HIV infection, prior to antibody seroconversion.

Neuropathogenesis of HAND

There are a number of proposed mechanisms in regard to how HIV gains entry into the CNS. These include translocation of infected monocytes and lymphocytes past the blood brain barrier (BBB), transcytosis of free virus across neuroendothelial cells, or direct infection of brain endothelial cells [9, 10]. HIV requires binding to the CD4 receptor and a chemokine co-receptor (CCR5 or CXCR4). After entering the CNS, HIV mainly infects macrophages and microglia cells given that they are the only cells in the brain that express CD4 and CCR5. Infection of astrocytes expressing CXCR4, however, can also occur [9].

The mechanisms of HIV-mediated neuropathology are multi-faceted. They involve direct neurotoxic effects of the virus and viral proteins [9, 10]. In addition to producing these viral products, infected macrophages and microglia also release inflammatory cytokines such as tumor necrosis factor (TNF), interleukin-1 beta (IL-1 β), and interferon-gamma (IFN- γ) that increase BBB permeability and also lead to direct damage of neurons and glia [10]. Production of cellular products such as matrix metalloproteinases (MMPs) by

activated macrophages aid in the disruption of the BBB, leading to increased trafficking of leukocytes into the CNS and subsequent neuroinflammation [11]. Chronic activation of these inflammatory responses has been implicated in development of HIV-associated cognitive dysfunction [12].

There is now evidence that CNS immunoactivation is present even in early HIV infection. In a study of 96 antiretroviral naïve HIV+ individuals at a median 77 days after estimated HIV exposure, it was found that these acute HIV subjects had elevations in markers of CNS inflammation and macrophage/microglial activation that were similar to that measured in chronically infected HIV subjects [13]. Given that these processes that lead to the neuronal damage and functional loss underlying HAND begin early in the course of HIV infection, it is possible that initiation of ART in the acute stages of infection can prevent development of HIV-associated neurocognitive impairment.

Negative Consequences of HAND

The most commonly described cognitive deficits in HIV infection occur in the domains of motor and psychomotor function, executive function, processing speed, and attention [14-16]. A meta-analysis of 41 neuropsychological (NP) studies evaluating cognitive function as HIV disease progresses from asymptomatic to symptomatic to AIDS found that domains with the greatest decline are motor function, executive function, and information processing speed [16]. This has been consistent with other literature that has noted cognitive impairment to worsen with disease progression [14]. Other domains

known to be affected by HIV infection include verbal memory [17-19], and visual memory and visuospatial function [16].

With the development of HAND, there are a number of adverse outcomes with respect to everyday functioning. It has been shown that HIV-infected individuals with NP impairment have nearly three times the rate of unemployment as unimpaired HIV+ individuals [20]. One study explored factors associated with difficulties returning to work among HIV+ individuals and found that verbal memory deficits were the greatest barrier to employment attainment [21]. NP impairment, specifically in the domains of memory and executive functioning, has been shown to be related to lower antiretroviral therapy adherence [22, 23]. Other major negative consequences of neurocognitive impairment in the HIV population include decreased quality of life [24] and increased risk of mortality [25]. In a prospective study of 414 HIV+ subjects over a median duration of approximately 2.5 years, subjects with NP impairment were found to have nearly twice the rate of death than unimpaired subjects [25]. Data regarding the specific causes of death were not available in this study, but this increased rate of mortality remained significant even after adjusting for other predictors of mortality such as older age, lower CD4 counts, presence of AIDS-defining opportunistic infections, low hemoglobin, and elevated serum β 2-microglobulin [25].

Causes of Persistent HAND

Different hypotheses have been proposed as possible causes for the persistence of HAND in the era of ART. One explanation is poor CNS penetration of some antiretrovirals

(ARVs) leading to ineffective treatment of CNS HIV disease [26]. Letendre et al. constructed a schema to quantify the CNS Penetration Effectiveness (CPE) of antiretroviral drugs. This construct was based on chemical properties of individual ARVs such as molecular weight, pharmacokinetic data demonstrating measurable drug concentration in human or animal cerebrospinal fluid (CSF), and clinical effectiveness studies showing reduction in CSF viral load or improvement in cognition. Each ARV drug was assigned a rank based on these qualities, and the rankings of individual drugs were combined to give regimens a collective CPE rank score. Higher CPE ranks were found to correlate with lower levels of CSF HIV viral load [26]. While other studies have supported this finding of successful CSF viral suppression with more potent ARV combinations [27], it is unclear whether such reduction in CSF viral translates to improved neurocognitive outcomes. Some data has shown that ART regimens with higher CNS penetration are associated with improved neurocognitive performance [28], while others have shown that they lead to poorer neurocognitive performance [27]

Such studies showing an adverse effect of ARVs on cognition lend evidence to another potential cause of persistent HAND: ART-mediated neurotoxicity in the CNS. There has been well-documented data on the negative neuropsychiatric effects of Efavirenz, predominately sleep disturbances, hallucinations, impaired memory and concentration, and increased anxiety [29, 30]. Some work has also been done looking into the effects of nucleoside reverse transcriptase inhibitors (NRTIs) on the CNS [31]. Using magnetic resonance spectroscopy, investigators evaluated the concentration of N-acetylaspartate (NAA, a marker of mitochondrial integrity) in the frontal white matter of HIV+

individuals on didanosine and/or stavudine, HIV+ individuals on zidovudine and lamivudine, HIV+ individuals on no antiretrovirals, and HIV-negative controls. They found significantly lower NAA concentrations in the frontal white matter of HIV-infected individuals on didanosine and/or stavudine when compared to HIV-negative controls, and the two other HIV+ groups had intermediate NAA levels [31]. Additionally, longer duration of didanosine and/or stavudine treatment and being on more than one NRTI correlated with lower NAA frontal white matter concentrations. This study took into account the severity and length of disease; so though HIV infection itself is associated with decreases in NAA, these findings suggest that NRTIs might lead to additive damage to CNS mitochondria and subsequent cognitive dysfunction [31].

A prospective study evaluating the effects of discontinuation of ART on cognitive performance had an unexpected finding that raises more speculation about adverse neurocognitive effects of ART [32]. In this study, HIV+ individuals who had been on a number of different ART regimens for ≥ 6 months discontinued ART at study entry and completed neurocognitive function test at different time points over a 2 year period. Surprisingly, neurocognitive performance improved significantly post-ART interruption for the entire study duration, even after taken into consideration the presence of practice effects. Additionally, individuals who restarted ART prior to the end of the study had no significant change in cognitive functioning. It is plausible that these unexpected results may have been due to ART-related neurotoxicity or other ART-induced neurocognitive side effects that improved with treatment cessation [32].

Another possible contributing factor to the persistence of HAND is the presence of viral resistance. Poor individual adherence is a common culprit of drug resistance, leading to the development of resistance-associated mutations. Some individuals might also be infected with HIV strains that already contain mutations that decrease drug susceptibility. An additional phenomenon that can arise is genetic compartmentalization of HIV-1 between the CNS and periphery, wherein the brain acts as a reservoir for the evolution of unique HIV-1 variants. Previous studies demonstrated increased compartmentalization in the CSF of individuals with chronic HIV infection (especially those with HAD), with minimal to no compartmentalization in those with mild to no neurological disease [33, 34]. More recent work, however, has elucidated that compartmentalization can begin earlier in the course of HIV disease during primary HIV infection, defined as the first year after HIV transmission, even in the absence of any neurological symptoms [35].

Other factors that likely play a role in the continued presence of mild neurocognitive impairment include incomplete HIV suppression while on ART. Data from a large multicenter study group of over 1,500 HIV+ individuals found that 44% of those on ART (482 of 1,105) had detectable plasma HIV viral load (>50 copies/mL) [5]. With such sustained peripheral viral replication, there can be continued seeding of the brain leading to persistent immune activation.

Even with treatment-controlled viral replication in the plasma, a phenomenon known as CSF “viral escape” can occur—in which there is detectable CSF HIV RNA in the setting of suppressed viremia in the blood [36-39]. This occurrence has been documented in

HIV-infected individuals presenting with neurological symptoms [37-39]. One study has demonstrated that this can occur in neurologically asymptomatic individuals as well [36]. In a cross-sectional study of 69 HIV+ subjects with no neurological symptoms and undetectable plasma HIV RNA after >6 months of ART, investigators found that 10% of these subjects exhibited CSF viral escape. Of note, the relative CNS penetrative rank of the ART regimen was not found to predict CSF viral escape [36]. Most of these cases of symptomatic CSF viral escape were found to harbor resistance mutations in the CSF strains, and subsequent therapy adjustments based on these genotypes led to clinical improvement [37-39].

Even with successful peripheral and central viral suppression, there has been evidence that some level of immune activation continues [40-43]. In a study of 15 HIV+ individuals on ART for at least 4 years with HIV RNA levels <50 copies/mL in plasma and CSF, investigators found that though markers of neuroinflammation (specifically CSF neopterin, CSF WBC, and CSF immunoglobulin (IgG)) were lower than pre-ART, neopterin and IgG production were still above the upper limit of normal in 60% of study participants, indicating an ongoing intrathecal immunoactivation [41]. Theories that have been proposed include continued low-grade viral replication in the brain or CSF that is not detectable by current assays of CSF HIV RNA, transient CSF exposure to migrating infected cells, or possibly a sustained level of cellular activation mediated by a non-specific immune response [40-42].

Efficacy of ART in Reducing HAND

The efficacy of ART in improving cognitive performance in individuals with advanced HIV disease is well understood [28, 44-46]. The incidence of more severe neurocognitive impairments such as HIV-associated dementia has greatly decreased since the advent of ART [5, 47, 48]. Specific domains that have been shown to improve once on therapy include concentration and psychomotor speed, fine motor function, and executive function [49, 50]. On the other hand, verbal and visual memory, and visuospatial function are domains that have not shown movement with ART [51].

However, studies demonstrate that a considerable proportion of chronically infected persons continue to have neurocognitive deficits despite ART [52]. Importantly, studies demonstrating chronic neurocognitive impairments despite treatment were focused on individuals who started ART 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. Additionally, many of these studies have not taken into account the CNS penetration of the drug regimens used and its possible impact on the presence of continued neurocognitive deficits.

One study longitudinally examined the effect of ART on cognitive performance during early infection [53], identifying mild deficits in NP performance pre-ART and stabilization of cognitive function following ART. However, this observational study did not control for practice effects and assessed participants about four months after estimated HIV transmission, well after the acute phase of infection. Further, in previous studies neurocognitive assessments were conducted at variable times after infection [53].

We are aware of no published work that has examined the impact on NP testing of starting ART very early after HIV identification during AHI.

Limited Research on Neurocognitive Status during Acute HIV Infection

It has been previously demonstrated that CSF HIV RNA can be detected as early as eight days post estimated date of transmission [54], with concurrent evidence of CNS inflammation, measured by magnetic resonance spectroscopy imaging and CSF markers of immune activation [13, 54]. There are limited data characterizing cognitive function in primary HIV infection, and these studies have not included individuals captured during the first month [55, 56]. Results from these studies have been mixed, with one study reporting impairments in processing speed, executive function and learning among ART-naïve patients with primary infection [53], while others have not demonstrated statistically significant differences in neuropsychological (NP) performance between primary infection participants and HIV-uninfected controls [57, 58]. No studies have examined NP performance and its associations with HIV disease biomarkers during acute HIV infection (AHI), prior to antibody seroconversion.

HIV/AIDS in Thailand

The first reported case of HIV/AIDS in Thailand occurred in 1984 [59]. When it was shown that a key driver of the ensuing epidemic was commercial sex work, the country implemented a successful nationwide HIV prevention campaign in the 1990s that was focused on increasing condom use among sex workers and their clients [60, 61]. Funding for HIV/AIDS in Thailand dramatically increased from just \$684,000 in 1988 to \$82

million in 1997 [62]. And more importantly, while the majority of funds in the late 1980s came from donors (e.g. in 1989, 90% of HIV funding was from international development assistance programs), by 1997, the Royal Thai government financed approximately 96% of the HIV/AIDS budget [62].

This impressive prevention campaign led to condom use in commercial sex establishments increasing to over 90%; as a result, HIV prevalence in Thailand only peaked to about 1.5% in 1996 [63]. Since then, there has been a steady decline in the number of new HIV infections and people living with HIV in Thailand [64]. As of 2012, HIV prevalence among adults in Thailand is approximately 1.1% with ~440,000 people living with HIV, and ~21,000 deaths associated with AIDS [65]. The highest prevalence rates are concentrated in high-risk populations, specifically sex workers, injection drug users, and men who have sex with men [66].

Since 1992, impoverished HIV-positive Thai citizens had access to free antiretrovirals [63]. And in 2001, the government integrated a universal antiretroviral treatment program into its universal health coverage [67]. ART is now accessible at 95% of the 1,066 Thai hospitals that provide HIV care [68]. Thailand has also started producing generic antiretrovirals to further decrease the cost of treatment [63].

In 2012, the Thai government's policy for initiating ART was based on an eligibility threshold of CD4 count of 350 cells/mm³ or less [64]. The WHO revised its recommendations on CD4 cell count threshold for ART initiation in 2013 and increased

from 350 cells/mm³ to 500 cells/mm³ or less [69]. At this time, however, Thailand decided to expand treatment eligibility even more and instituted policies in October 2014 that extended ART access to all HIV+ individuals regardless of CD4 count [64]. Based on a CD4 cell count threshold of 350, data on access to HIV treatment in Thailand showed that approximately 80% of eligible individuals are receiving ART [64].

Thailand has created a number of domestic and international HIV/AIDS research collaborations. One such partnership is SEARCH, which was the site of this thesis project. SEARCH is a research partnership initially established in 2005 among three partners: the Thai Red Cross AIDS Research Centre (TRCARC), the University of Hawaii (UH), and the Armed Forces Research Institute of Medical Sciences (AFRIMS, a US army laboratory in Bangkok). SEARCH initiated a unique neurological study of individuals identified during acute HIV to identify and characterize the earliest immunological and virological events in the CNS beginning as early as the first week post HIV exposure. Among its several aims, this study in particular also looks to determine if early ART initiation during acute HIV impacts CNS complications during chronic HIV. Study participants were recruited from the Thai Red Cross Anonymous Clinic in Bangkok. Participants were identified and consented to HIV screening when getting STD testing at the Red Cross. This thesis project investigated the presence of NP impairment in acute HIV and the effects of early ART in longitudinal NP assessment.

STATEMENT OF PURPOSE AND HYPOTHESES

The current study evaluated Thai participants who were identified within days of estimated HIV exposure and before antibody seroconversion. We examined neuropsychological performance at two time points (3 months and 6 months) following ART initiation, and compared change in NP performance in the AHI cohort with that of Thai normative controls to account for practice effects.

The two primary aims of this study are:

1) To investigate the presence of neuropsychological (NP) testing impairment in participants with acute HIV infection and characterize baseline predictors of NP performance in this population.

Hypothesis: NP testing impairment will be detected in acute HIV infection and will correlate with baseline clinical biomarkers.

2) To evaluate whether immediate treatment with ART leads to improvement in NP performance in follow-up. Baseline performance in ART naïve participants will be compared to performance at 6 months of follow-up after ART.

Hypothesis: NP performance will improve above and beyond practice effects following ART 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 Fiebig stage defined by the sequential appearance of viral RNA, antigen, and antibodies, as previously described [70, 71]. 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 ART. 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 prior to starting ART. Due to the nature of the parent study, individuals were randomized either to standard ART (efavirenz, tenofovir, and emtricitabine or lamivudine) or standard ART plus raltegravir and maraviroc (MVC). There were no significant differences in baseline characteristics (age, gender, days post HIV transmission, CD4 count, CD8 count, plasma HIV RNA, and CSF HIV RNA) between the two 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 0-3, 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 was elicited from participants through structured interviews. *Time of HIV transmission:* AHI was confirmed by serial laboratory testing at 2, 4, 8, 12, 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 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, non-dominant hand), psychomotor speed (Color Trails 1, Trail Making A), and executive function/set shifting (Color Trails 2).

We utilized an existing normative NP testing database of HIV-uninfected Thai control participants (n= 449) [72]. For the purpose of this study, we utilized only the 251 HIV-uninfected controls in the similar age range as our AHI participants. The normative sample had a median (IQR) age of 34 (27-42) years; 46% (n=115) were male 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 longitudinal NP performance analyses, only the 45 controls that had complete NP data for the six-month study period were utilized.

The raw NP scores of 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 via 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 due to testing platform change during the parent study. The lower limit of detection in CSF was 100 copies/ml due to dilution correction. CD4 and CD8 cell counts were determined by flow cytometry.

Statistical Analysis:

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 post transmission). Data that were found to not be normally distributed were analyzed using the appropriate non-parametric tests. The non-parametric repeated measures ANOVA, the Friedman test, was employed to compare baseline to follow up NP values at the 3 and 6 month time point after treatment. The Mann Whitney U test was utilized to compare the change in longitudinal NP performance of the AHI group to that of the matched controls at the 6-month time point.

Study concept and design, participant recruitment, and acquisition of data were performed by others. The student was involved solely in the analysis and interpretation of data.

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% male, 58% with bachelor's degree or higher). The median estimated days since HIV exposure was 19 days (interquartile range 15-24 days). Over half (64%) were classified as Fiebig stage I (HIV RNA+, p24 antigen-, HIV IgM-) and II (HIV RNA+, p24 antigen+, HIV IgM-). Most (86%) were infected with circulating recombinant form (CRF) 01_AE, the predominant subtype in Thailand, with the remaining being recombinant CRF01_AE and clade B. HIV-1 tropism data were available for 34 participants; all were R5-tropic. The median (interquartile range) CD4 and CD8 counts were 411 (338-568) cell/mm³ and 578 (399-1013) cells/mm³,

respectively. Plasma and CSF HIV RNA was 5.52 (4.56-5.87) \log_{10} copies/ml and 3.37 (2.19-4.35) \log_{10} copies/ml, respectively. Almost three-quarters (72%) denied lifetime drug use or drug use in the four months prior to enrollment.

	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%)
CRF01_AE	31 (86%)
CD4 Count (cells/mm ³)	411 (338 – 568)
CD8 Count (cells/mm ³)	578 (399 – 1013)
Plasma HIV RNA (\log_{10} copies/ml)	5.52 (4.56 – 5.87)
CSF HIV RNA (\log_{10} copies/ml)	3.37 (2.19 – 4.35)
No drug use**	26 (72%)

Table 1. Baseline Characteristics of AHI Subjects, N=36.

*Fiebig I: HIV RNA+; Fiebig II: HIV RNA+, p24 antigen +. **Denies any lifetime drug use or any drug use in 4 months prior to enrollment

Baseline NP Performance and Correlates

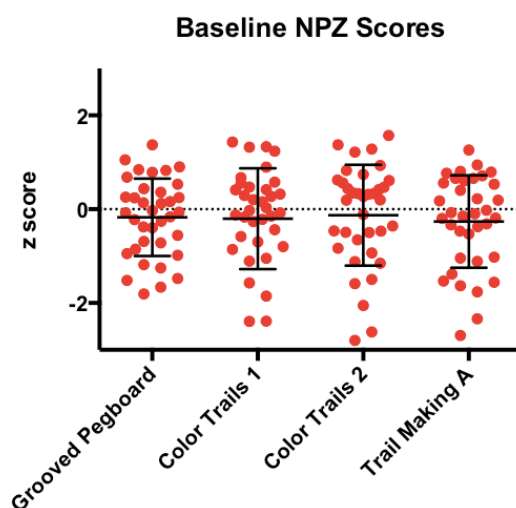


Figure 1. Baseline Neuropsychological (NP) Performance of Acute HIV Subjects.

The mean z-scores were close to zero for each NP test supportive of normal performance compared to controls (**Figure 1**). Specifically, the mean z-scores on Grooved Pegboard, Color Trails 1, Color Trails 2 and Trail Making A were -0.17, -0.20, -0.13, and -0.26, respectively. Mean

NPZ4 was -0.19. However, eight participants performed greater than one standard deviation below the mean performance of matched participants on at least two NP tests. A subset met threshold criteria for anxiety (n=16, 44%), or depression (n=8, 22%) on the HADS scale. The composite NP score, NPZ-4, did not correlate to 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 post transmission ($r=-0.389, p=0.019$) (**Figure 2**).

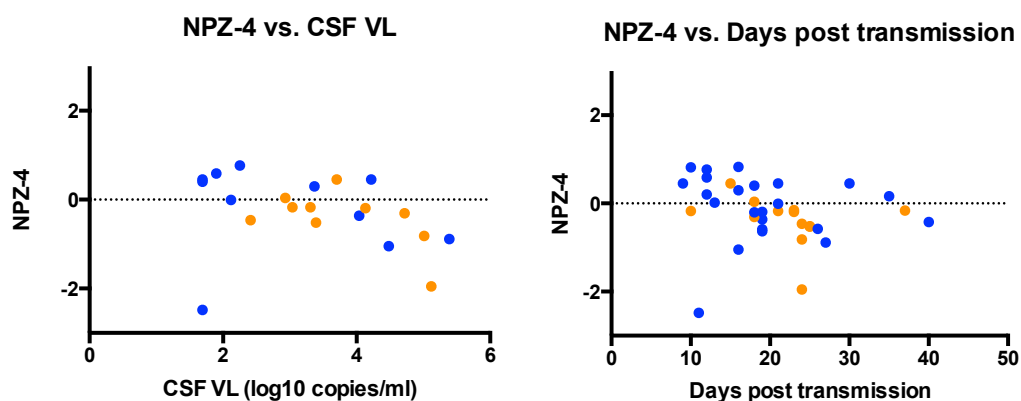


Figure 2. Baseline Correlations. Blue dot = Fiebig I/II (HIV RNA+, HIV IgM-), Orange dot = Fiebig III/IV (HIV IgM+, HIV IgG-). NP performance was negatively correlated with cerebrospinal fluid (CSF) viral load (VL) ($r=-0.493, p=0.023$) and days post-transmission ($r=-0.389, p=0.019$). NPZ4 scores did not correlate with depression ($p=0.336$) or anxiety measures ($p=0.861$).

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 WBC ($p=0.073$), 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 (adjusted R-square = 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 LP were separated into 3 equal groups of high, moderate, and low CD4 count with ranges of 132-338 cells/mm³, 339-555 cells/mm³, and 565-970 cells/mm³, 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 non-impaired 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 thirty six participants completed NP testing at both the three month and six month follow-up period. There were no baseline characteristics 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 Color Trails 1, $\chi^2(2) = 20.387$, $p=0.000$ Trail Making A, $\chi^2(2) = 8.581$, $p=0.014$) and Color Trails 2, $\chi^2(2) = 9.484$, $p=0.009$) over the 6 month period. Post-hoc analysis with Wilcoxon signed-ranks tests identified significant improvement only in the initial 3 months following initial assessment (p s <0.01) with no significant change in performance during the last 3 months, **Figure 3**.

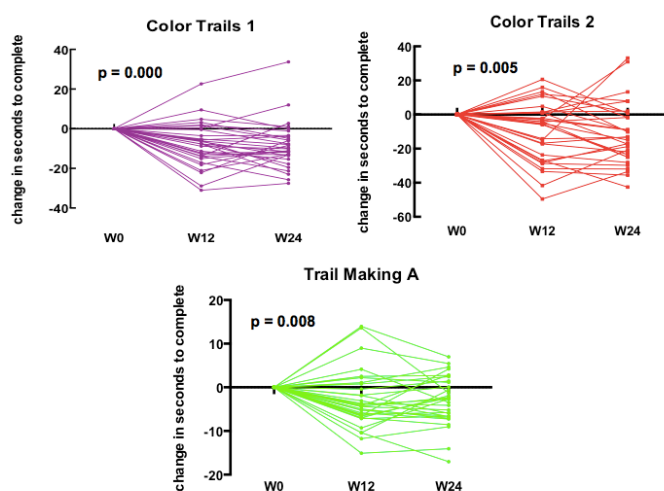


Figure 3. Longitudinal Neuropsychological Performance after ART Initiation.

Figure 3. Significant improvement was seen in week 0 to week 12 in processing speed (Color Trials 1, $p = 0.000$; Trail Making A, $p = 0.008$) and executive functioning (Color Trails 2, $p=0.005$) in the total cohort. No change in motor performance.

In the 8 participants who initially performed greater than one standard deviation below the mean of their matched controls on two or more NP tests, NP performance did not significantly change at either the 3 or 6 month time point in any domain ((Color Trails 1, $\chi^2(2) = 5.250$, $p=0.072$; Color Trails 2, $\chi^2(2) = 4.750$, $p=0.093$; Trail Making A, $\chi^2(2) = 1.750$, $p=0.417$; Grooved Pegboard, $\chi^2(2) = 1.750$, $p=0.417$)).

In order to determine how much of the improvement in the AHI group could be due to practice effects, we compared the change in longitudinal performance of the AHI group (n=31) to 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 six-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 male 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), predominately male (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 (CT 2, $U = 516$, $p = 0.055$; TM A, $U = 612$, $p = 0.366$; 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 post 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: $\beta = -0.418$, $p = 0.069$).

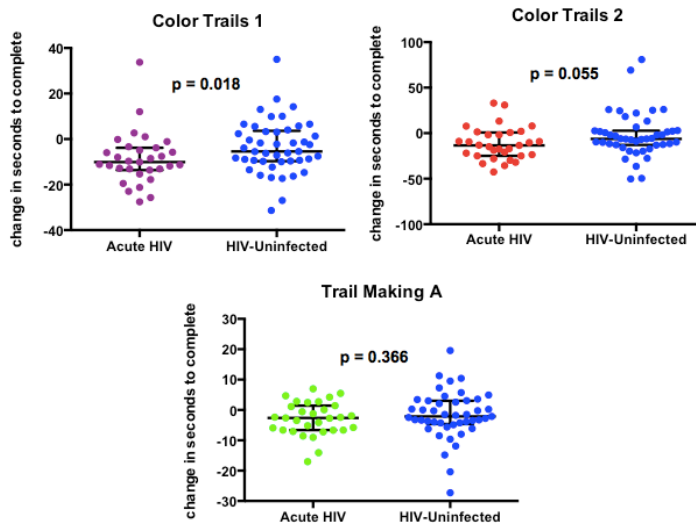


Figure 4. Comparison of Neuropsychological Performance Improvement in Acute HIV and HIV-Uninfected Controls.

Figure 4. When compared to HIV-uninfected controls in NP performance at 6 months, AHI participants only had a greater improvement in one processing test (Color Trails 1, $p = 0.018$).

DISCUSSION

This prospective longitudinal study characterized NP performance in Thai participants during AHI, beginning a median estimated 19 days since history of HIV exposure and up to six months after ART. The performance of the AHI group did not significantly differ from that of 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 following estimated exposure, participants may have been at too early of a stage to have incurred processes such as neuronal injury that would underlie any NP impairment. Neuronal injury can be measured by CSF neurofilament light chain (NFL); and it has been shown that ART-naïve HIV participants have normal CSF NFL levels and no evidence of axonal injury during very acute HIV infection [73]. Taking into consideration the finding of a notable subset of participants (~25%) that demonstrated 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.

Secondly, small sample size could have limited our ability to identify very small differences in NP performance. And lastly, 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 [44], these brief batteries may be more useful in chronic HIV rather than acute HIV.

Factors such as drug use, anxiety, and depression can impact NP performance [74-76]. It is difficult to ascertain how much of an effect prior drug use and psychiatric symptoms has on neurocognitive performance, but the relatively low incidence of reported illicit drug use (72% reported no lifetime drug use or drug use in the 4 months prior to enrollment) and the lack of correlation between anxiety/depressive symptoms and NP

scores in this cohort reduces concern regarding the confounding nature of these premorbid factors.

We investigated clinical and biological markers that might put AHI participants at a higher risk for cognitive impairment. NP performance inversely correlated to CSF HIV RNA and estimated days post 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 that 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.

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 [77, 78]. Our findings might be explained by differential effects of the CD4 count in acute versus chronic HIV infection. Unlike in chronic infection, low CD4 counts during AHI are less of a marker of sustained immunosuppression and infection associated with 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 analysis, a significant relationship was found in multivariable modeling between these two factors. In addition to CD4 count, CSF HIV RNA and days post-transmission were also significant predictors of NP performance in a multivariable regression model. As expected, CSF HIV RNA and days post transmission had an inverse relationship with cognitive performance. However, there was an unexpected inverse relationship between CD4 count and NP performance on regression analysis. Because CD4 count drops and plasma viral load increases during the initial weeks of HIV infection [79], 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 two 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. Further, preventing advanced immune suppression and initiating ART at higher CD4 counts may result in better overall cognitive outcomes among HIV-infected individuals.

Following immediate ART initiation, we observed improvement in most tests during the first 3 months, but change in only one test (CT 1) 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 ART on cognition [27, 32]. 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, but it is noteworthy that only two of the eight individuals reported recent illicit drug use. As such, premorbid substance abuse is not a key driver of poor neuropsychological outcome after ART among individuals with impaired performance at baseline.

Psychomotor performance and processing speed are regarded as more reliable markers of cognitive impairment longitudinally, given that they are less influenced by practice effects [53]. 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 [16]. The use of culturally matched longitudinal control data is a strength of our study; but, since 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 in AHI at baseline with improvement following treatment. We also identify about one-quarter of participants having performance in an impaired range during AHI with limited

improvement after 6 months of ART. This study and future research should compare the long-term NP performance trajectory from AHI to chronic disease compared to those who initiate treatment later in disease. Such comparison may provide conclusive evidence to support the need for earlier initiation of ART in order to prevent risk of developing HIV-associated neurocognitive impairment.

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