Impact of Early ART Initiation on Neurocognitive Function in HIV – A Randomized Trial

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Abstract

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Objective During the early stages of HIV infection, the virus invades the central nervous system (CNS), causing inflammation and neuronal damage. Untreated, this damage may cause cognitive impairment known as HIV-associated neurocognitive disorder (HAND). The optimal timing of antiretroviral therapy (ART) initiation required to prevent HAND remains unknown. We hypothesized that immediate ART initiation prevents neurocognitive impairment.

Design Prospective longitudinal randomized study.

Method Between 2012 and 2017 in Lima, Peru, HIV infection was identified by monthly HIV Ab/RNA testing in the Sabes study of HIV-negative men who have sex with men and transgender women. Participants with CD4 counts greater than 350 were randomized to receive ART (FTC/TDF/EFV or FTC/TDF/COBI/EVG) immediately or at 24 weeks after diagnosis. Participants underwent full neuropsychological (NP) testing of 8 functional domains at baseline and 12, 24, and 48 weeks from enrollment. Total neurocognitive performance was measured via total z scores using site-specific normative data. We compared total z score and change in total z score (from baseline) at week 48 between immediate and deferred ART groups.

Result 88 subjects were enrolled into this neuropsychological study and had their baseline NP assessment at a median of 47 days from estimated infection date. There was an increase in total z score over time in both arms, consistent with neurocognitive improvement. At week 48, the NP domain of processing speed had a change from baseline that was lower among subjects randomized to deferred treatment than among those treated immediately. Overall the change in total z score from baseline was the same amongst randomization arms.

Conclusion These preliminary results suggest that HIV care that includes ART initiation very shortly after HIV acquisition led to improvement in participants' speed of processing performance over time. This unique randomized cohort offers a rigorous assessment of the consequences that delays in ART initiation may have on neurocognitive function. Long term follow-up will provide valuable insights on the further evolution of neurocognitive functioning.

Keywords Neurocognitive, Acute Infection, Antiretroviral Treatment, Central Nervous System (CNS)

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Thanks to the Sabes study ("¿Sabes?" in Spanish means "do you know?") participants and IMPACTA staff for your time and involvement.

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SIGNIFICANCE

A large proportion of people infected with HIV develop HIV associated neurological disorder (HAND) (1). HAND occurs when HIV enters the central nervous system (CNS) and causes neuronal inflammation and damage (1-4). The injury caused by HIV in the CNS can lead to a range of cognitive disorders that encompass: asymptomatic neurocognitive impairment (ANI), mildly symptomatic neurocognitive disorder (MND), and severely symptomatic dementia (HAD) (5). The most severe form, HAD, is more common amongst the ART naïve than experienced individuals (6-13). Studies estimate that up to 20% of those that are HIV-positive ART naïve are affected by HAD (6-13). Meanwhile, milder forms, MND and ANI, are common (40%) in both ART naïve and experienced populations (3, 7, 14). Consequently, HAND has adverse health, economic, and societal impacts on all HIV-positive populations (15-18).

The initiation of ART in established infection ameliorates, but does not eradicate, HAND. The prevailing belief is that early identification and treatment of HIV is crucial in improving neurological outcomes (19). HIV RNA is detectable in the CSF within days of estimated HIV acquisition (11, 20). In the acute stage, Fiebig I-II, the majority of individuals are HIV RNA positive but HIV non-reactive on the enzyme immunoassays (EIA). In the recent stage of HIV infection, Fiebig III-V, individuals are both HIV RNA positive and EIA positive. Intervention during the early stages of HIV infection may limit the creation of CNS HIV reservoirs and lower inflammation (21, 22). Thus there is an opportunity to markedly reduce the incidence, not just severity, of HAND.

ART initiated in early infection may preserve neurocognitive function and prevent the establishment of irreversible chronic inflammation. Currently there are only a few studies that

examine the impact of ART initiation on HAND amongst those with acute HIV infection (AHI) (12, 23-25). For example, in Thailand, the RV254/SEARCH 010 Study Group identified 36 people with AHI that were ART naïve and performed a neurocognitive evaluation pre-ART at, median, 19 days after the estimated date of infection (24). They were then re-evaluated at 3 and 6 month post ART (24). The majority of participants had normal NP performance, and the initiation of ART led to an improvement in their psychomotor function (24). However, a quarter already had a neurocognitive impairment. Amongst those with this impairment ART did not improve any aspect of their NP performance (24). Considering these data from Thailand, we believe that ART should be initiated as soon as possible after HIV acquisition, to prevent cognitive dysfunction.

CONTEXTUAL BACKGROUND

In 2015 UNAIDS estimated that 0.4% of adults between the age of 15 and 49 in the Republic of Peru have HIV (26, 27). Amongst the highest risk populations are men who have sex with men (MSM), among which the prevalence is 22.3%, and transgender women (TGW), among which the prevalence is 30.0% (28-31). Unfortunately, the prevalence of HAND in this population is unknown. Only a couple studies have published HAND prevalence in high-risk Peruvian populations (32, 33). For example, a prospective study performed by Guevara-Silva in 2011 in Peru of 21 of HIV infected ART-naïve MSM adult participants suggests that up to 76.3% have a psychomotor impairment and 68.4% have executive dysfunction (6, 32). Given this study's size, and other limitations, the true prevalence of HAND cannot be extrapolated to the Peruvian HIV-positive population. However, it is likely that prevalence of HAND in Peru is in line with epidemiological data recorded elsewhere, which have shown that 40% or more of those with HIV, even on ART, have HAND (6, 7, 34).

Despite the prevalence of HAND amongst those with HIV in Peru, there is a complete lack of information regarding the impact that timely initiation of ART has on neurocognitive outcomes within this and other populations. Our research investigate the effect that immediate, vs. deferred ART initiation, has on neurocognitive test results amongst MSM and TGW with early HIV infection.

METHODS

Study design: Prospective longitudinal randomized study.

Project period: Participants were recruited between 2015 and 2017.

Recruitment: From the multi-site Sabes study cohort in Lima, Peru. In the Sabes study, HIV-negative MSM/TGW were followed monthly with HIV antibody & RNA testing to detect HIV infection. Newly identified HIV positive participants with CD4 counts greater than 350 were randomized to receive ART (FTC/TDF/EFV or FTC/TDF/COBI/EVG) immediately or at 24 weeks after diagnosis; randomization was stratified by acute/recent HIV status at enrollment. A subset of 88 participants were co-enrolled to participate in this sub-cohort with neuropsychiatric testing and lumbar punctures according to the eligibility of the Sabes study study and the criteria listed below **(Figure 1)**. Herein, I report the analysis of the neuropsychiatric testing data obtained from the enrolled participants.

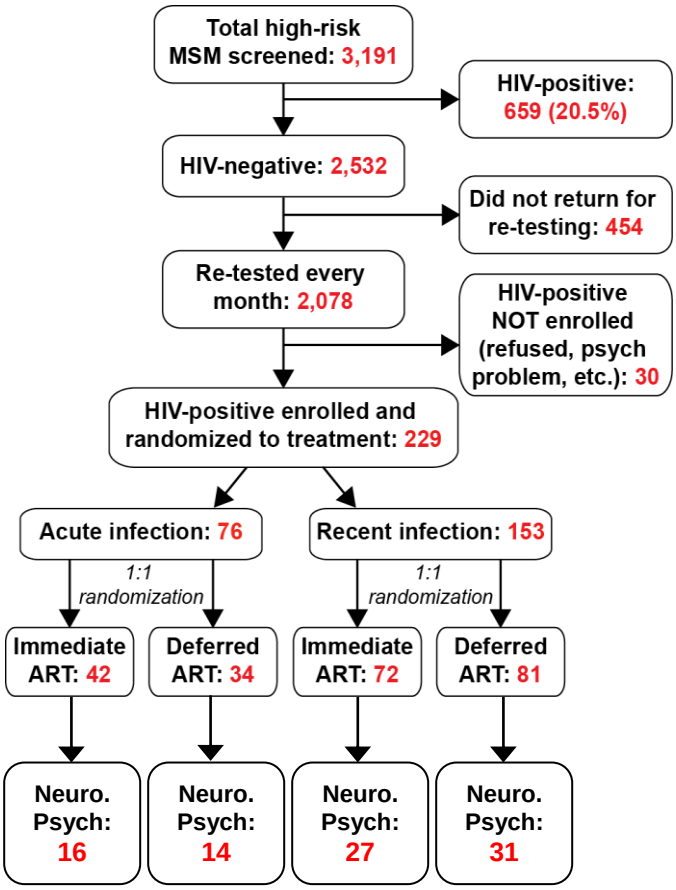

Figure 1. Sabes study? Cohort study consort diagram (35)

Study site: Four sites participated in the *Sabes* study; two from Asociación Civil Impacta Salud y Educación and one each from Asociación Vía Libre and Epicentro. The Alberto Barton Healthcare Center, a Ministry of Health clinic, also referred some participants. Neuropsychological evaluation was carried out at the Asociación Civil Impacta Salud y Educación sites (36).

Study population: According to the SABES study team to be eligible for the SABES study persons were male at birth, who reported having had sex with a male partner in the past 12 months, and who were 18 years of age or older (36, 37). In addition, they must have been unaware of their HIV status and have been at high risk for acquiring HIV because: They were a

partner of a person with newly diagnosed acute or recent HIV infection; They were seeking HIV testing because they had symptoms of acute retroviral syndrome; or, they reported high-risk sexual behavior. High-risk sexual behavior was defined by any of the following (38): 1) No condom use during anal intercourse in the last six months; 2) Anal intercourse with >5 male sex partners during the last six months; 3) Self-identification as a sex worker; 4) Diagnosis of an STI during the last six months or at screening; or 5) Sexual partner of an HIV-infected man in the last six months (36, 37).

Eligibility criteria: To be eligible for the neuropsychological study participants had to have been **e**nrolled into Sabes study step 3 where they had been diagnosed with acute or recent infection. In the Sabes study acute infection was operationally defined as positive plasma HIV RNA test in a person with a negative third-generation HIV antibody test. Recent infection was defined as a positive third-generation rapid HIV test that confirmed by a separate enzyme immunoassay with a documented negative third-generation HIV-antibody or HIV-RNA test in the previous 90 days (36).

Exclusion criteria: Participants were excluded from the Sabes study if they had prior receipt of investigational anti-HIV vaccine (37). They were also excluded if they had ongoing therapy with systemic chemotherapeutic agents, nephrotoxic systemic agents, immunomodulatory treatments, investigational agents, or systemic corticosteroids that lasted longer than 21 days. According to the Sabes study team participants were also excluded if they had known allergy/sensitivity or any hypersensitivity to components of study drugs (ART) or their formulations; active drug or alcohol use or dependence that would interfere with adherence to study requirements; serious

medical or psychiatric illness that would interfere with the ability to adhere to study requirements; chronic or acute hepatitis B infection; used female hormonal products based on estrogen or derivatives (37). For the NP study, participants were illegible if they had a history of a CNS disorder, past head injury, or were unable to undergo the process of informed consent.

NP Assessment procedure: The diagnosis of HAND is a diagnosis of exclusion achieved using specialist NP test batteries ideally performed alongside clinical evaluation, laboratory tests, and imaging (19). NP tests used to identify HAND assess for sub-cortical and frontal dysfunction by evaluating between 5-8 of the following cognitive domains: psychomotor speed, gross and fine motor speed, executive skills/speed of information processing, attention, learning, memory, language, and visual-constructional–perceptual ability (15, 39, 40). These test batteries are valid and sensitive to mild forms of HIV related CNS compromise and are valid in many languages, including Spanish (41, 42).

After consent, trained physicians completed a neurological examination, detailed neurological history, and symptom review at two sites in Lima Peru. The physician then performed the NP test battery that covered 8 domains. The tests administered were selected from ACTG 5199 The International Neurological Study (9, 10). The tests include Timed Gait, Grooved Pegboard Dominant, Grooved Pegboard Non-Dominant, Finger Tap Dominant, Finger Tap Non-Dominant, Color Trails 1, Colors Trail 2, Semantic Verbal Fluency, Stroop Color, Stroop Word, Stroop Color Word, and Activities of Daily Living. The individual test scores were calculated by subtracting the raw score from normative score then divided by the standard deviation (36).The results of each of these individual tests were averaged to produce a total z score (36). Lumbar

punctures and CSF analysis were also performed, the results of which are not discussed in this work.

The NP tests were performed at baseline and repeated at week 12, 24, and 48.

Follow up: Medical providers were informed if participants demonstrated evidence of cognitive impairment and their results were recorded in their medical charts. The medical teams were then asked to inform the participant of the studies' findings at their out-patient consultation and management was initiated as per best practice. This treatment could entail repeated out-patient visits or change of ART. These actions ensured proper delivery of care to all study participants.

Ethics: The neuropsychological study was approved by FHCRC, and the, Asociacion Civil Impacta Salud y Educacion institutional review boards (IRB). A separate Institutional Review Board application was submitted to and considered by the UW Human Subjects Division, for this thesis.

Hypothesis testing:

- Aim 1: Analyze total z scores of participants with early HIV infection over time at 48 weeks of follow up. Null hypothesis (Ho) is that there is no difference in total z scores over time.
- Aim 2: Analyze effect of timing of ART initiation on total z scores of participants with early HIV at 48 weeks of follow up. Null hypothesis (Ho) is that there is no difference

between total z scores of participants that received immediate treatment vs. those that received deferred treatment.

- Aim 3: Analyze effect of timing of ART initiation on the change in total z scores of participants with early HIV at 48 weeks of follow up. Null hypothesis (Ho) is that there is no difference in total z scores change between participants that received immediate treatment vs. those that received deferred treatment.
- Aim 4: Analyze effect of timing of ART initiation on the change in functional domain scores of participants with early HIV at 48 weeks of follow up. Null hypothesis (Ho) is that there is no difference between the functional domain scores change of participants that received immediate treatment vs. those that received deferred treatment.

Statistical analysis: The variables analyzed were age, education, acute/recent HIV diagnosis CD4 counts, time to baseline NP test, viral load, ART regimen, immediate/deferred randomization arm, total z score, change in total z score from baseline, time to ART initiation. For the variables listed, histograms and summary statistics were evaluated to assess distribution for skew and kurtosis.

The estimated date of infection (EDDI) was evaluated using viral load in methods described by Pilcher et al (43). This EDDI was then used to estimate time to first NP and time to ART. Plasma HIV RNA copies <40 were considered undetectable and recoded as 0. Plasma HIV RNA copies were then transformed using the $\log_{10}$ function. Due to skewness, age and education were recoded from a continuous variable into an binary variables 18-29 & 30-49 and High school & College respectively. Age and the other categorical variables (ART regiment, acute/recent HIV

diagnosis, and randomization arm) were described by the number and percent in each group. The continuous variables CD4 count, CD8 count, HIV RNA copies, and total z score were described by median and interquartile range (IQR) to be more robust against outliers. The continuous variable (time on ART) was described by mean and standard deviation (SD).

Bivariate analysis: Bivariate analyses were completed to evaluate group differences between immediate and deferred randomization arm. For categorical variables from two independent groups a bivariate Chi square or Fischer exact analysis were used. For continuous variables from two independent groups, a two-sample Wilcoxon rank-sum (Mann-Whitney) test or a two sample t-test was performed on the median(IQR) or mean(SD) variables.

General linear mixed model (GLM) analyses: A mixed model was used to evaluate between-subject differences of immediate vs. deferred and acute vs. recent groups as well as within subject effects at the 4 time points baseline, 12, 24, and 48 weeks. In this model, the dependent variable was the Total z score. The covariance structure was the SAS default VC setting. The subject effect was governed by participant ID. The estimation method used restricted maximum likelihood (REML). The fixed effect SE was model-based. Linear regression was then used to evaluate differences in 'change in Total Z score' at 48 weeks. A secondary analysis was performed to evaluate the change in NP score by functional domain.

All statistical tests were conducted at the alpha level of 0.05. The analysis was carried out using Stata version 14.1 and SAS version 9.4.

Sample size: A sample size of 40 per group has a power of over 90% to detect a difference between the means 0.5 and 0.25 for a one tailed two-sample pooled t test (44). Thus this study was powered to evaluate the difference between immediate and deferred ART treatment arms.

RESULTS

Baseline demographic and clinical variables): Eighty-eight participants with early stage HIV infection were enrolled in this study **(Table 1)**. All participants were ≥ 18 years of age. Of these, 48% were between the age of 18 and 24 and 52% were 25 years of age or older. All participants were assigned male at birth. The majority (60%) of participants received 12 or fewer years of education. The difference in age and education were not statistically significantly different between those that were randomized to receive immediate or deferred ART.

The proportion of those diagnosed with recent infection was 63% in the immediate arm and 69% in the deferred arm. The median time from EDDI to baseline NP evaluation was 47 days. For the participants randomized to receive immediate ART upon diagnosis, the median number of days between the EDDI and baseline NP assessment was 43. For those that were randomized for receive deferred ART, the median number of days was 50. Overall the median CD4 count (cells/mm3) at baseline was 428. The median CD4 cell count was 491 for those randomized to the immediate arm and 413 for those randomized to the deferred arm. The median viral load, measured by plasma HIV RNA (log10 copies per milliliter), at baseline was 5.82. For the participants randomized to receive immediate ART upon diagnosis, the median viral load was 5.96. For those that were randomized for receive deferred ART, the median CD4 count was 5.71. The majority (58%) of participants were diagnosed with recent HIV infection. The majority (70%) of participants received an Efavirenz (EFV) containing regimen (68% in the immediate

arm and 71% in the deferred arm). The difference in acute/recent diagnosis, days between EDDI and baseline NP testing, CD4 count, viral load and ART regimen between the randomization arms was not statistically significant. The median time from EDDI to ART initiation was 118 days. For the participants randomized to receive immediate ART upon diagnosis, the median number of days between the EDDI and baseline NP assessment was 40. For those that were randomized for receive deferred ART, the median number of days was 196. In total the mean total z score at baseline was 0.02 with as SD of 0.43. The mean total z score at baseline in those randomized to immediate ART was 0.05(0.42) whereas the total mean z score in those randomized to deferred ART was -0.02(0.44). There were no statistically significant differences between these two means, (P=0.55).

Table 1. Baseline Demographic and Clinical Variables

Variable/Category at Baseline	Total, N (%) N=88	Immediate ART, N (%) N=43	Deferred ART, N (%) N=45	X^2 p-value	df
Age (years)					
18-24	42(47.73)	18(41.86)	24(53.33)	0.28	1
25+	46(52.27)	25(58.14)	21(46.67)		
Male	88(100.00)	43(100.00)	45(100.00)	-	-
Education					
High School (≤12 years)	53(60.23)	23(53.49)	30(66.67)	0.21	1
College (>12 years)	35(39.77)	20(46.51)	15(33.33)		
HIV Stage				0.55	1
Acute	30(34.09)	16(37.21)	14(31.11)		
Recent	58(65.91)	27(62.79)	31(68.89)		
EDDI to baseline NP test (days)[1]	47(32-58)	43(31-58)	50(32-58)	0.75	-
CD4 count (cells/mm3) [1]	427.5(286.5-581.5)	491(258-586)	413(317-532)	0.90	-
Plasma HIV RNA (log10 copies per milliliter)[2]	5.82(4.97-6.50)	5.96(5.07-6.45)	5.71(4.95-6.2)	0.90	-
ART					
FTC/TDF/EFV	62(70.45)	30(69.77)	32(71.11)	0.89	1
FTC/TDF/COBI/EVG	26(29.55)	13(30.23.91)	13(28.89)		
EDDI to ART initiation (days)[2]	117.81(85.85)	39.89(17.49)	195.75(46.37)	<0.01	70
Total z score[2]	0.02(0.43)	0.05(0.42)	-0.02(0.44)	0.45	86

[1]Median(IQR) with Two-sample Wilcoxon rank-sum (Mann-Whitney) test
[2]Mean(SD) with Two-sample t-test

Overall NP performance (Table 3): Eighty-two of the 88 participants completed NP testing at baseline and 48 weeks of follow-up. In the mixed model, overall NP performance, indicated by total z score, improved over time (P<0.01). There was not a statistically significant difference in total z score by randomization arm or HIV stage, (P>0.05).

A parallel model that included age and education was performed. In this parallel model, age and education were not independent predictor's of total z score and did not impact the inference derived.

Table 2. Overall NP performance

Effect on total Z score	df	F Value	Pr>F
Time	4	30.97	<0.01
Randomization arm (Immediate and deferred)	1	0.43	0.51
HIV Stage (Acute and Recent)	1	0.15	0.70
Time and randomization arm	4	1.07	0.37
Time and HIV stage	4	0.71	0.59
Time and randomization arm and HIV stage	4	0.53	0.71

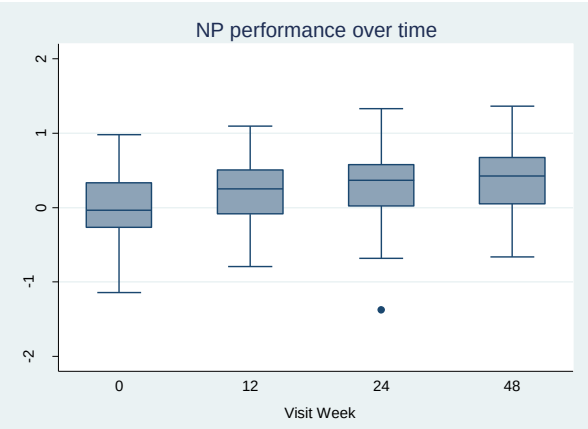

Figure 2.

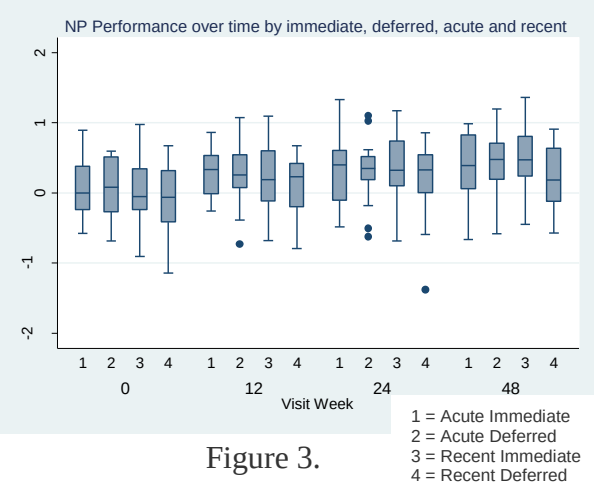

Figure 3.

The difference in NP performance changes per randomization arm at 48 weeks (Table 3): Amongst the 82 participants that completed NP testing at 48 weeks, there is no statistically significant, (P>0.05), difference in the overall total z score change per randomization arm

(Figure 4). However, there was a difference in the NP test score change related to the functional domain speed of processing. Participants randomized to receive immediate ART had a larger difference between baseline and week 48 than those randomized to receive deferred ART. This difference was statistically significant, (P<0.05). There were no statistically significant differences in the change from baseline to 48 weeks per randomization arm that related to the functional domains of verbal fluency, attention, fine motor, gross motor, executive functioning, learning or memory.

Table 3. Difference in NP performance changes per randomization arm at 48 weeks

Source	df	F Value	Pr>F
Δ Change in total z score	1	1.33	0.25
Δ Change in verbal fluency	1	0.87	0.33
Δ Change in attention	1	0.99	0.32
Δ Change in fine motor movements	1	0.20	0.66
Δ Change in gross motor movements	1	0.01	0.94
Δ Change in speed of processing	1	4.73	0.03
Δ Change in executive function	1	0.36	0.55
Δ Change in learning	1	0.00	0.97
Δ Change in memory	1	0.03	0.86

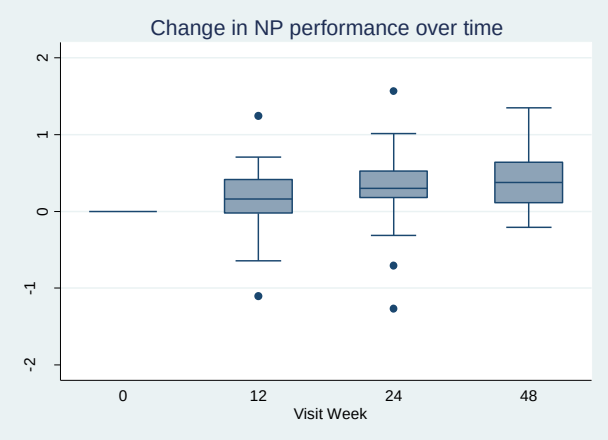

Figure 4.

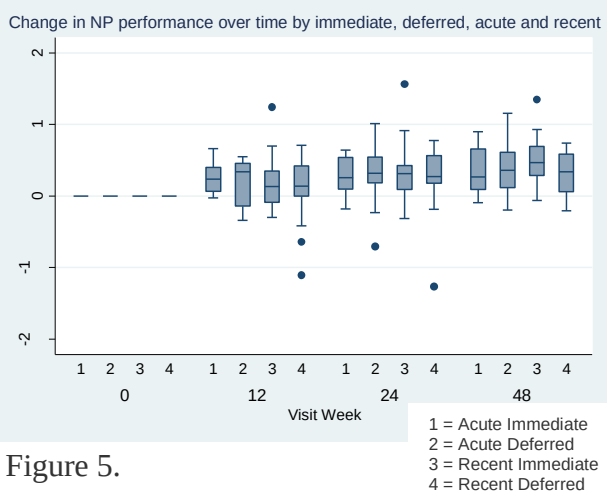

Figure 5.

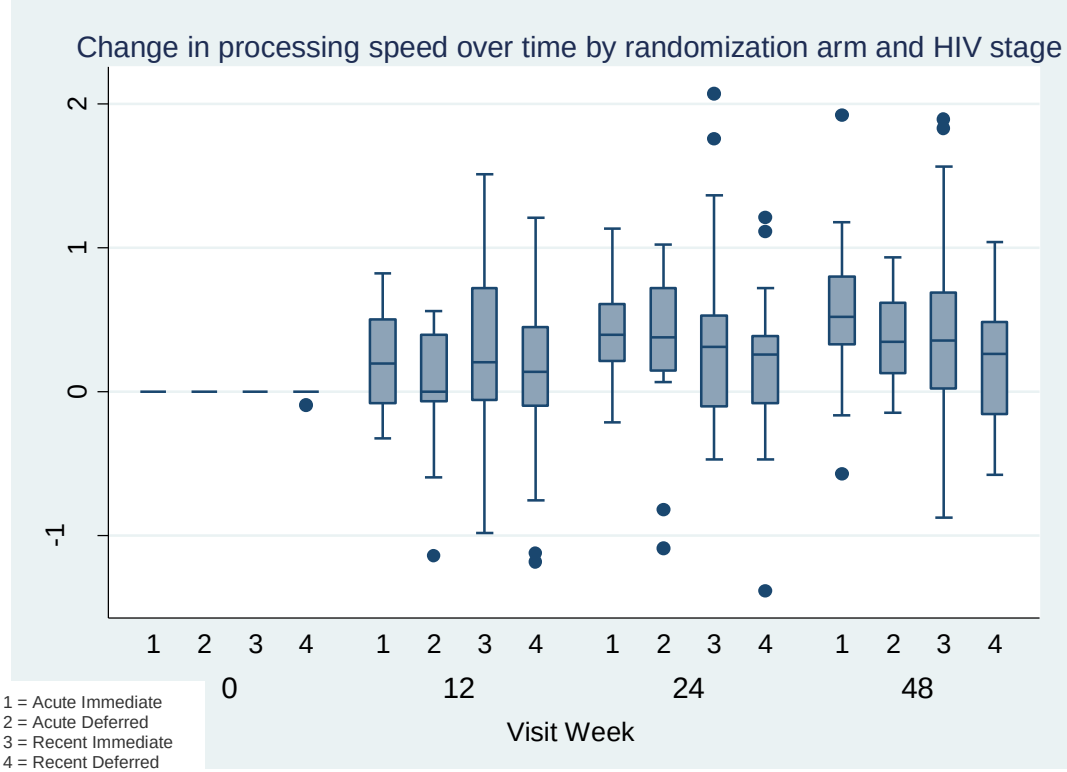

Figure 6.

DISCUSSION

There is growing evidence that NP test scores improve over time amongst those with acute/recent HIV. The results of this study suggest that those that receive immediate treatment ART may experience some neuro protective effects earlier treatment. In this study, participants randomized to receive immediate treatment had a larger improvement in processing speed compared to those that were randomized to start ART at 24 weeks. As the speed of information processing is an early sign of cognitive impairment, we believe this find to have potential relevance (45). Further, follow up of this cohort could inform new strategies for HAND prevention.

Both randomization arms demonstrated a statistically significant improvement in NP test scores over time. In 2015, Valcour et al. identified AHI in 62 Thai participants and treated them with standard combination ART or ART plus Integrase Inhibitor(12). In his study, there was also an improvement in neuropsychological test scores over time (12). Recent START study findings also corroborate these findings (25). The overall changes in neurocognitive performance over time were not significantly different between those randomized to immediate or deferred treatment. Similarly, the "Neuro START sub-study found that there were no differences in neurocognitive performance between treatment naïve patients initiating ART at 500 CD4+ cells over those who deferred starting ART until CD4 counts of 350 were reached"(25). However, the change in participant's speed of information processing was significantly different between those randomized to immediate or deferred treatment. Kamat et al. also found that speed of information processing was impaired in those with AHI (46). In Thailand, the RV254/SEARCH 010 Study Group also showed benefits if immediate treatment with ART on a single functional domain, psychomotor function (24).

Strengths: This study was done as a sub-study building off of the established Sabes study trials. It is unlikely that this trial could be performed as a standalone trial due to the immense resources and cost needed to identify and immediately treat acute HIV infection. Furthermore, this study cannot be repeated as deferral of ART by 24 weeks after diagnosis is no longer supported by clinical trial data and WHO guidelines (47).

This study used a NP test battery that has been validated for the assessment of neurocognitive function among HIV positive individuals. The tests administered were selected from ACTG 5199 The International Neurological Study (9, 10).

Limitations: The sample size of this study was 88. The study was powered to detect the difference in total z scores between the immediate and deferred randomization arms. However, the sample size was too small to detect small differences in the randomization arms stratified by any other variable such acute/recent HIV. In this study acute and recent HIV stages were operational definitions. Work is ongoing on the Fiebig staging of participants.

NP tests can take up to 2 hours to perform and require high concentration. The more tests that are performed, the worse the performance may become due to test fatigue. However, since this effect is the same across all groups and all visits, it should not introduce bias. Since the participants underwent NP testing repeatedly their NP testing abilities are likely to improve due to practice. To control for practice effect comparisons were made between randomization arms on the same visit schedule. It is possible that participants that start with a lower total z score will not have the same NP improvement pattern as those that start with a higher score. Therefore, baseline total z score was added to the model to account for the potential difference in learning effects amongst participants that began with a lower total z score (48). NP tests were carried out by psychologists at two sites. In this study there was no formal evaluation of inter-rater reliability. However, site sites visits and training were provided to promote consistent evaluation.

This study has the potential to be both valid and reliable for the MSM and TGW population. However, since this study has been performed in such a particular population, the results cannot be extrapolated to those of the female gender, who also are at risk of developing HAND. The MIND exchange meta-analysis suggests that being female at birth may, in fact, be a risk factor for developing HAND (19). If results in this trial are significant, it will be important to develop further trials in women as well.

In San Francisco, Peterson et al. demonstrated that there could be an initial neurocognitive performance deterioration, then the improvement amongst those recently infected and treated with ART. To account for these changes in NP results over time, the researchers involved with this study intend to continue the follow up of their participants for up to 5 years (49).

CONCLUSION

In the first randomized controlled trial to study acute HIV treatment and neurologic outcomes, we found that immediate ART resulted in better neurocognitive performance, specifically related to speed of information processing, over time compared with ART deferred by 6 months. This suggests that there are modest cognitive benefits to initiating immediate ART in the first 6 months of HIV infection.

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