Neuropsychological Performance in Acute HIV

Determinants of Baseline Performance and Effects of Immediate Antiretroviral Therapy

I. Kore[1], J. Ananworanich[2,3,4], V. Valcour[5], J. Fletcher[2], D. Suttichom[2], P. Mangum[2], L. Jagodzinski[6], J. Kim[6], S. Spudich[1], and RV254/SEARCH 010 Study Group

[1]Yale University, New Haven, CT; [2]SEARCH, Bangkok, Thailand; [3]HIV-NAT, Bangkok, Thailand; [4]Chulalongkorn University, Bangkok, Thailand; [5]University of California, San Francisco, CA; [6]US Military HIV Research Program, Silver Spring, MD

Background

- Despite antiretroviral therapy, some individuals with chronic HIV infection still manifest mild neurocognitive impairment.
- Is neurocognitive impairment present in the acute stages of HIV infection?
- Are there disease markers that correlate with impairment on neuropsychological testing?
- Does immediate antiretroviral therapy associate with improved neuropsychological performance in follow up?

Methods

- In a unique cohort of subjects identified during acute HIV infection by nucleic acid testing in Bangkok, we:
  - Investigated baseline predictors of neuropsychological performance
    - *Days post HIV transmission, CD4 count, CD8 count, CSF HIV RNA, plasma HIV RNA, CSF WBC, CSF protein*
  - Evaluated effect of immediate antiretroviral therapy on longitudinal neuropsychological performance
    - *HAART = Tenofovir, Emtricitabine, Efavirenz*
    - *Mega-HAART = HAART + Raltegravir, Maraviroc*

Methods

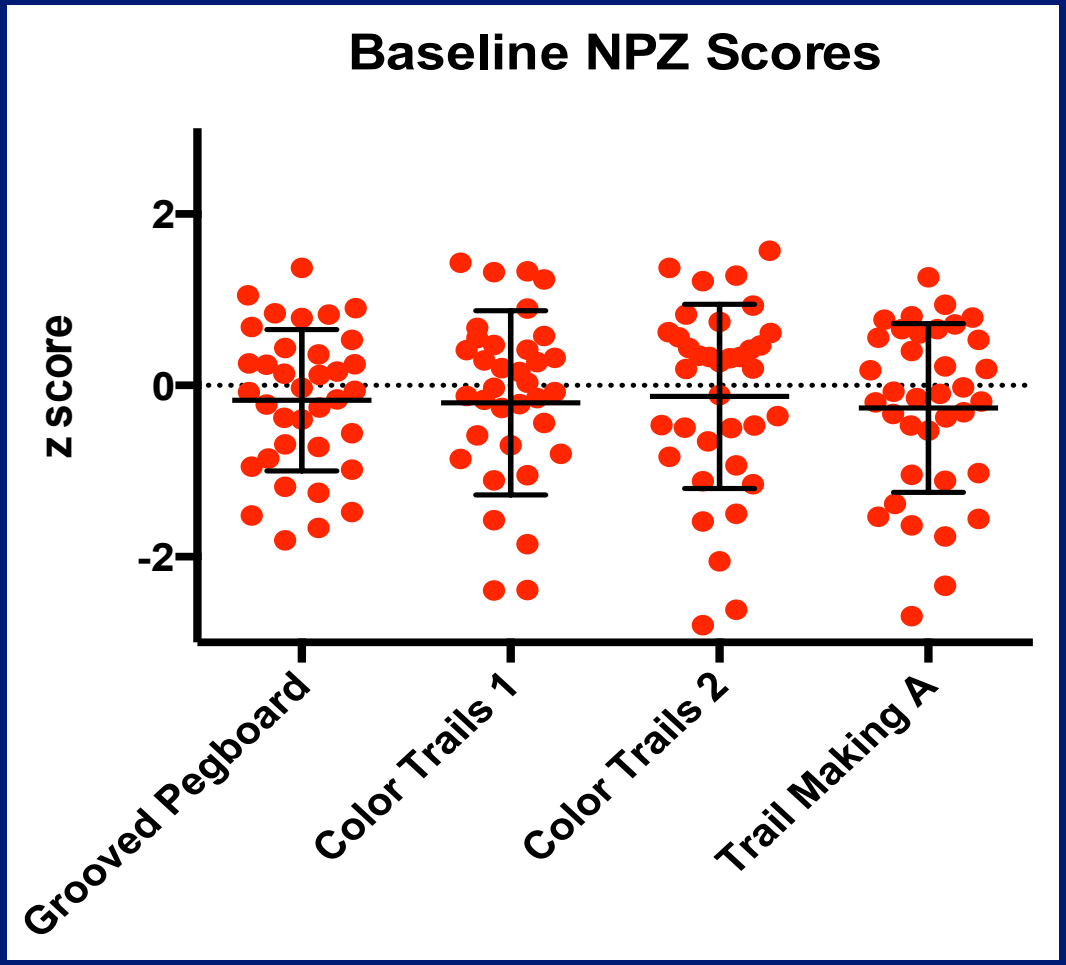
- 36 subjects assessed at baseline, 3 months, and 6 months
  - Neuropsychological testing (summarized as NPZ-4)
    - Motor = Grooved Pegboard
    - Processing speed = Color Trails 1, Trail Making A
    - Executive Function = Color Trails 2
  - Neuropsychological performance standardized to age/education matched HIV-uninfected Thai controls (n = 45)
- Blood and CSF measures
- Randomized to HAART or Mega-HAART
- Analysis: multivariable regression model, nonparametric tests

Baseline Characteristics of Acute HIV Subjects (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%)
CRF01_AE	31 (86%)
CD4 Count (cells/mm3)	411 (338 – 568)
CD8 Count (cells/mm3)	578 (399 – 1013)
Plasma HIV RNA (log10 copies/ml)	5.52 (4.56 – 5.87)
CSF HIV RNA (log10 copies/ml)	3.37 (2.19 – 4.35)
No drug use*	26 (72%)

*Denies any lifetime drug use or any drug use in 4 months prior to enrollment

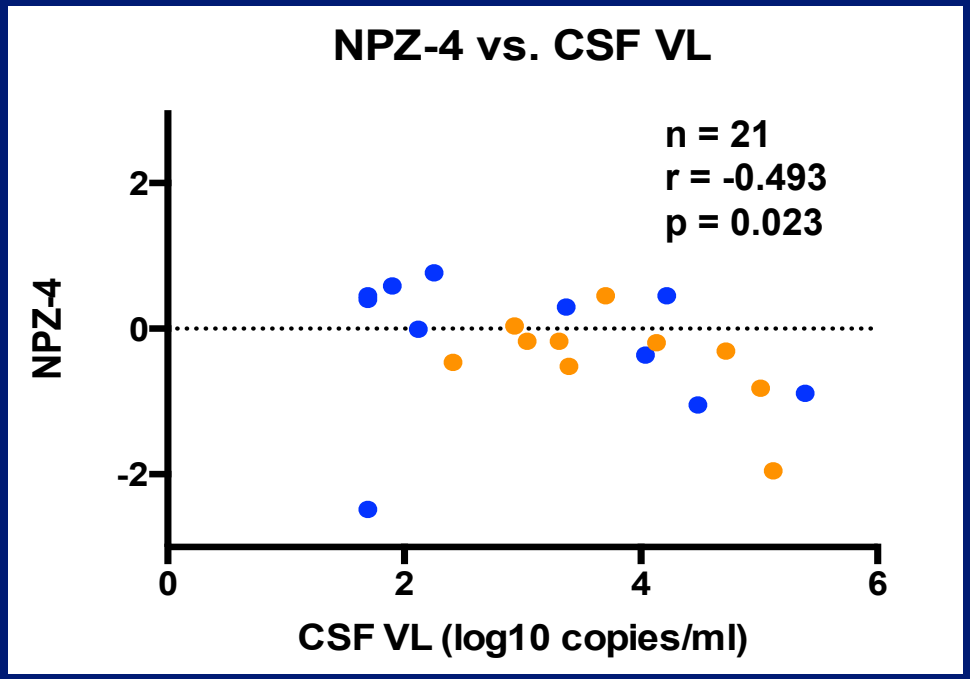
Baseline Neuropsychological Performance of Acute HIV Subjects

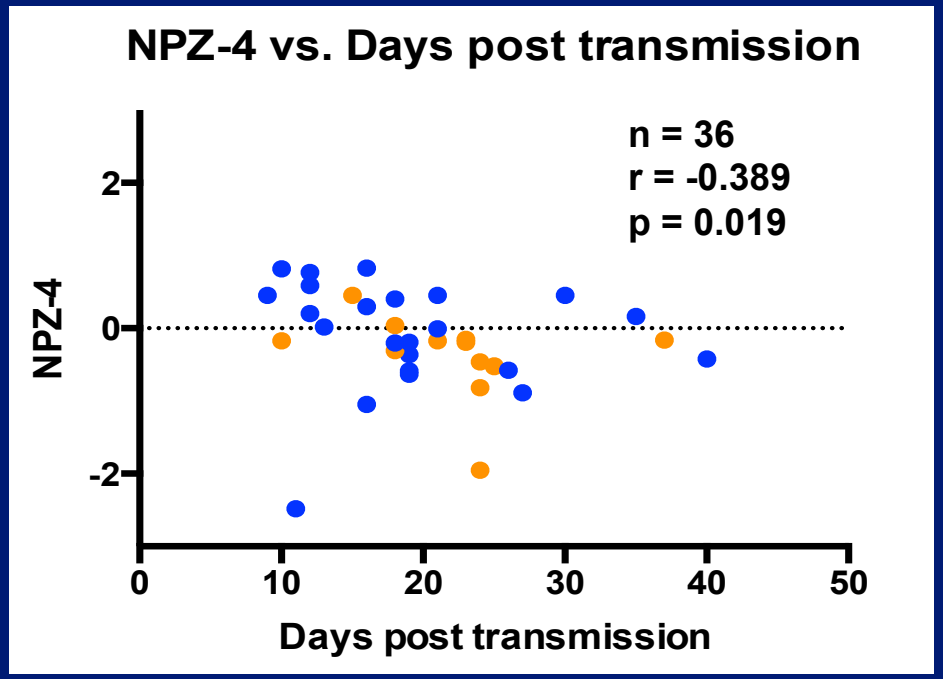


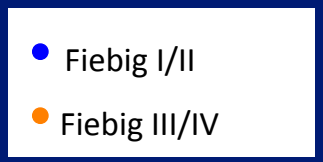
22% (n = 8) performed >1 SD below norm means on ≥2 NP tests

Lines and error bars represent means and SD

Baseline Neuropsychological Performance Modestly Correlated with CSF HIV RNA and Days Post HIV Transmission



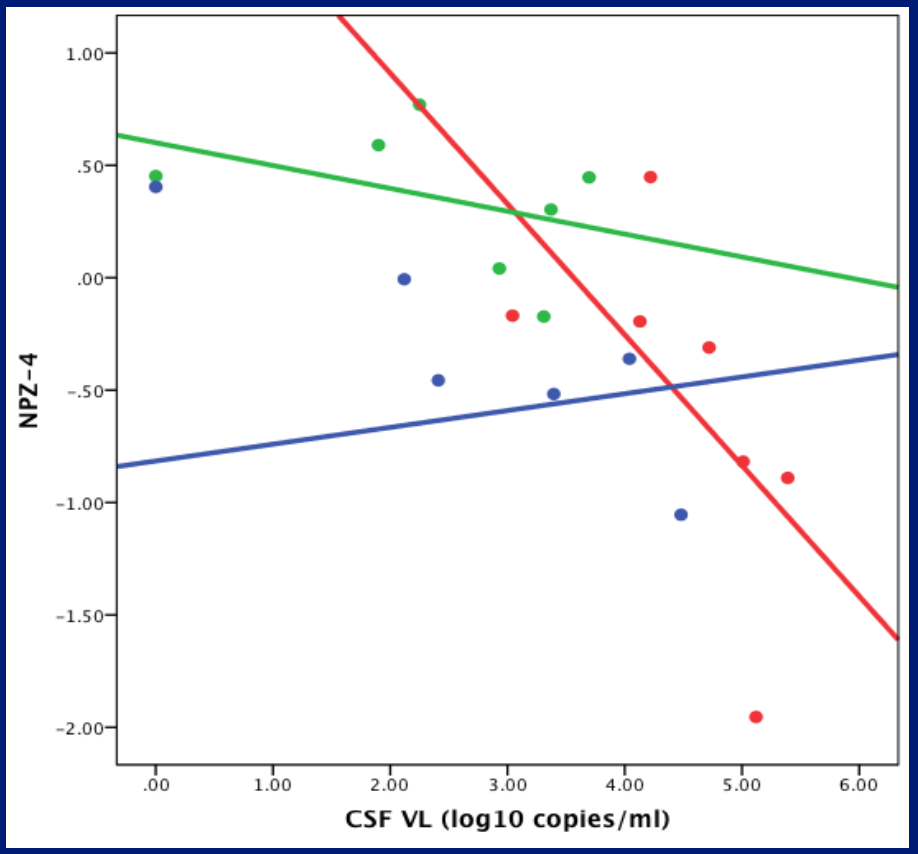




Neuropsychological performance scores did not significantly correlate with depression or anxiety measures at baseline or follow up

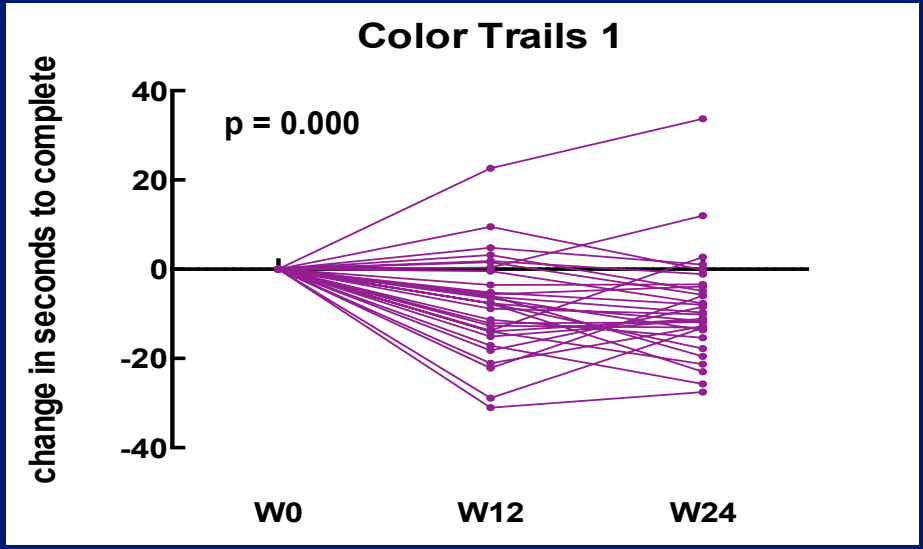
Moderating Effect of CD4 on Neuropsychological Performance

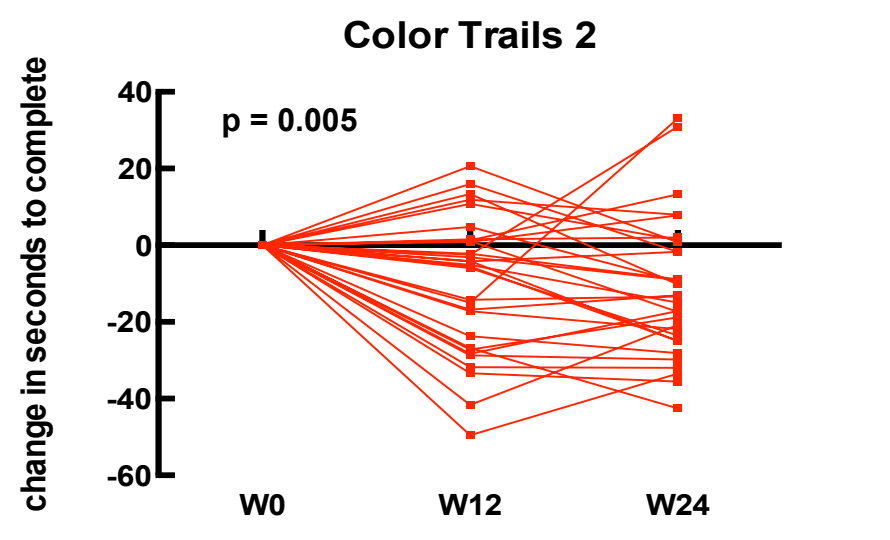
	Standard B coefficient	p-value
CD4	-.822	.004
CSF VL (log 10 copies/ml)	-.725	.013
Days post transmission	-.040	.849
CD4 CSFVL interaction	.663	.000

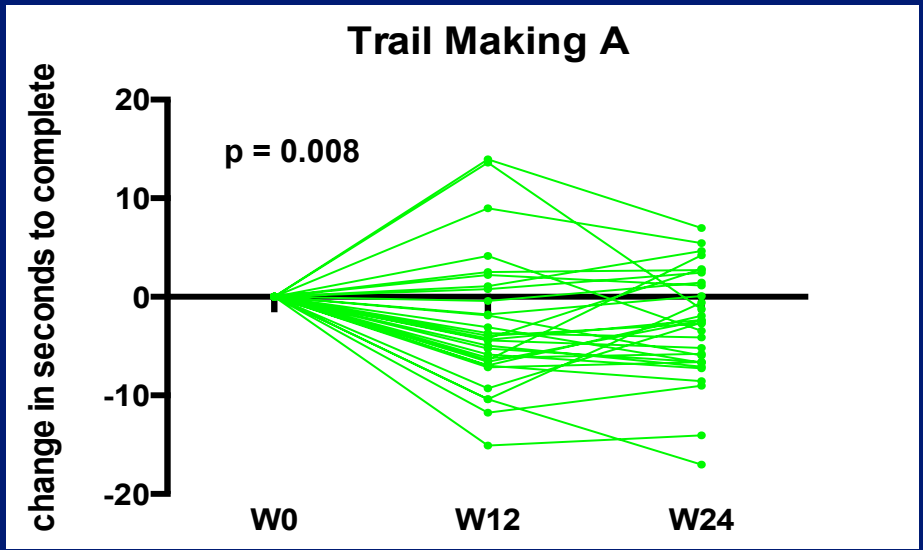


- Low CD4 (132-338 cells/mm3) $R^2 = 0.37$
- Moderate CD4 (339-555 cells/mm3) $R^2 = 0.16$
- High CD4 (565-970 cells/mm3) $R^2 = 0.02$

Improvement in Neuropsychological Performance after ART Initiated at Week 0

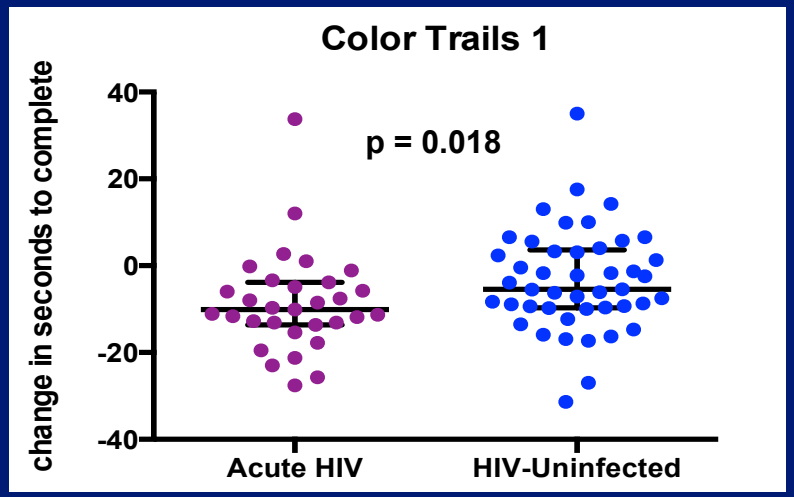


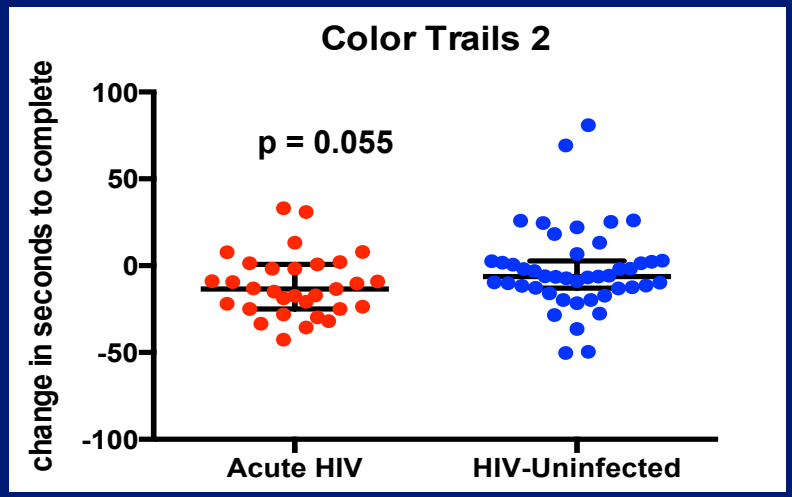


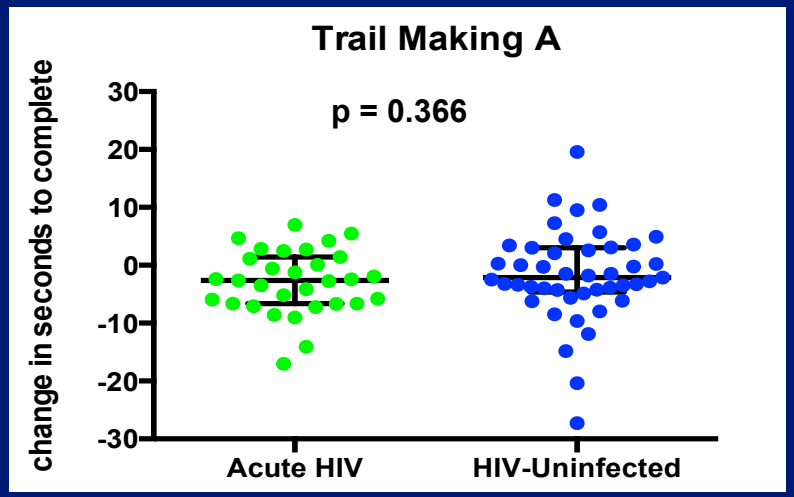


- Significant improvement from week 0 to week 12 in processing speed and executive functioning tests (no change in motor)

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



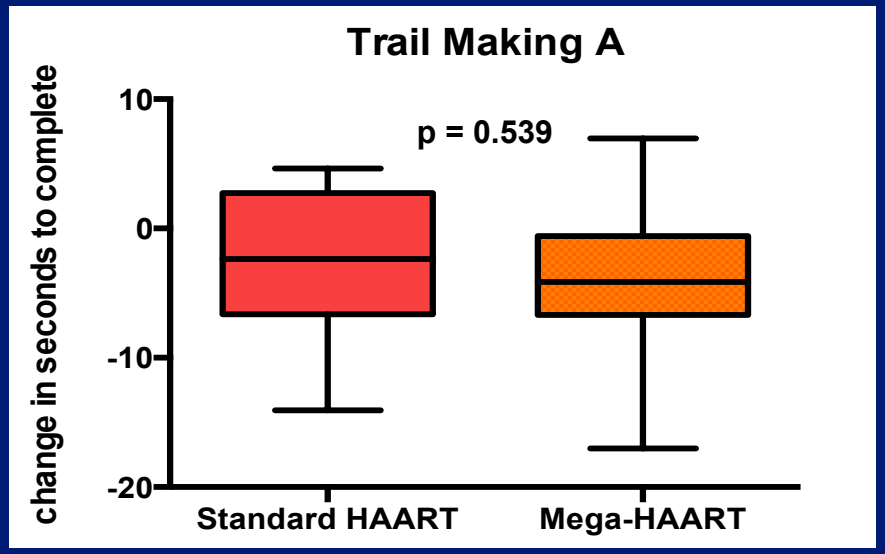


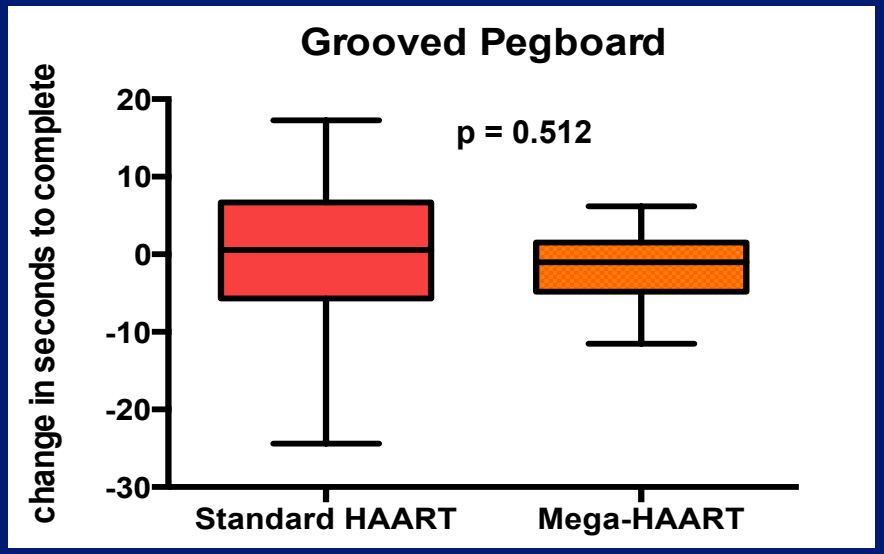


Only Color Trails 1 had greater change from baseline than HIV-uninfected controls at week 24

Lines and error bars represent medians and IQR

Comparison of Neuropsychological Performance in Standard HAART and Mega-HAART Groups after 6 months of Treatment





Similar longitudinal improvement in all domains between Standard HAART (n = 15) and Mega-HAART groups (n = 15)

Standard HAART = Tenofovir, Emtricitabine, Efavirenz
Mega=HAART = HAART + Raltegravir, Maraviroc

Study Limitations

- Small sample size and short follow up time
- Unclear generalizability; predominantly Thai men, HIV clade CRF01_AE
- Brief neuropsychological battery
- Confounding factors of existing drug use and other variable demographic factors at baseline

Study Conclusions

- Neuropsychological performance inversely correlated with CSF HIV RNA and days post HIV transmission.
- No correlation between neuropsychological performance and depression/anxiety scores.
- CD4 – possible protective factor, moderates association between CSF HIV RNA and neuropsychological performance.
- Only one processing speed test (Color Trails 1) had greater improvement than HIV-uninfected controls.
- Mega-HAART was not associated with greater neuropsychological improvement vs. standard HAART.

Acknowledgments

- Study participants
- Yale
  - Courtney Grimm
  - Jesse Reynolds
- SEARCH, Thailand
  - Jintanat Ananworanich
  - James Fletcher
  - Jing Ratchapong Kanaprach
  - Fon Varaporn Pothipala
- UCSF
  - Victor Valcour
  - Akash Desai

Financial support:

- NIH/NIMH
  - R01MH095613
  - R21MH086341
- US Military HIV Research Program
- NIMH Administrative Supplement Program Providing Research Experiences for Physicians and Medical Students from Diverse Backgrounds (R01MH09561302-S1)
- Yale School of Medicine Summer Research Grant

SEARCH 10/RV254 Acknowledgements

SEARCH

- Jintanat Ananworanich
- James Fletcher
- Jing Ratchapong Kanaprach
- Fon Varaporn Pothipala
- Jerome Kim
- Cecilia Shikima
- Praphan Phanuphak
- Mark de Souza
- Nittaya Phanuphak
- Frits van Griensven
- Thep Chalermchai
- Eugene Kroon
- Nipat Teeratakulpisarn
- Rungsun Rerknimitr
- Wiriyaporn Ridtitid
- Sukalya Lerdlum
- Duanghathai Suttichom
- Nitiya Chomchey
- Somprartthana Rattanamanee
- Peeraya Mangu
- Sasiwimol Ubolyam
- Mantana Pothisri
- Suteeraporn Pinyakorn

Yale

- Serena Spudich
- Courtney Grimm
- Jesse Reynolds

UCSF

- Victor Valcour
- Akash Desai
- Lauren Wendelken
- Edgar Busovaca

WRAIR

- Bonnie Slike
- Sodsai Tovanabutra
- Gustavo Kijak

NCI

- Jacob Estes
- Robin Dewar
- Adam Rupert

SAIC-Frederick

- Frank Maldarelli
- Mary Kearney
- Ann Wiggins

Huntington Memorial

- Napaporn Sailasuta

VGTI

- Elias Haddad
- Lydie Trautmann

NIAID

- Irini Sereti
- Daniel Douek
- Netanya Sandler
- Mary Marovich

AFRIMS

- Alexandra Schuetz
- Rapee Trichavaroj
- Vatcharain Assawadarachai
- Yuwadee Phuangngern
- Wiriya Rutvisuttinunt
- Nantana Tantibul
- Panadda Sawangsinth
- Bessara Nuntapinit
- Siriwat Akapirat
- Wanwarang Khobchit
- Sakuna Suksawad
- Ajchariyarat Sangdara
- Kultida Poltavee
- Hathairat Savadsuk
- Suwittra Chaemchuen
- Robert Paris
- Surat Jongrakthaitae
- Chayada Sajiaweerawan
- Nipattra Tragonlugsana
- Putida Saetun

Funding

- NIH/NIMH
  - R01MH095613
  - R21MH086341
- US Military HIV Research Program
- NIMH Administrative Supplement Program Providing Research Experiences for Physicians and Medical Students from Diverse Backgrounds (R01MH09561302-S1)
- Yale School of Medicine Summer Research Grant

Industry

- Gilead (TDF, FTC)
- Merck (EEV, RAL)
- Pfizer (MVC)
- Monogram (Trofile)
- GPO (TDF, 3TC, EFV)