

Cognitive Trajectories in Suppressed HIV Infection Indicate Evolving Disease Activity

From Jules: HIV+ showed worse cognitive decline over 18 months vs healthy controls

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Conclusion

- Despite long-term viral suppression and immune recovery, we showed mostly subclinical levels of decline in psychomotor speed and executive functioning
- This may reflect HAND progression at a gradual rate beyond the 18 month study period
- 57% of the cohort show evolution of their disease, challenging the notion of neurocognitive stability in virally suppressed HIV+ persons
- Could survivor bias explain the lack of interaction between historical HAND and baseline HAND on cognitive decline?
- Findings will need to be confirmed in larger and more diverse HIV cohorts (particularly in terms of gender and ethnicity)

Introduction

There is a lack of research examining neuropsychological (NP) changes in HIV-infected (HIV+) persons with long-term viral suppression.

In this context, mostly mild forms of HIV-associated neurocognitive disorders (HAND) are prevalent.

Inconsistent estimates of rates of cognitive decline in previous studies of combined antiretroviral therapy (cART)-treated persons ($N=9$) may be due to methodological shortcomings in the definition(s) used:

- Low clinical relevance
- No practice effect corrections
- Decline as an “absorbing” state (vs. fluctuating in studies with multiple follow-up visits)
- Focus on single tests or very short NP batteries ($n \leq 3$ tests)
- None took historical HAND diagnosis into account

Aims

1. To quantify the **rate of incident neurocognitive decline** in chronic treated HIV+ persons relative to healthy controls of the same age over an 18-month period.
2. To investigate the historical and baseline cognitive **determinants of cognitive decline** and to determine the **profile of cognitive trajectories** in functions of historical and baseline HAND status.
3. To determine whether standard HIV disease biomarkers contribute to cognitive decline.

Method

Participants were enrolled in the Australian HIV and Brain Aging Research Program, a prospective study investigating the effects of HIV infection on the brain in middle-aged (45+ years) virally-suppressed HIV+ and HIV- persons. The majority are men who have sex with men (MSM) with a high level of pre-morbid cognitive functioning.

Participants completed a comprehensive NP battery assessing seven cognitive domains at baseline and 18 month follow-up visits.

Table 1. NP Test Battery

| Domain | Tests |
|-----------------------------------|--|
| Motor Coordination | Grooved Pegboard (DH and NDH) (score in seconds) |
| Psychomotor Speed | TMT-A (score in seconds) WAIS-III Digit Symbol Coding (total correct/120 seconds) D-KEFS Color Naming (score in seconds) |
| Working Memory | WAIS-III Letter-Number Sequencing (total correct responses) WMS-III Spatial Span (total correct responses) |
| Verbal Learning | HVLT-R total learning (total correct Trials 1-3) |
| Verbal Recall | HVLT-R delayed recall (total correct) |
| Verbal Fluency | Letter – FAS (total correct responses) Semantic – Animals (total correct responses) |
| Mental Flexibility/ Inhibition | TMT-B (score in seconds) D-KEFS Inhibition (score in seconds) |

Table 2. Sample Baseline Characteristics

| | HIV+ M (SD)/% | HIV- M (SD)/% | <i>p</i> |
|---------------------|------------------|------------------|----------|
| N | 96 | 44 | |
| Age | 56.06 (7.87) | 53.53 (6.50) | .06 |
| Education (y) | 13.99 (2.86) | 15.23 (2.62) | .02* |
| Sex (%M) | 97.92 | 86.26 | .01* |
| Ethnicity (% White) | 97.92 | 97.73 | .94 |
| Impairment rate (%) | 55.21 | 15.91 | <.001** |

Mean test-retest interval = 19.56 months, *SD* = 7.73 months.

Loss to follow-up (LTFU): HIV+ = 6%; HIV- = 12%

No significant differences between retained & LTFU *except for*: higher proportion of HIV+ LTFU had HAND at baseline (100%) compared to retained (55%) (*p* = .03)

HAND Status Definitions

Historical HAND:

- Formal clinical diagnosis of MND and HAD by neurological and NP review
- 15/96 had Historical HAND. All diagnosed pre-HAART era (Med diagnosis year=2001; 8 years pre-study entry)
- Following HAND diagnosis, ART optimized in all participants
- Historical HAND analysed as a dichotomous variable (Yes/No)

Baseline HAND:

- Defined per FRASCATI criteria:
 - GDS \geq 0.5 & no IADL decline = ANI
 - GDS \geq 0.5 & IADL decline = MND
 - GDS \geq 1.5 & IADL decline = HAD

Cognitive Decline:

- Based on standard regression-based norms for change correcting for practice effect, demographics, baseline NP performance and overall competence
- Individual change scores averaged into a summary regression-based change score (similar to z-score with *Mean* of 0 and *SD* of 1)
- Clinically significant decline (Y/N) determined based on a 95%CI around the normative mean

Results

- A greater proportion of HIV+ (**14.0%**) participants **declined** as compared to HIV- cases (**4.5%**) (*NB.* non-significant difference: $p = .11$, $\phi = .13$) (Fig 1).
- Participants with historical HAND more likely to also have baseline HAND ($p = .035$)
- No relationship between cognitive decline (taking into account historical and baseline HAND) and traditional HIV disease biomarkers (Table 3).

Figure 1. Mean Neurocognitive Change Score Globally and by Cognitive Domain

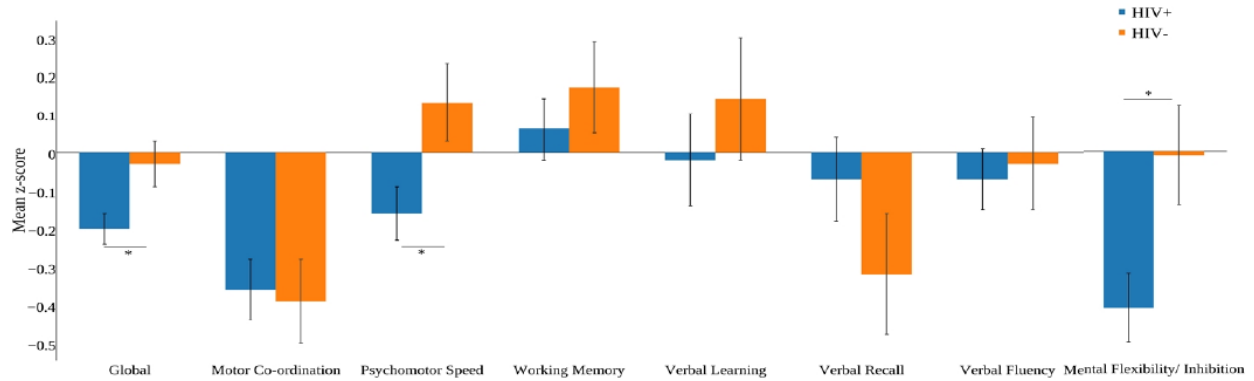


Figure 2. Trajectories of Cognitive Decline

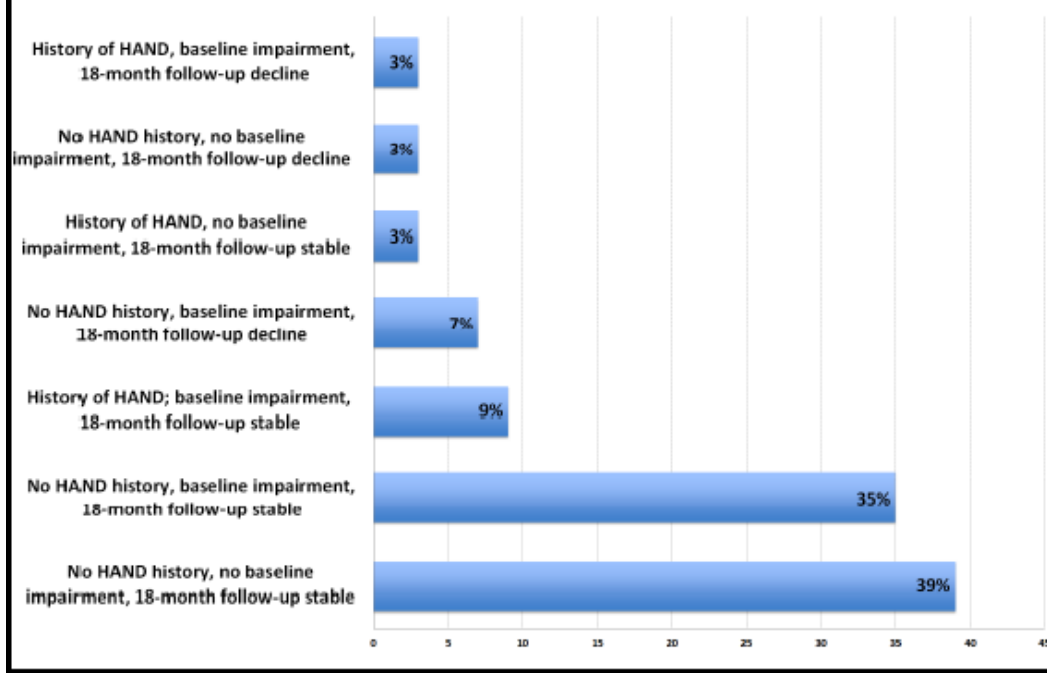


Table 3. HIV+ Disease Characteristics

| | Baseline | Follow Up | <i>p</i> |
|-----------------------------------|-----------------|-----------------|----------|
| HIV duration (years) | 19.18 (6.81) | - | |
| Nadir CD4-T cell (median cp/mL) | 181.21 (125.93) | - | |
| Historical AIDS (%) | 69.79% | No new AIDS | |
| Current CD4-T cell (median cp/mL) | 543.03 (262.07) | 638.61 (300.21) | <.001 |
| Plasma HIV RNA (% undetectable) | 97.91% | 90.63% | .65 |
| Formal Historical HAND Diagnosis | 15.6% (15/96) | | |

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