HIV-1 Dual Infection and Neurocognitive Impairment

Gabriel Wagner, MD
Assistant Professor of Medicine
Infectious Diseases & Global Public Health
UC San Diego
HIV-Associated End Organ Damage

• Antiretroviral therapy (ART) reduces HIV morbidity and mortality.
• Even if a person takes ART, they can develop end organ damage.
  • Cardiovascular disease
  • Renal disease
  • Neurocognitive impairment
• Mechanisms are often multifactorial.
  • Natural aging
  • Persistent inflammation
  • Drug toxicities
  • Low-level residual viral replication

HIV-Associated Neurocognitive Disorder (HAND)

- Despite ART, 30-50% of individuals demonstrate mild impairment.
  - Even when HIV RNA levels in blood and cerebrospinal fluid (CSF) are undetectable
- Higher viral genetic diversity associated with HAND.

Heaton et al., *Neurology* 2010
Hightower et al., *Virology* 2012
HIV-1 Dual Infection

Co-infection

Strain 1 + Strain 2

Superinfection

Strain 1

Strain 2

Intrasubtype (same subtype)

or

Intersubtype (different subtypes)

Smith et al., JID 2005
HIV-1 Dual Infection

• Frequency estimates vary.
• In San Diego Primary Infection Resource Consortium, cumulative prevalence was **14.4%** (95% CI 8.6%–22.1%).
• Dual infection is associated with higher HIV viral loads and lower CD4 T-cell counts, *similar to HAND*.

• *Are HIV-1 dual infection and HIV-associated neurocognitive impairment related?*

Pacold et al., *AIDS* 2012
Wagner et al., *JID* 2014
Study Cohort

• CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study.
• Participants had at least two longitudinal blood samples.
• All participants had neurocognitive assessments.
• Comorbid conditions that may contribute to HAND classified as:
  • Incidental
  • Contributing
  • Confounding
• CHARTER participants with confounding comorbidities were excluded.
Dual Infection Detection

Blood → PBMC → DNA → PCR
Dual Infection Detection

Blood $\rightarrow$ PBMC $\rightarrow$ DNA $\rightarrow$ PCR

5' LTR gag

pol

3' LTR nef

5' LTR gag

1 2 3

p24 (253 bp) RT (534 bp) vpr

Deep sequencing Deep sequencing Deep sequencing

vpu rev tat

V3 (416 bp)

Deep sequencing

Wagner et al., JID 2014
• DI: nucleotide divergence exceeds intrahost evolution.
• Phylogenetic reconstruction and contamination check.
HIV Monoinfection

HIV Dual infection

Wagner et al., Poster 201, CROI Seattle 2017
Dual infection in study cohort

• Chronically infected participants on ART, N=38.
  • 87% men; 55% were MSM
  • Main HIV risk factor was sexual exposures (95%).
  • Median age was 50 years (IQR: 45 – 53 years).
  • Despite ART, 12 had detectable plasma HIV viral load > 500 copies/ml.

• Nine (24%) had two viruses in multiple samplings and were categorized as having dual infection.
  • No significant differences in plasma viral loads or CD4 T-cell counts
  • Detectable plasma and CSF viral loads were not associated with dual infection
  • Greater IV drug use in dual infection group marginally significant (P = 0.051)

Wagner et al., AIDS 2016
Dual infection and neurocognitive impairment

• Using first TP, global neurocognitive impairment identified in 21
  • Significantly lower CD4 T-cell counts (current and nadir) associated with impairment ($P = 0.028$ and $P = 0.043$, respectively)
  • No association with detectable plasma or CSF viral load

• After adjustment, multivariate analysis demonstrated a significant association between dual infection and HAND; OR = 18.30 (95% CI 1.94-414.16), $P = 0.028$.

| Adjusted analysis of effect of dual infection on neurocognitive impairment |
|-----------------------------|-----------------------------|-----------------------------|
| Predictor                   | OR (95% CI)                 | $p$ value                   |
| Dual vs. mono-infection     | 18.30 (1.94, 414.16)        | 0.028                       |
| Estimated duration of infection, per year | 0.87 (0.74, 0.99)   | 0.17                        |
| Current CD4 T-cell count, per cell | 0.997 (0.994, 0.999)  | 0.017                       |

Wagner et al., AIDS 2016
Conclusions

• Dual infection was common (24%) among chronically infected individuals receiving ART.

• Dual infection was associated with HAND.
  • Dual infection may increase risk of HAND
  • HAND may increase risk of dual infection
  • Both conditions may have a third condition in common

• Greater viral genetic diversity could increase risk of viral adaptation and fitness in the CNS:
  • HIV enters CNS early in infection
  • Dual infection most frequent in first 1–2 years after primary infection

Wagner et al., JID 2014
Davis et al., Neurology 1992
Future work

• Deep sequencing of CSF cell pellets to interrogate for two viral lineages in the CNS.
• Analysis of viral motifs associated with HAND.
• Deep sequencing of full-length HIV DNA to better characterize intrahost viral evolution in dual infection.
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HIV-1 genome
Targeted amplicon sequencing

1. 5' LTR
2. gag
3. pol
4. vpr
5. 3' LTR
6. nef
7. vpu
8. rev
9. tat
10. env
Targeted amplicon sequencing

target-specific primers → adaptors, barcodes → PCR enrichment → sequencing → read filtering and correction → reference mapping → functional annotations → variant calling