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Neurologic signs and symptoms frequently manifest in acute HIV infection

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Aims

- To determine the incidence, timing, and severity of neurologic findings in pre-antibody seroconversion acute HIV infection.
- To assess persistence of neurologic findings after early combination antiretroviral therapy (cART).

Methods

- Prospective cohort of participants diagnosed with Fiebig I-V acute HIV, identified through laboratory screening at an HIV/STD testing center in Bangkok, Thailand.
- Participants underwent structured neurologic evaluations, immediately initiated standardized cART or mega cART (cART augmented with maraviroc and raltegravir), and were followed with neurologic evaluations at 4 and 12 weeks.
- Concurrent viral and inflammatory markers in the blood and cerebrospinal fluid (CSF) were obtained prior to cART initiation, as was magnetic resonance imaging (MRI).
- Chi-squared tests were used for comparing percents between groups and unpaired t-tests were used for comparing means between groups.

Results

Table 1. Demographic and laboratory characteristics of acute HIV participants who are neurologically normal and those with neurologic findings.

	Normal	Neurologic findings	p-value
Number	66	73	
% Male	94	92	0.48
Age (SD)	27 (±7)	29 (±8)	0.10
Education years (SD)	16 (±5)	16 (±4)	0.49
Est. days of infection (range)	19 (3-56)	19 (7-34)	0.66
% with Drug use (n)	16 (9/55)	30 (18/61)	0.12
% with ARS (n)	70 (46)	75 (55)	0.44
% in Fiebig I/II (n)	52 (34)	44 (32)	0.52
% in Fiebig III-V (n)	49 (32)	56 (41)	0.52
% on mega cART (n)	61 (40)	45 (33)	0.09
CD4 count cells/mm^3 (SD)	394 (±22)	390 (±25)	0.91
Plamsa log$_{10}$HIV RNA (SD)	5.4 (±0.12)	5.9 (±0.13)	0.01*
CSF log$_{10}$HIV RNA (SD)	3.12 (±0.24)	3.73 (±0.32)	0.14

ARS = acute retroviral syndrome.

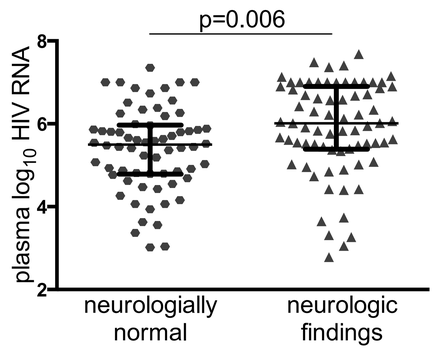
Results

Table 2. Neurologic findings in acute HIV by week following diagnosis.

		Number of neurologic findings			
	# Subjects (%)	Week 0	Week 4	Week 12	Total (%)
Concentration	34 (24)	19	12	11	42 (17)
Cognitive effort	11 (8)	4	4	4	12 (5)
Memory	22 (16)	10	7	10	27 (11)
Speech	10 (7)	5	3	2	10 (4)
Gait	13 (9)	10	1	3	14 (6)
UE coordination	5 (4)	4	2	0	6 (3)
Involuntary movements	5 (4)	2	3	0	5 (2)
Slowed responses	6 (4)	4	1	1	6 (3)
Smooth pursuit	3 (2)	2	0	1	3 (1)
Saccades	0 (0)	0	0	0	0 (0)
Limb strength*	3 (2)	3	0	1	4 (2)
Neuropathy	23 (17)	10	9	7	26 (11)
Deep tendon reflexes	5 (4)	1	3	1	5 (2)
Limb coordination	2 (1)	2	0	0	2 (1)
Gait coordination	1 (1)	0	0	1	1 (1)
Speech	2 (1)	2	0	0	2 (1)
Facial expression	5 (4)	4	0	1	5 (2)
Resting tremor*	0 (0)	0	0	0	0 (0)
Action tremor*	1 (1)	0	0	2	2 (1)
Rigidity*	0 (0)	0	0	0	0 (0)
Finger taps*	22 (16)	17	11	7	35 (14)
Fist opening, closing*	6 (4)	6	0	6	12 (5)
Rapid alt. movements*	7 (5)	8	0	6	14 (6)
Leg agility*	3 (2)	3	0	2	5 (2)
Arising from chair	0 (0)	0	0	0	0 (0)
Gait	3 (2)	2	0	1	3 (1)
Postural stability	2 (1)	1	1	0	2 (1)
Posture	0 (0)	0	0	0	0 (0)
Bradykinesia	2 (1)	2	0	0	2 (1)
Total (%)	**73 (53)**	**121 (49)**	**57 (23)**	**67 (27)**	**245**

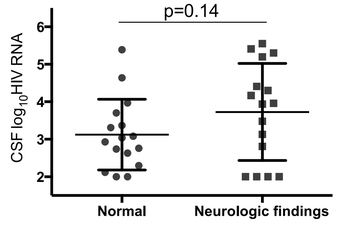
Abbreviations: UE = upper extremity; invol = involuntary; DTR = deep tendon reflexes; alt = alternating; mvmts = movements. Star indicates categories that reflect a sum of right and left sided findings, or multiple limb findings.

Figure 1. Participants with neurologic findings had a higher mean plasma log$_{10}$ HIV RNA at baseline (5.9 vs. 5.4; p=0.006) compared to those without neurologic findings**.** Presence of neurologic findings associated with plasma HIV RNA but not CSF HIV RNA, blood CD4+ T lymphocyte count, or CSF or plasma neopterin (a macrophage activation marker).



Results

Figure 3. Participants with neurologic findings had similar baseline CSF log$_{10}$ HIV RNA compared to neurologically normal participants (3.73 vs. 3.12; p=0.14; n=32)



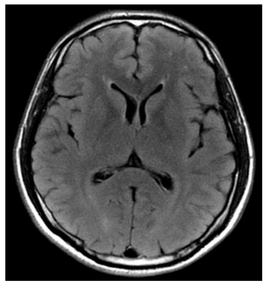


Figure 4. Representative mild white matter hyperintensities on brain MRI during acute HIV. Axial T2 FLAIR obtained in a 37 year-old Thai man in Fiebig I of acute HIV infection, estimated 14 days post infection, demonstrating punctate white matter T2 hyperintensities in the right and left frontal subcortical white matter. Follow up MRI after six months of cART was unchanged.

Additional Key Findings

- 53% of participants in acute HIV experienced one or more neurologic finding in the 12 weeks after diagnosis.
- 49% of neurologic findings occurred at diagnosis, prior to cART initiation.
- 96% of neurologic findings were categorized as mild in severity.
- One participant developed a fulminant neurologic manifestation, Guillain-Barré syndrome.
- Of the neurologic findings:
  - 33% were cognitive symptoms
  - 34% were motor findings
  - 11% were neuropathy
- Those reporting cognitive symptoms experienced higher rates of anxiety (χ^2= 4.1; p=0.04), and had lower composite neuropsychological test scores across weeks 0, 12, and 24, although still within normal range.
- 90% of neurologic findings present at diagnosis remitted concurrent with one month on treatment.
- Only 9% of neurologic findings persisted at 24 weeks on cART.
- No significant structural neuroimaging abnormalities were observed.

Case details fulminant Guillain-Barré Syndrome (GBS) in acute HIV:

A 34 year-old participant with presumed dengue fever over a month prior to HIV diagnosis experienced a defined, HIV-attributable ARS syndrome. He presented in Fiebig III with a CD4+ count of 7 cells/mm^3 that increased to 180 cells/mm^3 after 4 weeks on cART. The neurologic exam revealed no deficits through week 4. Three days later, he developed reduced proximal arm strength, and within 48 hours, had ascending distal parasthesias, followed by diffuse areflexia and weakness in the lower extremities. He was hospitalized and diagnosed with GBS, supported by nerve conduction and CSF studies, and was treated with intravenous immunoglobulins (IVIG). At most extreme, he experienced facial diplegia, profound limb weakness, and sensory deficits. After discharge, he progressively improved, with return to normal function in six months. Fifteen months after GBS diagnosis, he remained functionally normal, with persistent areflexia in the arms, diminished reflexes in the left leg, and mildly decreased vibratory sense distally.

Conclusions

- Acute HIV infection is commonly associated with mild neurologic findings that largely remit while on treatment.
- Of HIV disease biomarkers, only plasma HIV RNA levels were elevated in participants with neurologic findings in acute HIV.
- Severe neurologic manifestations are infrequent in acute HIV in the setting of immediate treatment.
- The case of GBS observed in our study may have resulted from aspects of acute HIV or may have been caused by IRIS in the setting of response to early cART.

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