CNS immune activation still present despite > 10 years of effective antiretroviral therapy of HIV-1

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Background

Antiretroviral therapy (ART) effectively suppresses viral load in plasma and cerebrospinal fluid (CSF) and substantially decreases the intrathecal immune activation that is commonly found in untreated HIV. Signs of low-grade intrathecal immune activation can, however, be found in a substantial proportion of people living with HIV (PLHIV) even after initiation of ART. CSF neopterin, a well characterized marker of microglial/macrophage activation, has been associated with HIV-associated neurocognitive disorders (HAND) in untreated as well as in patients on suppressive ART. The aim of this study was to examine residual intrathecal immune activation in correlation to signs of neuronal injury and neurocognitive impairment in PLHIV virally suppressed on ART for more than 10 years.

Patient	Age. years (follow-up)	Gender	Months < 50 HIV RNA copies/mL	Number of plasma blips	CD4 nadir	CD4 (baseline)	CD4 (follow-up)
1	50	Male	136	0	204	unknown	530
2	51	Male	197	5	149	unknown	480
3	56	Male	142	3	45	140	650
4	65	Female	175	1	280	304	1000
5	50	Male	174	3	60	61	1200
6	50	Male	135	3	150	150	660
7	53	Male	160	2	30	32	400
8	68	Male	154	0	130	369	720
9	67	Male	140	2	340	unknown	630
10	45	Male	126	1	260	unknown	1200
11	66	Male	167	1	10	52	510
12	60	Male	166	0	200	unknown	430
13	42	Female	174	0	220	307	290
14	50	Male	149	0	90	164	740
15	57	Male	125	1	190	190	390
16	54	Male	117	0	160	250	700
17	53	Female	148	1	20	31	300
18	49	Female	114	0	40	42	860
19	43	Male	136	1	20	20	190
20	67	Male	117	3	160	170	280
21	21	Male	135	unknown	unknown	unknown	1300
22	50	Male	136	unknown	250	unknown	310

Table 1. Characteristics of included patients.

Methods

Neurologically asymptomatic PLHIV on ART ≥ 10 years with plasma HIV-RNA levels < 50 copies/mL for ≥ 9.5 years were retrospectively included. HIV-RNA, neopterin, and neurofilament light protein (NFL), a sensitive marker of neuronal injury, were analyzed in paired plasma and CSF samples in 22 patients. Pre-treatment samples were available in 15 subjects. Cognitive function in five domains was assessed by CogState (a computerized cognitive testing system validated in PLHIV). The CogStateBrief Battery consists of four tests: detection (DET) measuring psychomotor function and attention, identification (ID) assessing speed of information processing and attention, one card learning (OCL) which is a learning test and one back (OB) test which assess working memory.

Results

- Neopterin decreased significantly ($p < 0.001$) in both plasma from in median 25.1 (IQR 13.3-37.7), to 7.40 (IQR 4.9-10.3) nmol/L and in CSF ($p < 0.001$) from in median 18.6 (IQR 10.9-28.8) to 5.95 (IQR 4.6-7.9 nmol/L) after treatment initiation.
- Twelve of twenty-two (55 %) participants still had CSF neopterin above the upper normal reference limit (5.8 nmol/L) despite ≥ 10 years of ART.
- CSF NFL decreased significantly ($p < 0.05$) from in median 1030, IQR 541-1220, to 480, IQR 290-750 ng/L after treatment initiation.
- No significant correlations were found between CSF neopterin and CSF NFL or neurocognitive performance.
- No difference was seen in CSF NFL or neurocognitive performance in subjects with normal compared to increased CSF neopterin.

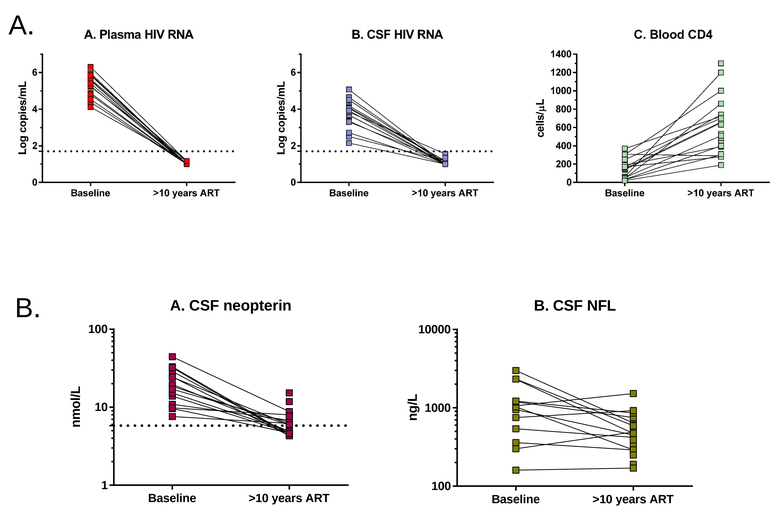

Figure 1
(A.) Effect of ART on viral load and CD4 count. N (Baseline) = 15, N (> 10 yrs ART) = 22
(B.) Effect of ART on neopterin in CSF and NFL in CSF. N (Baseline) = 15, N (> 10 yrs ART) = 22

Conclusions

- ART significantly decreases intrathecal immune activation, but, despite effective treatment for > 10 years, 55% of PLHIV continue to show signs of macrophage/microglia activation (elevated neopterin in CSF) in the CNS.
- Importantly, no associations was found between elevated neopterin and neurocognitive performance or signs of neuronal injury (as measured by CSF NFL).

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