REBOUND HIV-1 IN CSF AFTER TI IS DOMINATED BY CLONALLY AMPLIFIED T CELL-TROPIC VIRUS

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Background

HIV-1 persists during suppressive antiretroviral therapy (ART) as a latent reservoir but reappears with treatment interruption (TI). In the absence of ART most viral replication takes place within the lymphoid system, although HIV-1 can be detected in cerebrospinal fluid (CSF). Most of what is known about the latent reservoir is based on studies of cells from peripheral blood and less is known about reservoirs in the central nervous system (CNS).

Methods

In this study we compare rebound virus in archived blood and CSF longitudinally sampled from 11 participants after TI to look for evidence of a distinct reservoir within the CNS. Single genome amplification (SGA) and/or Illumina MiSeq deep sequencing with Primer ID were used to assess *env* diversity and drug resistance in *pro-pol*. Full-length *env* genes were cloned from the rebound virus of 4 participants and assessed for their ability to efficiently facilitate entry into cells with a low surface density of CD4 (a proxy for macrophage tropism; M-tropism).

Cohort

Study Site[a]	PID[b]	Year of TI	Age (years)	Sex	ARV[c] Before TI	Years From HIV Diagnosis	CD4 Nadir (cells/ul)	Suppressed (S) or Viremic (V) Before TI[d]
UCSF	4026	1998	51	M	NFV/d4T/ddi		118	V
	6004	1999	51	M	3TC/d4T/IDV	16	116	V
	6005	1999	53	M	3TC/d4T/IDV	12	3	V
	6006	1999	39	M	EFV/NFV/ABC/Adefovir	17	69	V
	6008	2000	35	M	SQV/RTV	6	360	S
	6011	2001	43	M	EFV/ZDV/3TC	20	191	S
	6012	2001	51	M	EFV/d4T/3TC	23	199	S
	6013	2001	42	M	EFV/d4T/3TC	12	275	V
GOT	5207	2001	56	F	d4T/3TC/IDV/r	1	110	S
	5299	2006	55	M	TDF/3TC/AZV/r	3	120	V
	51126	2016	53	M	ABC/3TC/DRV/r	5	60	V

[a]Study sites were the University of California San Francisco (UCSF) and the University of Gothenburg (GOT)
[b]Personal identification (PID) number for each participant
[c]Antiretriviral (ARV) regimen
[d]Designation for detectable viral load in the blood

Acknowledgements

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CSF compartmentalized rebound virus is influence by the influx of WBC

Figure 1.

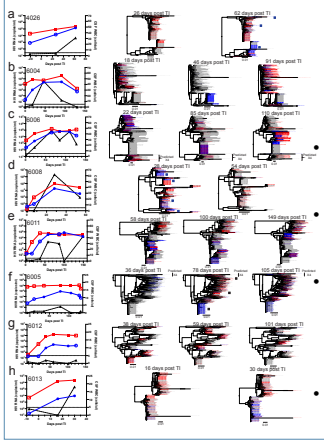
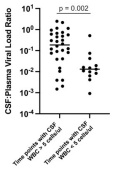


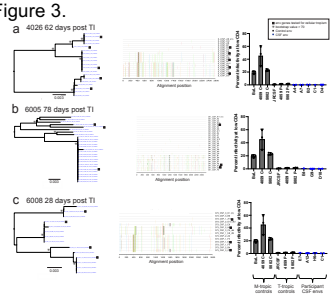
Figure 2.



- Viral load in the CSF approached that of the blood (Fig 1a-e) or remained 10-fold lower than the blood VL (Fig 1f-g).
- In the absence of pleocytosis, virus in the CSF was generally mixed with virus in the blood (Fig 1b, c, and d first time point)
- In the presence of elevated CSF white blood cells (WBC), CSF VL was increased and the CSF viral population was dominated by clonal expanded lineages. (Fig 1a, second time point and Fig 1d first time point)
- Elevation of CSF VL relative to the blood was significantly associated with pleocytosis (Fig 2).

Clonally amplified virus in the CSF is adapted to replication in CD4+ T cells

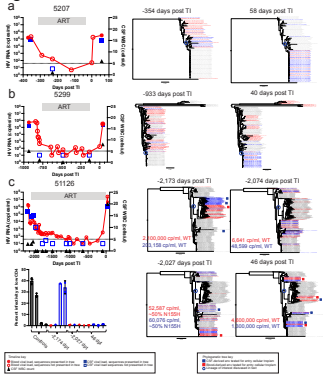
Figure 3.



- Diversity in amplified CSF sequences is low but greater than the expected error rate of reverse transcriptase suggesting this virus has undergone brief replication (Fig 3, middle panels).
- Compartmentalized, clonal rebound virus in the CSF is T cell tropic (Fig 3, right panels).

Viral lineages over-represented in CSF at therapy initiation can contribute to rebound

Figure 4.



- Clonal rebound virus in the CSF appears to be from a lineage that was rare pretherapy (Fig 4a and b middle and left panels).
- Participant 51126 (Fig 4c) had compartmentalized, macrophage-tropic in the CSF pretherapy that was not detected as rebound virus after therapy interruption

The initial increase in CSF VL and CSF WBC after TI are associated with several inflammatory markers

Figure 5.

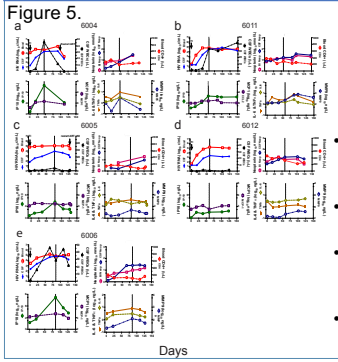
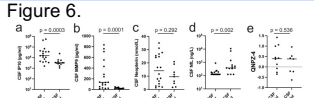


Figure 6.



- Rising IP10 levels were closely linked to peaking CSF WBC (Fig 5a-c, e)
- IP10 and MMP9 were elevated during pleocytosis (Fig 6a and b)
- Neopterin and the neurocognitive score QNPZ-4 were not significantly linked to pleocytosis (Fig 6c and e)
- NFL was not linked to elevated CSF WBC during TI rebound (Fig 6d)

Conclusions

- The most abundant portion of viral rebound populations in the CSF during TI are clonally amplified and T cell-tropic suggesting that the major rebounding populations in the CNS are likely produced by T cell reservoirs.
- Transient pleocytosis in the CSF during TI is linked to clonal amplification, elevated viral loads, and elevated inflammatory markers in the CSF
- We did not identify evidence of viral rebound from HIV-infected myeloid cells in the CNS, even when macrophage-tropic virus was documented pretherapy, suggesting if a myeloid cell reservoir exists in the CNS it is poorly represented in the CSF during TI.