Abstract #363

CNS Monitoring of cART Interruption in Individuals Treated during Fiebig I Acute HIV

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P Chan, D Colby, V Valcour, N Sailasuta, S Krebs, L Jagodzinski, R Paul, J Ananworanich, S Spudich
on behalf of the RV411 and RV254/SEARCH 010 study groups

SEARCH, The Thai Red Cross AIDS Research Centre, Bangkok, Thailand; University of California, San Francisco; University of Hawaii, Honolulu, USA; U.S. Military HIV Research Program, Walter Reed Army Institute of Research, MD, USA; Henry M. Jackson Foundation for the Advancement of Military Medicine, MD, USA; University of Missouri, St. Louis, USA; Yale University, New Haven, CT, USA.

Background

- Monitored treatment interruption (TI) of combination antiretroviral therapy (cART) is a frequent strategy in studies of HIV remission.
- TI may have adverse consequences of inflammation or dysfunction in the central nervous system (CNS) and reveal potential CNS sources of viral rebound following withdrawal of cART.
- We assessed the CNS effects of TI after sustained treatment started in early acute HIV infection (AHI) in the RV 411 study in Bangkok, Thailand (Oral abstract #124).

Methods

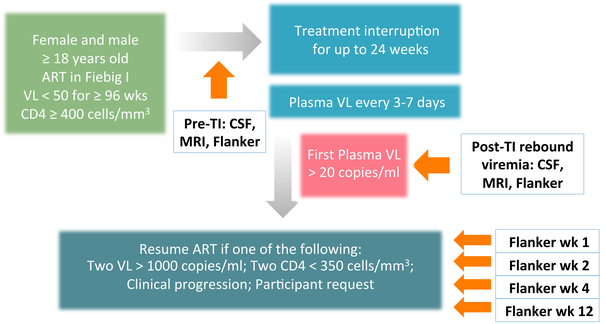


Figure 1. Study Schema of RV411 study with CNS assessments indicated by orange arrows.

- Participants initiated cART during Fiebig I (HIV RNA+, p24-, IgM-) AHI in the SEARCH 010/RV254 study.
- TI was undertaken after >24 months of continuous cART.
- TI was followed by plasma HIV RNA monitoring every 3-7 days and cART resumption once plasma HIV RNA >1,000 cps/ml.
- Optional CNS measures prior to TI (**Pre-TI**) and after plasma HIV RNA > 20 copies/ml (**Post-TI rebound viremia**):
  - Cerebrospinal fluid (CSF) HIV RNA by both standard Roche COBAS TaqMan HIV-1 Test V2.0 (LLOD 80 cps/ml) and ultrasensitive (measuring a target region of HIV-1 gag RNA transcript, LLOD 0.44 cps/ml)[1] HIV-1 assays.
  - Soluble CSF immune activation markers (neopterin, sCD14, MCP-1, IP-10).
  - Cerebral metabolites via 3T brain magnetic resonance spectroscopy (MRS).
- **Flanker test** (in all participants)**:** Novel tablet-based measure of attention and inhibitory control (NIH-Toolbox) at pre-TI, post-TI rebound viremia, and 2, 4, and 12 weeks after resuming cART.

[1] Somsouk et al. 2014. *PLoS ONE* 9:e116306.

Results

n = 8	Pre-ART in AHI	Pre-TI	First Post-TI Rebound Viremia
Sex (F/M)	1/7	-	-
Age, years	25 (19 - 30)	-	
HIV subtype	CRF01_AE or _AE/B	-	-
Estimated duration of infection prior to cART, days	19 (18-22)	-	-
Duration of cART*, years	-	2.8 (2.5 - 5.5)	-
CD4, cells/mm^3	413 (227 - 565)	577 (391 - 703)	-
CD4/CD8 ratio	0.8 (0.6 - 1.6)	1.1 (0.5 - 1.4)	-
HIV RNA, copies/ml	12,908 (11,493 - 20,083)	All <20	122 (26 – 7784)
TI to first rebound viremia, days	-	-	26 (13 – 48)
First rebound viremia to cART resumption, days	-	-	4 (1 – 21)

*TDF/3TC/EFV in 7/8 participants; ZDV/3TC/EFV in one participant. Values shown are medians (interquartile range).

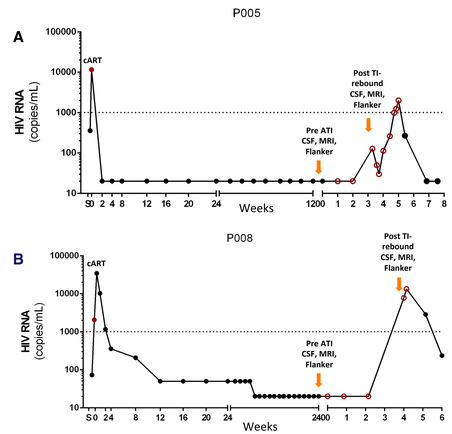


Figure 2: Figures **2 A & B** show plasma viral loads over time since Fiebig I AHI in two representative participants (P005 & P008) and timing of CNS sampling during the current TI study. Solid red circles denote timing of start of cART, open red circles indicate study intervals during treatment interruption, dotted line indicates threshold for re-starting cART.

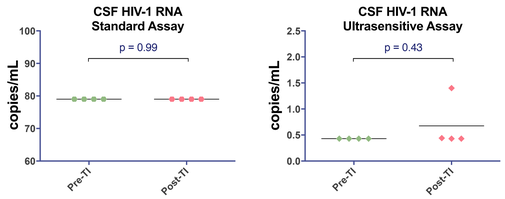


Figure 3: Four participants underwent CSF sampling, revealing no detectable CSF HIV RNA (<80 copies/ml) pre-TI and during post-TI rebound viremia using a standard HIV RNA assay (with corresponding plasma HIV RNA 30, 78, 739 and 13,462 copies/ml). Ultrasensitive assay revealed detectable values (0.44 and 1.4 copies/ml) in CSF in two participants at post-TI rebound viremia.

Results

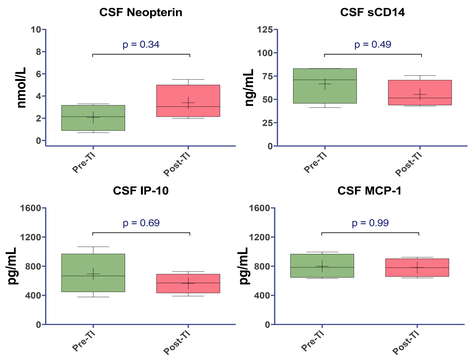


Figure 4: Levels of CSF neopterin, MCP1, IP10, and sCD14 in four participants did not significantly change from pre-TI to rebound viremia. Lines and whiskers indicate medians and interquartile range; means are denoted by +.

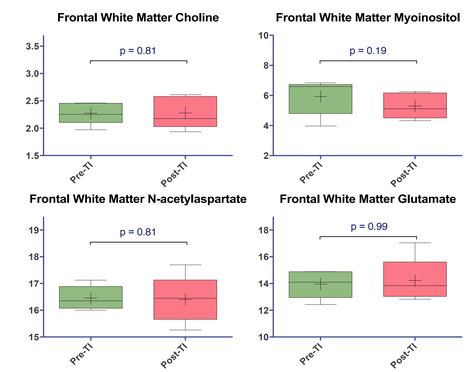


Figure 5: 3 Tesla brain MRS in frontal white matter (above) and basal ganglia (not shown) in five participants revealed no significant changes in neuronal or inflammatory measures from pre-TI to rebound viremia. Lines and whiskers indicate medians and interquartile range; means are denoted by +.

Results

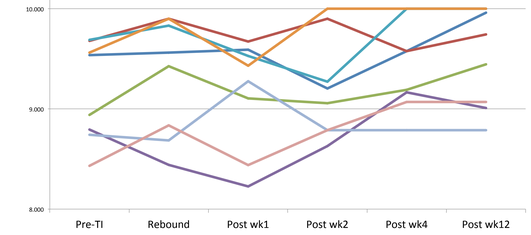


Figure 6: Performance on the NIH Toolbox Flanker task (y axis) prior to TI, at rebound, and again after week 1, 2, 4 and 12 (x axis). Flanker task score reflects a combination of accuracy and reaction time with each vector ranging in value between 0 and 5. If accuracy is less than or equal to 80%, the computed score is equal to the accuracy score.

Flanker task performance remained similar across intervals of pre-TI wk 0 to plasma rebound (p=0.30).

Flanker scores improved from the end of the TI to 12 weeks after resumption of cART (p=0.045) to levels exceeding performance at pre-TI.

Conclusions

- In a small study focused on the potential beneficial effects of cART started during Fiebig I acute HIV on viral reservoirs, longitudinal monitoring of the CNS did not reveal evidence of adverse CNS effects of closely monitored TI with rapid resumption of cART.
- The four participants who had CSF sampling had no detected HIV RNA in the CSF by a standard assay during rebound plasma viremia.
- Very low level CSF HIV RNA was detected by an ultrasensitive assay during post-TI rebound viremia in two of four participants.

Implications for future studies

- Examination of the CNS is feasible to integrate in systemic HIV studies and is critical for a comprehensive understanding of the impact of interventions aimed at viral remission.

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