IMPACT OF TREATMENT INTERRUPTION ON COLONIC MUCOSA IN ACUTELY TREATED PARTICIPANTS

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Schuetz A.[1,2,3], Brands C.[4], Morcock DR.[4], Colby DJ.[2,3], Crowell TA.[2,3], Rerknimitr R.[6], Sacdalan C.[5], Pinyakorn S.[2,3], Phuang-Ngern Y.[1], Keele BF.[4], Lifson JD.[4], Ananworanich J.[7], Hsu D. [2,3] **Deleage C.**[4]

on behalf of the RV411/397 Study Groups

1.Department of Retrovirology, Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand. 2.US Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD, USA.3.Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, MD, USA .4.AIDS and Cancer Virus Program, Frederick National Laboratory for Cancer Research, Frederick, MD, USA.5.SEARCH, The Thai Red Cross AIDS Research Center, Bangkok, Thailand.6.Department of Medicine, Chulalongkorn University, Bangkok, Thailand.7.Department of Global Health, Amsterdam Medical Center, Amsterdam Institute Global Health and Development, Amsterdam, The Netherlands

BACKGROUND

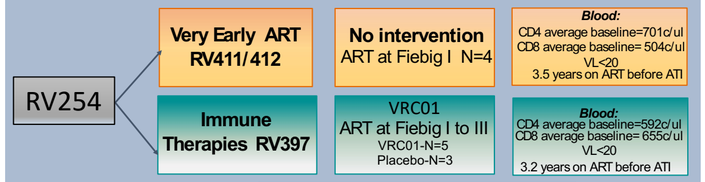
Lymphoid tissues, like the colon, can be the site of residual viral replication in successfully treated patients who initiated cART during acute phase.

Despite antiretroviral therapy (ART) initiation during acute HIV infection and viral suppression for years, most individuals experience viral rebound shortly after treatment interruption. The major obstacles to HIV cure are tissue reservoirs that are established early during infection. We had the unique opportunity to analyze sigmoid colon biopsies prior to and during analytical treatment interruption (ATI) from participants who initiated ART during acute HIV infection at Fiebig I, II or III.

METHODS

A total of 12 individuals with plasma viral suppression from two ATI trials, who received no intervention (n=5) or VRC01 during ATI (n=7) were included. Participants underwent sigmoidoscopy at baseline (while on ART, n=12), at the time of viral rebound after ATI (n=6, 2 of 6 were VRC01 recipients) and 6- 12 months after ART resumption (n=6, 2 of 6 were VRC01 recipients). We performed immunohistochemistry (IHC) and flow cytometry to assess immune cell numbers and frequency (CD4, CD8, CD68, CD163), quantify activation and inflammatory markers (Ki67, Mx1, TNF) and localization and phenotype of vRNA+ cells and vDNA+ cells by *in situ* hybridization (RNAscope). Changes from baseline ATI to rebound were tested using Wilcoxon signed-rank test.

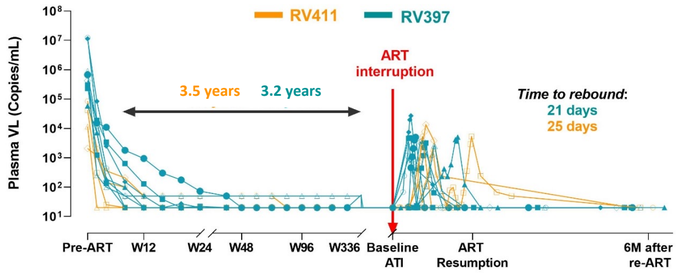
Participants Trial randomization and clinical information



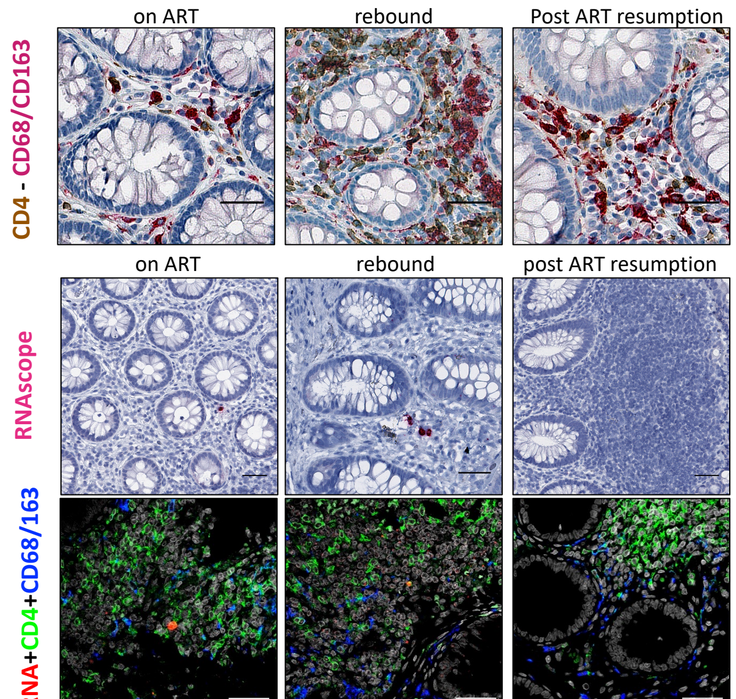
Masked ID	Study	Fiebig	treatment arm	Plasma VL Baseline	Plasma VL ART resumption	Plasma VL 6M post ART resumption	CD4 Plasma Baseline	CD4 Plasma ART resumption	CD4 Plasma 6M post ART resumption	years on ART before ATI	vRNA+ cells while on ART in GI
4878	RV411/412	1	No intervention	<20	1019	<20	671	654	673	2.7	yes
6579	RV411/412	1	No intervention	<20	30	<20	601	526	604	2.6	yes
4320	RV411/412	1	No intervention	<20	5253	<20	391	419	505	2.6	no
8534	RV411/412	1	No intervention	<20	3843	<20	703	616	820	4.7	yes
4233	RV397	2	VRC01	<20	3440	<20	864	685	954	3.6	yes
4011	RV397	3	VRC01	<20	1320	<20	886	638	844	6.6	no
5040	RV397	2	VRC01	<20	3174	<20	476	559	485	2.4	no
3183	RV397	2	Placebo	<20	3845	<20	716	774	670	3.8	no
5382	RV397	3	VRC01	<20	5013	<20	1032	960	889	4.5	no
3500	RV397	1	VRC01	<20	5038	<20	814	777	674	2.5	no
4584	RV397	3	Placebo	<20	4691	<20	523	477	571	2.6	no
9090	RV397	2	Placebo	<20	26865	<20	735	484	563	2.3	no

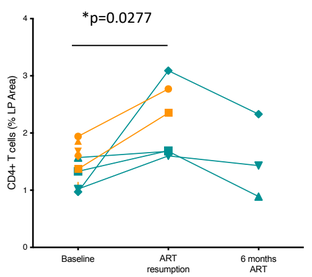
Despite plasma viral suppression and early treatment initiation, vRNA+ CD4+T cells were found in a third of participants while on ART and detected in all at ATI, reinforcing the importance of the GALT as essential site of viral replication during ART interruption.

RESULTS

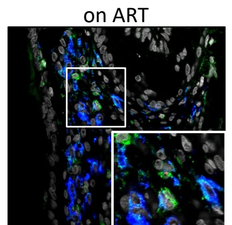


All participants rebounded within 25 days post ATI, after being fully suppressed for more than 3 years regarding of their treatment arm.





In situ analysis of the sigmoid biopsies shows increase of CD4+T cells within the LP at rebound and CD4+T cells harboring vRNA before ATI in 5 out of 12 participants.



CONCLUSIONS

- We observed a significant increase in colonic CD4+ T cells within the LP at the time of rebound.
- Activated CD8+ T (HLA-DR+CD38+) cells were increased at the time of rebound.
- Despite plasma viral suppression, CD4+T harboring vRNA+ were found in a third of participants while on ART.
- All participants presented actively replicating infected cells and virion within GI biopsies at rebound.
- No vRNA+ cells were found in the biopsies collected 6 to 12 month after ART resumption.
- CD4+T cells harboring vDNA were found in all participants at all time point collected.

These observations are reinforcing the importance of the GALT as essential site of viral replication during treatment interruption and as a reservoir and potential site of on-going low replication during cART.

The 4 participants presenting vRNA+cells while on ART received treatment early on as 3 were classified in Fiebig I and the 4th participant was in Fiebig II when treatment was initiated. This support a notion published by us and others, early treatment as many advantages (decrease inflammation, restore CD4+T cell count, decrease the risk of transmission) however it is not sufficient to eradicate the infection.

ACKNOWLEDGMENTS

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DISCLAIMER

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