Endothelial and Hemostasis Perturbations During Acute HIV Infection and After Immediate Therapy

Phillip Chan[1,2], Kirati Tayutivutikul[1], Bonnie Slike[3,4], Suteeraporn Pinyakorn[3,4], Kathryn Holroyd[5], Carlo Sacdalan[6,7], Lily Metzger[3,4], Eugène Kroon[6], Donn Colby[3,4], Somchai Sriplienchan[6], Nittaya Phanuphak[8], Robert Paul[9], Lydie Trautmann[3,4], Shelly Krebs[3], Serena Spudich[1,2], on behalf of the RV254/SEARCH 010 Study Team

1. Department of Neurology, Yale University School of Medicine, New Haven, CT, USA; 2. Yale Center for Brain and Mind Health, Yale University School of Medicine, New Haven, CT, USA; 3. Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD, USA; 4. Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, MD, USA; 5. Department of Neurology, Columbia University Irving Medical Center, New York, NY; 6. SEARCH Research Foundation, Bangkok, Thailand; 7. Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; 8. Institute of HIV Research and Innovation (IHRI), Bangkok, Thailand ; 9. Faculty of Psychological Sciences, Missouri Institute of Mental Health, University of Missouri-St. Louis, St. Louis, MO, USA

INHCC International NeuroHIV Cure Consortium

Abstract # 247

BACKGROUND

- Compared to people without HIV (PWoH), people with HIV (PWH) have elevated risk of vascular complications that persist despite suppressive antiretroviral therapy (ART).
- This analysis examines endothelial and hemostasis perturbations during acute HIV infection (AHI) and 6 years after immediate ART initiation.

METHODS

- The study included 83 RV254 AHI cohort participants who initiated ART during Fiebig stage I-V of AHI.
- We measured endothelial, hemostasis, and inflammatory biomarkers in plasma collected during pre-ART AHI and week 288 post-ART (see **Table 1** for the list of biomarkers).
- Results were compared with cross-sectional data from 32 Thai PWoH. Nonparametric tests were employed to assess group differences, longitudinal changes within RV254 participants, and correlations between biomarkers and HIV-related parameters.
- Utilizing biomarker outcomes from PWoH and RV254 participants at week 288, hierarchical clustering was applied to identify distinctive biomarker phenotype subgroups.

Table 1. List of Plasma Biomarkers

Endothelial	ICAM-1; ICAM-2; VCAM-1; VEGF-A, C, D; sP-selectin; sE-selectin
Hemostasis	Tissue plasminogen activator (t-PA); Tissue Factor (TF); Thrombomodulin (TM)
General Inflammatory	Neopterin; Myeloperoxidase (MPO)

Abbreviations: ICAM: Intercellular Adhesion Molecule; VCAM: Vascular Adhesion Molecule

RESULTS

Table 2. Baseline Demographics

	Week 0 RV254 (n=83)	PWoH (n=32)	P-value
Male, n (%)	81 (98)	24 (75)	**0.001**
Age, year	28 (23-32)	33 (26-39)	**0.038**
HIV RNA, log_{10} cps/ml	6.05 (5.38-6.86)	-	-
CD4 T-cell count	395 (267-484)	-	-
CD8 T-cell count	512 (301-959)	-	-
CD4/CD8	0.76 (0.4-1.08)	-	-
Fiebig Stage, n (%)			
I-II	40 (48)	-	-
III-V	43 (52)		

Endothelial & hemostasis perturbations emerge during acute HIV infection and persist at 6-year follow-up despite immediate ART initiation.

Over 40% of these individuals who initiated and maintained ART since acute HIV exhibited a phenotype characterized by multiple endothelial biomarker elevations.

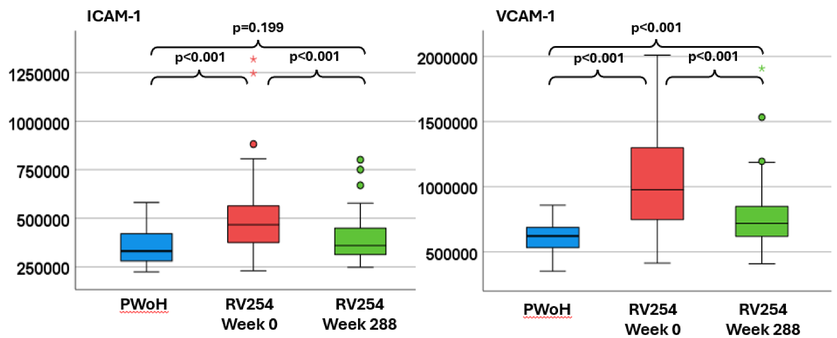
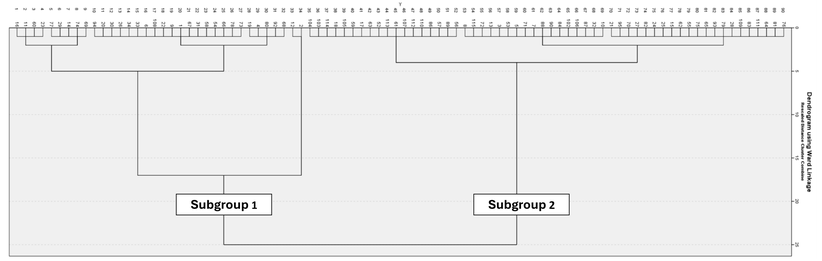


Table 3	RV254 AHI (n=83)	RV254 Wk 288 (n=83)	PWoH (n=32)	RV254 AHI vs. PWoH p-value	RV254 Wk 288 vs. PWoH p-value
****ICAM-1, x 10^3 pg/mL**	467 (375-564)	359 (313-449)	331 (280-420)	**<0.001**	0.199
****VCAM-1, x 10^3 pg/mL**	976 (738-1314)	719 (618-859)	622 (532-686)	**<0.001**	**<0.001**
P-selectin, x 10^3 pg/mL	34 (32-38)	34 (31-36)	32 (28-35)	**0.017**	0.082
E-selectin, x 10^3 pg/mL	191 (160-228)	189 (155-228)	176 (140-214)	0.166	0.182
***t-PA, pg/mL**	1676 (1082-2081)	2116 (1635-2830)	1901 (1320-2288)	0.302	0.075
TF, pg/mL	3752 (3135-4618)	3579 (2872-4033)	2562 (1989-3601)	**<0.001**	**0.001**
TM, x 10^3 pg/mL	15 (13-18)	16 (14-19)	13 (10–16)	**0.006**	**<0.001**
Neopterin, pg/mL	3583 (2160-4793)	1459 (1087-1750)	1249 (1031-1564)	**<0.001**	0.162
MPO, x 10^3 pg/mL	54 (39-79)	29 (20-41)	27 (13-44)	**<0.001**	0.202

Remarks: Data are presented as median (interquartile range); Comparisons were performed using the Mann–Whitney U test. * n=112; ** n=92. Age, sex and body mass index adjustment yielded similar biomarker differences between RV254 and PWoH at AHI and week 288.

Clustering Analysis



- Identified two major biomarker phenotype subgroups (1 and 2) with no statistical differences in age or sex.
- **Compared to subgroup 2, subgroup 1 showed:**
  - A significantly higher rate of PWH (31/34 (91%) vs. 35/56 (63%), p=0.003)
  - Higher levels of ICAM-1, ICAM-2, VCAM-1, E-selectin, neopterin and week 288 CD4/CD8 ratio ($p < 0.05$)

SUMMARY OF KEY FINDINGS

- RV254 participants exhibited elevated plasma biomarkers reflecting endothelial and hemostasis disturbances during pre-ART AHI.
- Most biomarkers rose with HIV-related parameters during AHI, underscoring their relationship with HIV viremia (not shown).
- After ART initiation at AHI, most of these biomarkers showed significant reductions by week 288.
- At week 288, median levels of these markers remained generally higher in RV254 participants, with VCAM-1, tissue factor, and thrombomodulin reaching statistical significance.
- Using data-driven hierarchical clustering of participants' biomarker outcomes, we identified two key biomarker phenotype subgroups.
- One subgroup, composed almost entirely of PWH, showed higher levels across multiple biomarkers compared with the other subgroup, particularly those associated with immune-cell recruitment in endothelial dysfunction.

ACKNOWLEDGMENTS

We would like to thank the study participants who committed so much of their time for this study. The participants were from the RV254/SEARCH 010, which is supported by cooperative agreements (WW81XWH-18-2-0040) between the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., and the U.S. Department of Defense (DOD) and by an intramural grant from the Thai Red Cross AIDS Research Centre and, in part, by the Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institute of Health (DAIDS, NIAID, NIH) (grant AAI20052001). Antiretroviral therapy for RV254/SEARCH 010 participants was supported by the Thai Government Pharmaceutical Organization, Gilead Sciences, Merck and ViiV Healthcare. This study was supported by NIH grants focused on neurological and cognitive outcomes in RV254/SEARCH010 including R01 MH113560 and by additional funds contributed by the National Institute of Mental Health.

DISCLAIMER

The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army, the Department of Defense, the National Institutes of Health, the Department of Health and Human Services, or the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. The investigators have adhered to the policies for protection of human subjects as prescribed in AR-70-25