Pre-treatment Interruption Plasma Metabolites and Glycans Correlate with Time to HIV Rebound and Reservoir Size in ACTG A5345

> Leila B. Giron, Ph.D. Staff Scientist Abdel-Mohsen Lab



Community Summary

Key questions of research

- Analytical Treatment Interruption (ATI) is the only definitive measure to evaluate the impact of potential curative agents on HIV control.
- HIV cure field has been searching for pre-ATI biomarkers of viral-rebound to mitigate some of the risks of ATI and to identify novel biological targets to develop an effective cure.
- Can we identify plasma non-invasive biomarkers of HIV rebound?

Key findings take-home message We describe several biological molecules that were measured in the plasma before stopping ART and their levels predicted time to viral rebound after ATI.



Metabolites and glycans enter circulation from tissues and can reflect tissue inflammatory states







Plasma glycans associate with time-to-viral-rebound in all donors





Early ART (n=12) 5 n= 6 (50%) n= 6 (50%) Slow Rapid rebound 4rebound 3. 2-1-0 24 2 3 4 5 6 Weeks to ≥1000 copies/ml plasma post-ATI

Within individuals who initiated ART early, HIV reservoir size do not differentiate Rapid vs Slow rebound



Within individuals who initiated ART early, plasma glycans differentiate Rapid vs Slow rebound



= glycans correlated with time-to-viral-rebound in previously-analyzed cohorts



ACG-binding glycans (α 2,3 Sialylated O glycans) 0.0022



Plasma glycomic markers of time-to-viral-rebound associate with HIV reservoir size in A5345



blue = negative spearman r correlation

Higher tryptophan catabolism is associated with faster rebound in people who initiated ART at the early/acute stages of HIV infection



Higher tryptophan catabolism is associated with faster rebound in people who initiated ART at the early/acute stages of HIV infection



Giron L., et al., Nature Comm. 2021

Clin Infect Dis. 2019 Apr 8;68(8):1274-1281. doi: 10.1093/cid/ciy676.

Plasma Indoleamine 2,3-Dioxygenase Activity Is Associated With the Size of the Human Immunodeficiency Virus Reservoir in Patients Receiving Antiretroviral Therapy

Jun Chen ¹ ² ³, Jingna Xun ¹, Junyang Yang ¹, Yongjia Ji ¹, Li Liu ¹, Tangkai Qi ¹, Zhenyan Wang ¹, Renfang Zhang ¹, Yinzhong Shen ¹, Rosalie Ponte ² ³, Vikram Mehraj ² ³, Jean-Pierre Routy ² ³ ⁴, Hongzhou Lu ¹ ⁵ ⁶

> J Virol. 2016 Aug 12;90(17):7967-79. doi: 10.1128/JVI.00994-16. Print 2016 Sep 1.

Kynurenine Reduces Memory CD4 T-Cell Survival by Interfering with Interleukin-2 Signaling Early during HIV-1 Infection

Xavier Dagenais-Lussier ¹, Mouna Aounallah ¹, Vikram Mehraj ², Mohamed El-Far ³, Cecile Tremblay ³, Rafick-Pierre Sekaly ⁴, Jean-Pierre Routy ², Julien van Grevenynghe ⁵

> PLoS One. 2008 Aug 13;3(8):e2961. doi: 10.1371/journal.pone.0002961.

HIV-induced type I interferon and tryptophan catabolism drive T cell dysfunction despite phenotypic activation

Adriano Boasso ¹, Andrew W Hardy, Stephanie A Anderson, Matthew J Dolan, Gene M Shearer

Sci Transl Med. 2010 May 19;2(32):32ra36. doi: 10.1126/scitranslmed.3000632.

Tryptophan catabolism by indoleamine 2,3dioxygenase 1 alters the balance of TH17 to regulatory T cells in HIV disease

David Favre ¹, Jeff Mold, Peter W Hunt, Bittoo Kanwar, P'ng Loke, Lillian Seu, Jason D Barbour, Margaret M Lowe, Anura Jayawardene, Francesca Aweeka, Yong Huang, Daniel C Douek, Jason M Brenchley, Jeffrey N Martin, Frederick M Hecht, Steven G Deeks, Joseph M McCune Plasma Tryptophan-Kynurenine Metabolites Are Altered in Human Immunodeficiency Virus Infection and Associated With Progression of Carotid Artery Atherosclerosis ^{Olin}G¹, ^{Sunin} Hua, ^{Clay E, Clin¹, ^JJustin M. Soct⁷, ^David B. Huma, ¹Teo Wang, ¹Savina A. Hader, ¹ Sanjir J. Shah, ¹Marshall J. Glesby,¹ Jacom M. Laza², ¹Mebort, ¹Burk¹, ¹Marval H. Laday, ¹Wondy, ¹Savina A. Master, ¹and Fober, ¹ Kaplan^{1,10}}

Serum Tryptophan-Derived Quinolinate and Indole-3-Acetate Are Associated With Carotid Intima-Media Thickness and its Evolution in HIV-Infected Treated Adults

Anders Boyd,^{1,*} Franck Boccara,^{2,3,*} Jean-Luc Meynard,⁴ Farid Ichou,³ Jean-Philippe Bastard,^{3,4} Soraya Fellahi,^{3,4} Assia Samri,¹ Delphine Sauce,⁷ Nabila Haddour,² Brighte Autran,¹ Ariel Cohen,² Pierro-Marie Girard,^{1,4} Jacqueline Capeau², and the Collaboration in HIV, Inflammation and Cardiovascular Disease study

Gut microbiota and plasma metabolites associated with diabetes in women with, or at high risk for, HIV infection

Jee-Young Moon ^a, Christine P. Zolnik ^{b.c}, Zheng Wang ^a, Yunping Qiu ^d, Mykhaylo Usyk ^c, Tao Wang ^a, Jorge R. Kizer ^{a.d}, Alan L. Landay ^e, Irwin J. Kurland ^d, Kathryn Anastos ^{a.d.f}, Robert C. Kaplan ^{a.g}, Robert D. Burk ^{a.c.f.h}, Qibin Qi ^{a.e}

High Kynurenine:Tryptophan Ratio Is Associated With Liver Fibrosis in HIV-Monoinfected and HIV/Hepatitis C Virus–Coinfected Women Ani Kardashian.¹⁰ Yifei Ma.² Michael T. Yin.² Rebecca Scherzer,² Olivia Nolan.⁴ Francesca Aweeka.² Phyllis C. Tien.²² and Jennifer C. Price²

Reversal of the Kynurenine Pathway of Tryptophan Catabolism May Improve Depression in ART-Treated HIV-Infected Ugandans

Priscilla Martinez, MPhil, PhD.*† Alexander C. Tsai, MD, PhD.<u>‡</u>\$ Conrad Muzoora, MBBCh, MMed.|| Annet Kembabazi, BA.|| Sheri D. Weiser, MD, MPH.¶ Yong Huang, PhD.¶ Jessica E. Haberer, MD, MS.<u>‡</u> Jeffrey N. Martin, MD,¶# David R. Bangsberg, MD, MPH.<u>‡</u>||**††<u>‡</u>‡ and Peter W. Hunt, MD¶#

Plasma metabolic markers of time-to-viral-rebound associate with HIV reservoir size in A5345



Ergothioneine as a Natural Antioxidant Against Oxidative Stress-Related Diseases

Tong-Tong Fu^{1,2} and Liang Shen^{1,2}*

BioFactors 27 (2006) 157–165	157
IOS Press	
Activity of the dietary antioxidan	t
Activity of the dietary antioxidan ergothioneine in a virus gene-bas	t ed assay for

Conclusions

Glycans, plasma immuno-modulatory <u>sialylated</u> glycans correlate with slow time-to-viral-rebound and small HIV reservoir size, consistent with our previously published results.

Metabolites, high levels of the plasma markers of <u>tryptophan catabolism</u> (microbiome-related metabolic pathway) are associated with fast time-to-viral-rebound and large HIV reservoir, consistent with our previously published results.

Metabolites, high levels of the anti-oxidative stress <u>L-Ergothioneine</u> are associated with slow timeto-viral-rebound and small HIV reservoir size.

In general, markers associated with rapid rebound (and vice versa for markers associated with delayed rebound) correlated with higher CD8⁺ T cell activation (CD38⁺ HLADR⁺ CD8⁺ T cells), lower % effector CD8 ⁺ T cells, higher % of TIM3⁺ T cells, higher plasma sCD163 levels.

Special Thanks To All Volunteer Participants in A5345!

HARVARD

UNIVERSITY



Abdel-Mohsen lab Mohamed Abdel-Mohsen

Pratima Saini Samson Adeniji Jane Koshy Ferlina Hong Angela Corrigan Shalini Singh



Wistar Collaborators <u>Qin Liu</u> Xiangfan Yin Luis J. Montaner Aaron R. Goldman Nicole Gorman Hsin-Yao Tang

BILL& MELINDA GATES foundation

Heather Ann Brauer Mike McCune IMeghan Melbergan YinAutumn KittilsonMontanerYijia LiR. GoldmanKentang



Jonathan Li

Raiesh Gandhi

VERI

TAS

University of Californ San Francisco Steven Deeks

MAKING AIDS HISTORY Bowena Johnston





Alan L. Landay



Jeffrey M. Jacobson

Pablo Tebas





Jay Kostman Karam Mounzer





lgiron@wistar.org



