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

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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.
ART Discontinuation

ACTG A5345/A5347s (45 HIV+ ART+ individuals)

- ART Switch (4 weeks)

12 initiated ART at the early/acute stages of HIV infection
33 initiated ART at the chronic stage of HIV infection

ART Re-initiation criteria met?

- Yes
  - Follow-up on ART (up to 24 weeks)
- No
  - Follow-up offART (24 weeks)

Monitored Antiretroviral Pause (up to 48 weeks)

All participants (n=45)

- n=29 (64%)
- n=16 (36%)

Weeks to ≥1000 copies/ml plasma post-ATI
ACTG A5345/A5347s
(45 HIV+ ART+ individuals)

Study Entry

NNRTI–

ART Switch
(4 weeks)

NNRTI+

ART Discontinuation
on ART tissue sampling

ATI tissue sampling

Monitored Antiretroviral Pause
(up to 48 weeks)

ART Re-initiation criteria met?

Yes

Follow-up on ART
(up to 24 weeks)

No

Follow-up offART
(24 weeks)

Analysis

Glycomics

Metabolomics

Lipidomics

Inflammation Markers

PLASMA

IgG

IgA

Total Gly

N-Gly

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

Only markers with $P<0.05$ after adjusting for ART initiation timing (acute/early vs chronic) in a multivariable model.
ACTG A5345/A5347s
(45 HIV+ ART+ individuals)

Study Entry

NNRTI–

ART Switch (4 weeks)

NNRTI+

ART Discontinuation

on ART tissue sampling

ATI tissue sampling

Monitored Antiretroviral Pause
(up to 48 weeks)

ART Re-initiation criteria met?

Yes

Follow-up on ART
(up to 24 weeks)

No

Follow-up offART
(24 weeks)

All participants (n=45)

Early ART (n=12)

Weeks to ≥1000 copies/ml plasma post-ATI

# of individuals

n= 29 (64%)
n= 16 (36%)

Rapid rebound

Slow rebound
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

Early ART initiation samples

<table>
<thead>
<tr>
<th>#</th>
<th>PNA-binding glycans</th>
<th>Rapid rebound</th>
<th>Slow rebound</th>
<th>P value</th>
<th>FDR</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.004</td>
<td>0.04</td>
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<tr>
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<td>ACA-binding glycans</td>
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<tr>
<td>#</td>
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<td>0.16</td>
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<tr>
<td>#</td>
<td>SNA-binding glycans</td>
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<tr>
<td>FA3G3S2 (plasma N-glycans)</td>
<td>0.03</td>
<td>0.35</td>
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<tr>
<td>A3F1F3S3 (plasma N-glycans)</td>
<td>0.009</td>
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<tr>
<td>FUC-A_group (plasma N-glycans)</td>
<td>0.009</td>
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</tr>
</tbody>
</table>

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

Acute/early ART initiation

Rapid rebound
Slow rebound

ACG-binding glycans

(α 2,3 Sialylated O glycans)

Relative levels

0.0022

Rapid rebound
Slow rebound

150
200
250
300
Plasma glycomic markers of time-to-viral-rebound associate with HIV reservoir size in A5345

Associate with rapid rebound (except rACG)

Red = positive spearman r correlation; 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.

![Diagram showing the relationship between tryptophan metabolism and ART initiation.](image)

<table>
<thead>
<tr>
<th>Acute/early ART initiation</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid rebound</td>
<td>0.015</td>
</tr>
<tr>
<td>Slow rebound</td>
<td>0.041</td>
</tr>
</tbody>
</table>

![Box plots showing the K/T and Q/T ratios for Rapid and Slow rebound initiators.](image)
Higher tryptophan catabolism is associated with faster rebound in people who initiated ART at the early/acute stages of HIV infection.

Plasma Tryptophan-Kynurenine Metabolites Are Altered in Human Immunodeficiency Virus Infection and Associated With Progression of Carotid Artery Atherosclerosis


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

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

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

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

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

High Kynurenine Tryptophan Ratio Is Associated With Liver Fibrosis in HIV-Monoinfected and HIV/Hepatitis C Virus–Coinfected Women

Reversal of the Kynurenine Pathway of Tryptophan Catabolism May Improve Depression in ART-Treated HIV-Infected Ugandans
Ergothioneine as a Natural Antioxidant Against Oxidative Stress-Related Diseases

Tong-Tong Fu¹,² and Liang Shen¹,²

Activity of the dietary antioxidant ergothioneine in a virus gene-based assay for inhibitors of HIV transcription
Conclusions

**Glycans**, plasma immuno-modulatory sialylated 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 tryptophan catabolism (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 L-Ergothioneine are associated with slow time-to-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!

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