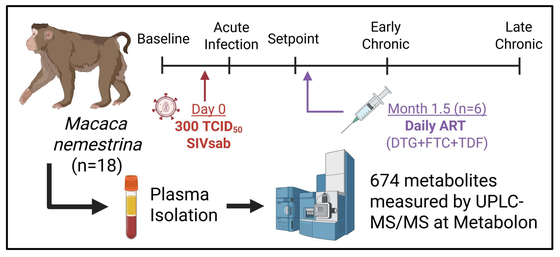
Plasma Metabolomics Uncover Multiple Dysregulations Indicating Gut Damage in SIV-Infected Macaques

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BACKGROUND: Despite effective antiretroviral therapies (ART), people living with HIV (PWH) have elevated rates of inflammation, hypercoagulation, and associated comorbidities. Gut damage correlates with immune dysfunction in PWH, but precise etiologies remain poorly defined. Due to heterogeneity of clinical cohorts, generalizable metabolomic studies from PWH are limited but can be augmented with animal models.

OBJECTIVE: To characterize plasma metabolite concentrations to identify biomarkers of HIV/SIV co-morbidities, disease progression, and novel therapeutic targets to improve the lives of PWH.



METHODS: Eighteen pigtailed macaques were infected with 300 TCID SIVsab. Beginning on day 48, six were administered ART (DTG+3TC+TDF) daily. Plasma metabolic profiling was performed by ultra-high performance liquid chromatography/tandem mass spectrometry. CBCs, serum chemistries, Luminex, and immunophenotyping were performed longitudinally, including at pre-, acute, setpoint, and chronic infection. **Fig. 1:** Study design. (above)

RESULTS:

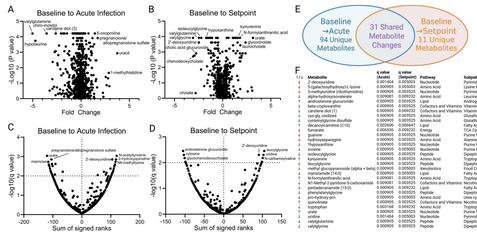


Fig. 2: Metabolite changes from A-B) Wilcoxon matched-pairs signed rank, C-D) sum of signed ranks, and E-F) shared discoveries with 1% FDR.

Metabolic changes during SIV are highly associated with markers of disease progression,

including markers of gut barrier integrity, CD4+ T cell counts, lymphocyte phenotypes, hypercoagulation, liver damage, and myeloid cell activation.

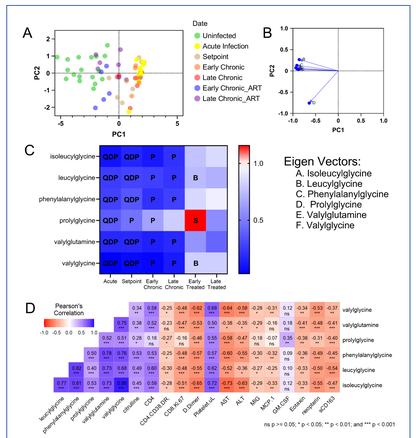


Fig. 3: SIV is associated with reduced dipeptide levels.

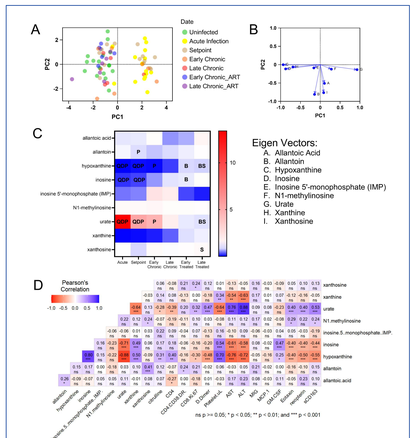


Fig. 4: Plasma urate levels increase during SIV.

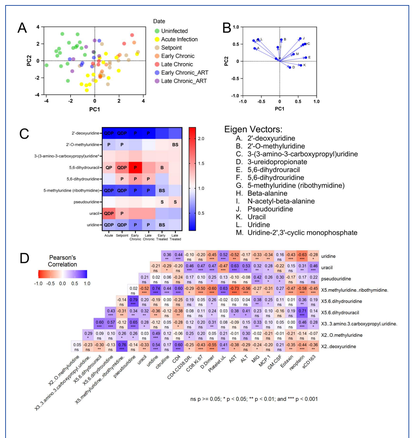


Fig. 5: SIV results in shifts to pyrimidine metabolite levels.

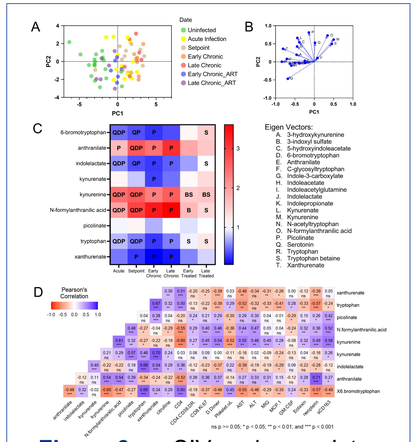


Fig. 6: SIV dysregulates tryptophan metabolism.

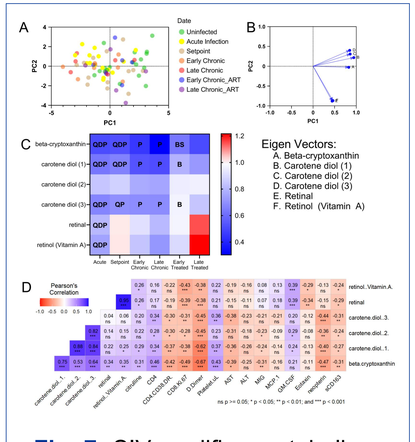


Fig. 7: SIV modifies metabolism of vitamin A compounds.

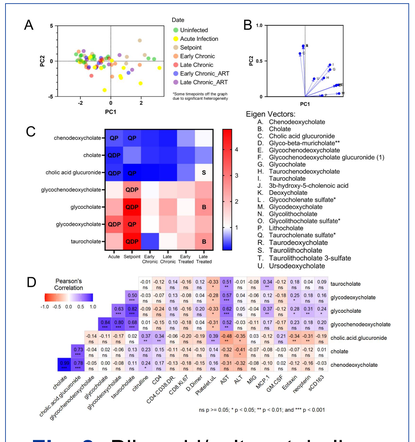


Fig. 8: Bile acid/salt metabolism changes in stages during SIV.

Figures 3-8: A) principal component analysis, B) loading plot, C) heatmap, and D) correlation matrix. Compared to baseline Q: q<0.05, D: discovery with FDR of 1%, P: p<0.05, and B: p<0.05; compared to setpoint S: p<0.05

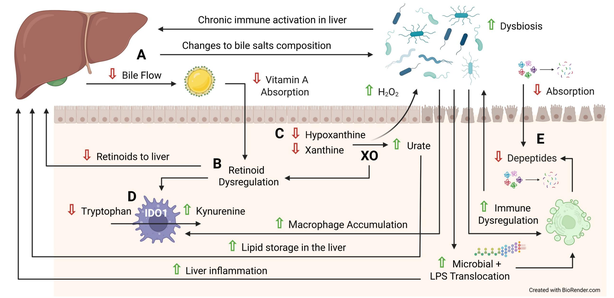


Fig. 9: Identified subpathways were highly inter-related and suggestive of dysregulated gut barrier function, mucosal immune response, and the gut-liver axis.

CONCLUSIONS:

- SIV is associated with rapid and persistent metabolic changes, many continuing in ART-naïve macaques.
- Not all metabolite levels were restored by ART.
- Several of the most changed metabolites were associated with markers of disease progression.
- Dysregulated metabolites may contribute to comorbidity development, as they have previously been linked to cardiovascular diseases (CKDs), neurodegeneration, chronic kidney diseases (CVDs), liver disease (MASLD), and metabolic syndrome.
- Tissue damage may be mediated by inflammation, oxidative stress, toxic byproducts, impaired energy metabolism, and mitochondrial dysfunction.
- Identification of previously uncharacterized dysregulations will facilitate therapeutic intervention development to improve immune responses during ART and reduce HIV-associated comorbidities.

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During SIV infection, metabolic subpathways are dysregulated in ways indicative of gut damage. These changes associate closely with markers of disease progression, uncovering new targets for therapeutic development to improve the lives of PWH