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# Kynurenine Pathway Activity Remains Abnormal Despite Very Early ART Initiation

Samuel R. Schnittman[1], Amelia Deitchman[1], Gabriele Beck-Engeser[1], HaeLee Ahn[1], Vanessa A. York[1], Heather Hartig[1], Frederick M. Hecht[1], Jeffrey N. Martin[1], Steven G. Deeks[1], Francesca Aweeka[1], Peter W. Hunt[1]

[1]University of California San Francisco, CA, USA

**Correspondence:**
Peter W. Hunt, MD
ZSFG Blg 3, Room 605B
1001 Potrero Avenue
San Francisco, CA 94110
peter.hunt@ucsf.edu

## Background

- Despite early antiretroviral therapy (ART), ART-suppressed people with HIV (PWH) remain at higher risk for Tuberculosis (TB) and infection-related malignancies than the general population.
- The immunologic pathways that remain abnormal in this setting – and may plausibly drive these complications – are unclear
- Recent studies suggest that some immune activation markers remain abnormal despite very early ART.
- None of these studies evaluated the kynurenine pathway of tryptophan catabolism, which confers adaptive immune defects and strongly predicts incident tuberculosis.
- Prior studies also had incomplete adjustment for health-related behaviors and all were restricted to efavirenz-treated participants.
- We addressed these limitations in our current study.

## Methods

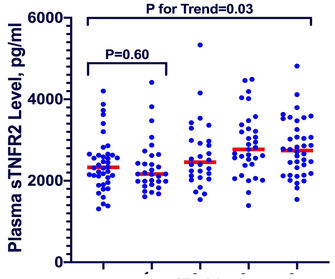
- **Study Design**
  - PWH maintaining ART-mediated viral suppression >1 year and HIV-negative controls, all CMV IgG+ enriched for HIV risk factors, were sampled from a study of influenza vaccine response.
  - Exclusion criteria: active viral hepatitis; injection drug use (IDU) within the past year; treatment with potent anti-inflammatory drugs, antibiotics, or hospitalization within the past 4 months
  - PWH were stratified by ART initiation (<6 months of estimated date of HIV infection [early ART] vs. later), and among later initiators, by nadir CD4 count (>350, 200-350, and <200 cells/mm$^3$)
  - Biomarkers of immune activation and the IDO-1-associated kynurenine pathway of tryptophan catabolism were compared across groups.
- **Measurements**
  - Cryopreserved plasma prior to vaccination was assessed via LC-MS (kynurenine/tryptophan [KT] ratio) or ELISA (sTNFR2, IL-6, sCD14, sC163, IP-10, and suPAR). All ELISAs were assessed in duplicate and averaged across two timepoints to improve precision.
- **Statistical Analysis**
  - Multivariable linear regression was conducted using baseline demographics, ART regimen (EFV vs non-EFV), and health-related behaviors, including confounders that changed beta coefficient by >10%.
  - Biomarkers were log-transformed as necessary.

## Characteristics of Participants

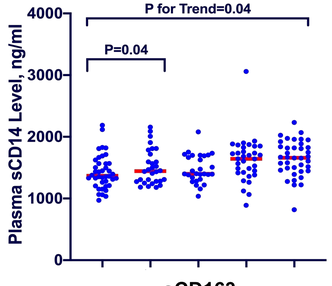
| Characteristic[a] | HIV- (n=41) | Early ART[b] (n=34) | Later ART by CD4 Nadir (cells/mm$^3$) >350 (n=32) | 200-350 (n=43) | <200 (n=55) |
|---|---|---|---|---|---|
| Age, years | 57 (51-60) | 51 (47-53) | 51 (46-56) | 55 (49-61) | 57 (53-62) |
| Male at birth[c], % | 88% | 100% | 100% | 86% | 91% |
| MSM[c], % | 56% | 97% | 91% | 79% | 85% |
| >100 Lifetime ♂ Partners, % | 41% | 79% | 69% | 66% | 55% |
| Years VL <40 c/ml | - | 6.8 (3.9-9.0) | 5.7 (3.9-7.2) | 7.5 (5.1-10.9) | 9.8 (7.3-13.2) |
| Current CD4, cells/mm$^3$ | 756 (641-990) | 735 (603-846) | 790 (673-956) | 647 (563-841) | 525 (328-686) |
| Nadir CD4, cells/mm$^3$ | - | 361 (277-501) | 433 (373-499) | 264 (221-309) | 79 (28-138) |
| EFV Regimen, % | - | 12% | 9% | 27% | 52% |
| Current Smoking, % | 34% | 6% | 6% | 14% | 22% |
| Distant IDU History, % | 15% | 9% | 6% | 17% | 35% |

*[a]Median (IQR) unless noted; [b]Started ART within 6 months of the estimated date of infection; [c]2 participants in "Later ART" groups were MTF transgender.*

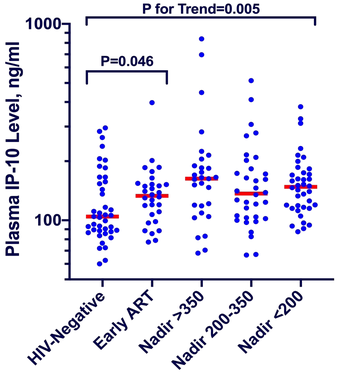
### sTNFR2



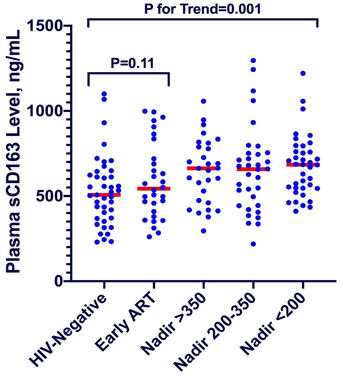

### sCD14



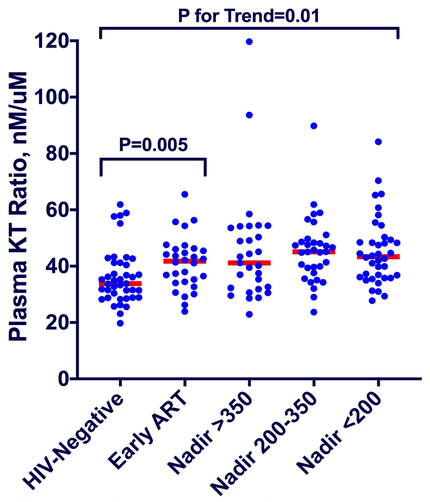

### IP-10




### sCD163




## KT Ratio




*P values are from models adjusted for sex at birth and age.*

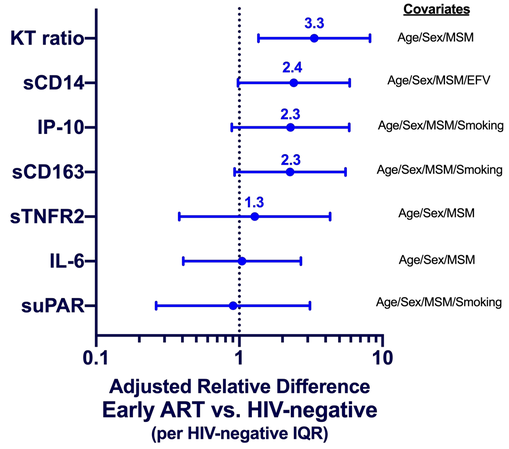
No evidence of a trend for increasing IL-6 or suPAR with delayed ART (P>0.17 for both).

## Efavirenz-based Regimens Appear to Selectively Increase sCD14

| Biomarker | Relative Difference Between EFV vs. Non-EFV-Containing Regimen (95% CI) | P Value |
|---|---|---|
| KT Ratio | 0.95 (0.85-1.1) | 0.35 |
| **sCD14** | **1.2 (1.1-1.3)** | **<0.001** |
| IP-10 | 1.0 (0.85-1.2) | 0.66 |
| sCD163 | 0.95 (0.83-1.1) | 0.62 |
| sTNFR2 | 0.97 (0.87-1.1) | 0.44 |
| IL-6 | 0.97 (0.76-1.2) | 0.98 |
| suPAR | 1.0 (0.91-1.1) | 0.85 |

*After adjustment, EFV-based regimens continued to be associated with increased sCD14 (relative difference 1.18, 95% CI 1.10-1.26, P < 0.001)*

## KT Ratio Remains Abnormal Despite Early ART After Confounder Adjustment




## Limitations

- Sample size may have limited our ability to detect differences in some biomarkers between groups.

## Conclusions / Implications

- Among ART-suppressed PWH, lower nadir CD4 counts are associated with higher levels of many immune activation markers.
- Efavirenz use may be associated with isolated sCD14 elevations.
- While PWH starting ART early restore near-normal levels of some immune activation markers, the kynurenine pathway of tryptophan catabolism remains abnormally high.
- As the kynurenine pathway confers adaptive immune defects, its elevation despite early ART may plausibly explain the persistently abnormal TB and infection-related cancer risk in this setting.
- The kynurenine pathway may be an important interventional target to study even for PWH who started ART early.

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