# Endothelial function and CNS measures in primary HIV infection pre- and post- early ART

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## Introduction

- HIV-infected individuals have increased rates of vascular disease (including ischemic stroke and small vessel cerebrovascular disease).
- Nitric oxide modulates vascular endothelial function.
- Asymmetric dimethylarginine (ADMA), a marker of cardiovascular disease, inhibits production of nitric oxide, is elevated during chronic HIV infection despite suppressive anti-retroviral therapy (ART) and is associated with vascular dysfunction.
- ADMA levels have not been examined during primary HIV infection (PHI, < 1 year since HIV transmission).

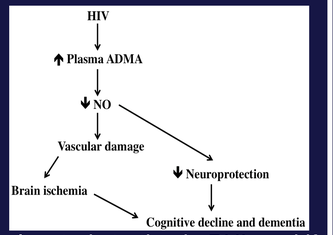



**Figure 1**. Possible link between ADMA and CNS function in HIV (Modified from Asif et al.[1])

## Objectives and Hypothesis

**(1)** To determine whether ADMA levels are elevated starting in PHI, and if so, whether levels decrease with initiation of ART.
**(2)** Because cerebrovascular disease may associate with CNS dysfunction in HIV, to explore associations between ADMA and neuropsychological testing performance pre- and post-ART.
We hypothesized that elevation in ADMA levels would start in PHI and decrease with ART, and that ADMA levels would correlate with neuropsychological testing performance.

## Methods

• 25 male subjects with primary HIV infection (PHI, < 1 year duration of HIV infection) underwent neurologic testing and blood sampling prior to and after ART.

• Vascular measure: **Plasma ADMA** (Oxonon BioAnalysis, CA)

• Neuropsychological (NP) testing: 11 test battery assessed by domain as well as as NPZ4 (average of timed gait, grooved pegboard, finger tap, digit symbol).

• Examined ADMA levels from pre- to post- ART and compared ADMA levels in PHI participants with published values measured in the same laboratory sampled from HIV- controls and chronically infected patients on ART. Examined ADMA/NP test relationships. All statistical tests and analyses were nonparametric.

## Results

**Table 1.** Participant characteristics at baseline and post-ART; median (IQR)

| | Pre-ART (n=25) | Post-ART (n=25) | P-value | | Pre-ART (n=25) | Post-ART (n=25) | P-value |
|---|---|---|---|---|---|---|---|
| Age, y | 37 (30, 44) | 39 (32, 45) | < 0.001 | Plasma HIV RNA (log10 copies/ml) | 4.69 (4.02, 5.12) | 1.69 (1.69, 1.69) | <0.001 |
| Days Post Infection | 139 (54, 179) | 556 (444, 1016) | <0.001 | CSF HIV RNA (log10 copies/ml) | 2.73 (2.20, 3.47) | 1.69 (1.69, 1.69) | <0.001 |
| Days on ART | NA | 281 (207, 370) | NA | CSF WBC (cells/ul) | 6 (4, 11) | 2 (1, 3) | <0.001 |
| Days before starting ART | NA | 256 (124, 760) | NA | Blood Neopterin | 15.38 (6.50, 21.70) | 7.60 (4.70, 9.10) | 0.001 |
| CD4+ T (cells/µl) | 377 (584, 735) | 671 (516, 835) | 0.001 | CSF Neopterin | 8.61 (6.90, 11.00) | 4.90 (4.60, 6.70) | 0.001 |
| CD8+ T (cells/µl) | 901 (708, 1399) | 801 (614, 1020) | 0.123 | NPZ4 | -0.11 (-0.33, 0.4) | 0.14 (-0.47, 0.44) | 0.504 |
| ADMA (µM) | 0.70 (0.62, 0.82) | 0.71 (0.58, 0.82) | 0.872 | Total Z | -0.20 (-0.90, 0.19) | 0.03 (-0.53, 0.30) | 0.010 |

### ADMA in Primary HIV Infection: ART Naive

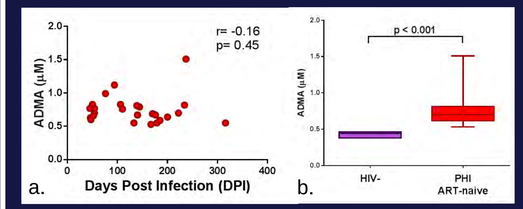



**Figure 2**. a) Pre-ART ADMA levels and days post infection b) PHI ADMA levels are elevated relative to published[2] HIV- controls

### PHI ADMA Levels Pre- and Post- ART

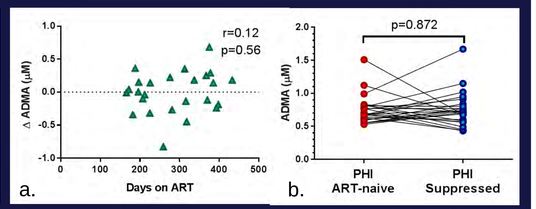



**Figure 3**. a) Change in PHI ADMA shows no correlation with duration of ART b) ADMA does not change after ART in PHI

### ADMA in Primary HIV Infection: ART Suppressed

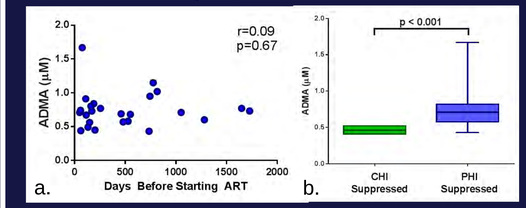



**Figure 4.** a) Post-ART ADMA levels and days before starting ART b) PHI ADMA levels are elevated relative to published[2] levels in chronically infected subjects (CHI) on suppressive ART

### ADMA and Neuropsychological Performance

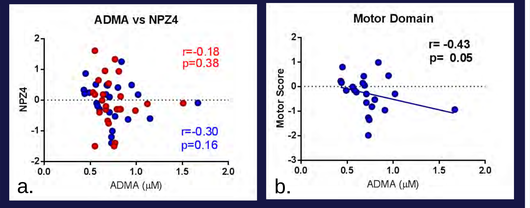



**Figure 5.** a) ADMA shows no correlation with pre- or post-ART NPZ4 b) Motor domain shows correlation with ADMA levels post-treatment (not corrected for MC)

## Conclusions

• ADMA levels in PHI subjects are elevated relative to previously reported levels in HIV- uninfected controls (measured in the same laboratory).

• ADMA in PHI subjects does not decrease after 6-12 months of ART.

• ADMA in PHI subjects on suppressive ART was elevated relative to previously reported ADMA levels in chronically infected subjects on suppressive ART (measured in the same laboratory).

• ADMA and cognitive function (as measured by NPZ4 score) did not show a correlation.

## Future Directions

• Heightened levels of ADMA in PHI may indicate a risk for early cerebrovascular disease in individuals with HIV that is not initially reduced by ART, suggesting a need for:
  - A longitudinal assessment of ADMA levels in individuals beginning during PHI.
  - Investigation of other cerebrovascular markers and measures in PHI.

• A borderline (p=0.05) association between motor domain performance and ADMA levels in PHI participants on suppressive ART may warrant further investigation.

**References:**
[1] Asif et al. Asymmetric Dimethylarginine: A possible link between Vascular Disease and Dementia. Current Alzheimer Research. 2013
[2] Parikh et al. Elevated Levels of Asymmetric Dimethylarginine are Associated with Lower CD4+ Count and Higher Viral Load in HIV-infected Individuals. Atherosclerosis. 2013; 229 (1

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