CP625 - #321

# DECREASED HIV-SPECIFIC POLYFUNCTIONAL RESPONSES FOLLOWING DIPYRIDAMOLE TREATMENT

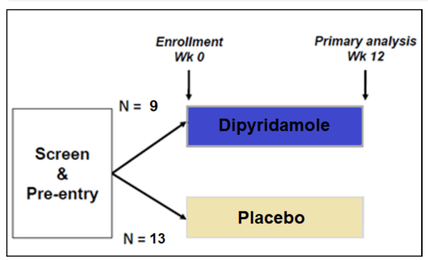
Benjamin C. Morris[1], Emily A. Hixson[1], Cynthia Klamar-Blain[1], Lori Caruso[1], Kaleab Z. Abebe[2], Edwin K. Jackson[3], John W. Mellors[1], Charles R. Rinaldo[1], Sharon A. Riddler[1], Bernard J.C. Macatangay[1]

[1]Division of Infectious Diseases, [2]Division of General Internal Medicine, and [3]Department of Pharmacology and Chemical Biology, University of Pittsburgh School of Medicine

## BACKGROUND

- Dysregulation of the anti-inflammatory adenosine (ADO) pathway could contribute to chronic HIV-associated inflammation and immune activation.
- In a randomized, placebo-controlled study, we show that 12 weeks of dipyridamole (DIPY), which can increase extracellular ADO levels by blocking cellular reuptake of ADO, significantly decreased T cell activation among ART-suppressed individuals.
- We evaluated whether this decrease in T cell activation also resulted in decreased HIV-specific immune responses, and determined whether any decrease is associated with virologic, purinergic, and immunologic parameters measured in the clinical trial.

## STUDY DESIGN AND METHODS

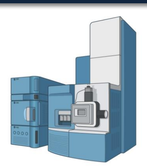



- 40 participants were randomized 1:1 to either 100mg of DIPY 4x daily or placebo for 12 wks.
- Following the 12-week treatment, all participants received open-label DIPY for an additional 12 weeks.
- Participants with available stored PBMCs at week 0 and week 12 (primary analysis visit) were included in this substudy.



**FLOW CYTOMETRY**

- Gag and Env-specific immune responses (IFNγ, TNFα, IL-2, CD107a, GrzB)
- T cell activation (DR/38) and cell cycling (Ki-67)



**UPLC-MASS SPEC**

- Blood and urine levels of purines in the ADO pathway including ADO, inosine, cAMP



**ELISA**

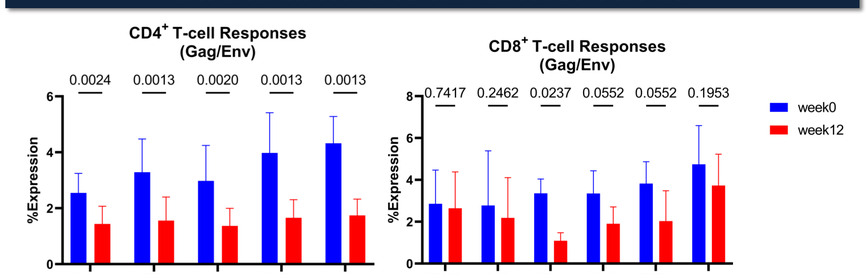
- sCD14, sCD163, IL-6, CRP, D-dimer, IP10, sCD27



**PCR**

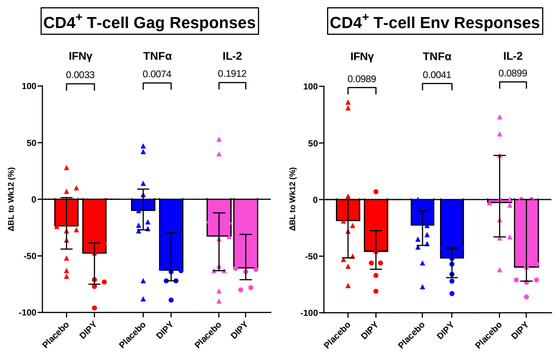
- SCA (residual viremia), HIV DNA, cell-associated RNA

## DIPY ARM WK 0 vs WK 12 RESPONSES

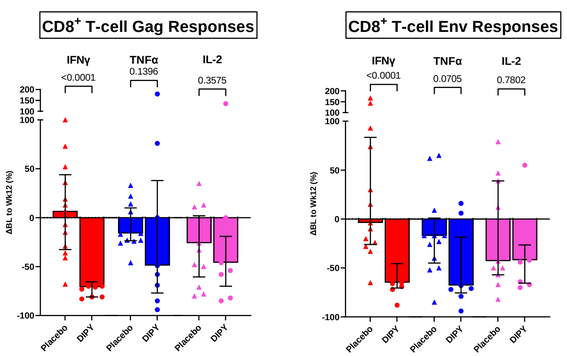



## DIPY VS PLACEBO IMMUNE RESPONSES

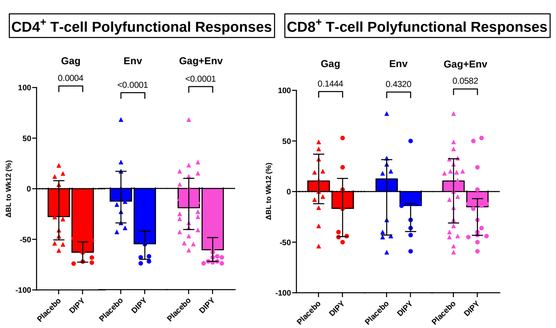
**CD4 T cell responses**
There were significant baseline (BL) to wk 12 decreases in the frequency of cells expressing IFNγ and TNFα in response to Gag peptide stimulation and cells expressing TNFα in response to Env peptide stimulation in the DIPY arm.



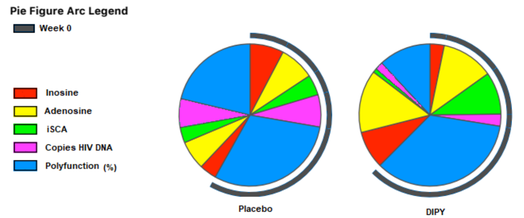

**CD8 T cell responses**
There were significant baseline to wk 12 decreases in the frequency of cells expressing IFNγ in response to Gag peptide and to Env peptide stimulation in the DIPY arm.




**Polyfunctional Responses**
There were significant baseline to wk 12 decreases in CD4+ T cell polyfunctional response (expression of 2 or more cytokines) to Gag and Env peptides in the DIPY arm.



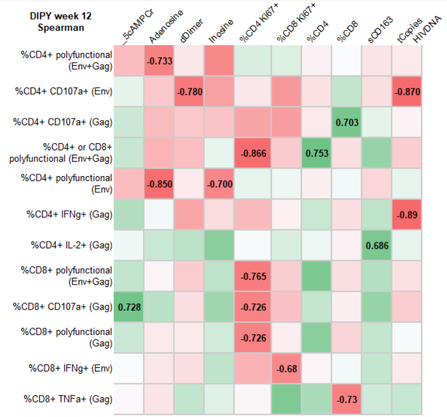

## WK 0 AND WK 12 DIFFERENCES IN DIPY AND PLACEBO




- In the DIPY arm, we observed marked decreases in CD4+ T cell polyfunctional response (Gag and Env responses combined) and decreases in inosine levels.
- The figure also shows an apparent decrease in residual viremia (via iSCA) in wk 12 but given the censoring due to participants having levels below the limit of detection, this difference was not statistically significant.

## CORRELATIONS

- The correlation matrix shows significant associations between various HIV-specific T cell responses and virologic, purinergic, and immunologic parameters measured in the main study. These include:
  - ADO and inosine levels negatively correlated with polyfunctional responses
  - CD8 T cell polyfunctional responses negatively correlated with levels of CD4+ T cell cycling
  - Frequencies of CD4+ T cells expressing IFNγ or CD107a following Gag or Env stimulation negatively correlated with HIV-1 DNA levels. It is important to note that there were no significant changes in HIV DNA levels in the main study.




## CONCLUSIONS

- Dipyridamole-induced increases in extracellular adenosine (and inosine, a surrogate marker) resulted in decreased HIV-specific CD4+ T cell polyfunctional responses.
- There were significant negative correlations between levels of adenosine and inosine and HIV-specific polyfunctional responses.
- Although the clinical implications of these findings are unclear, trials of interventions targeting immune activation and chronic inflammation in treated HIV should evaluate their impact on HIV-specific immune responses.

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