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Introduction

- Administration of a TLR7 agonist in combination with a therapeutic vaccine induces CD8+ T cell-mediated control of SIV in a non-human primate model¹
- The investigational oral TLR7 agonist vesatolimod (VES; GS-9620) may enhance immunologic control in PLH with a partially effective CD8+ T cell response prior to ART (viremic controllers)
- In a Phase 1b randomized, double-blind, placebo-controlled study of VES in controllers on ART, VES was associated with a modestly increased time to viral rebound, decrease in viral set point and decreased intact proviral DNA²
- We investigated the potential immunologic mechanisms of these findings

ART, antiretroviral therapy; PLH, people living with HIV; SIV, simian HIV; TLR7, toll-like receptor 7.

1. Borducchi E, et al. Nature 2016;540:284-7; Riddler S, et al. IAS 2019, abstr WEAA0304. 2. SenGupta D, et al. CROI 2020

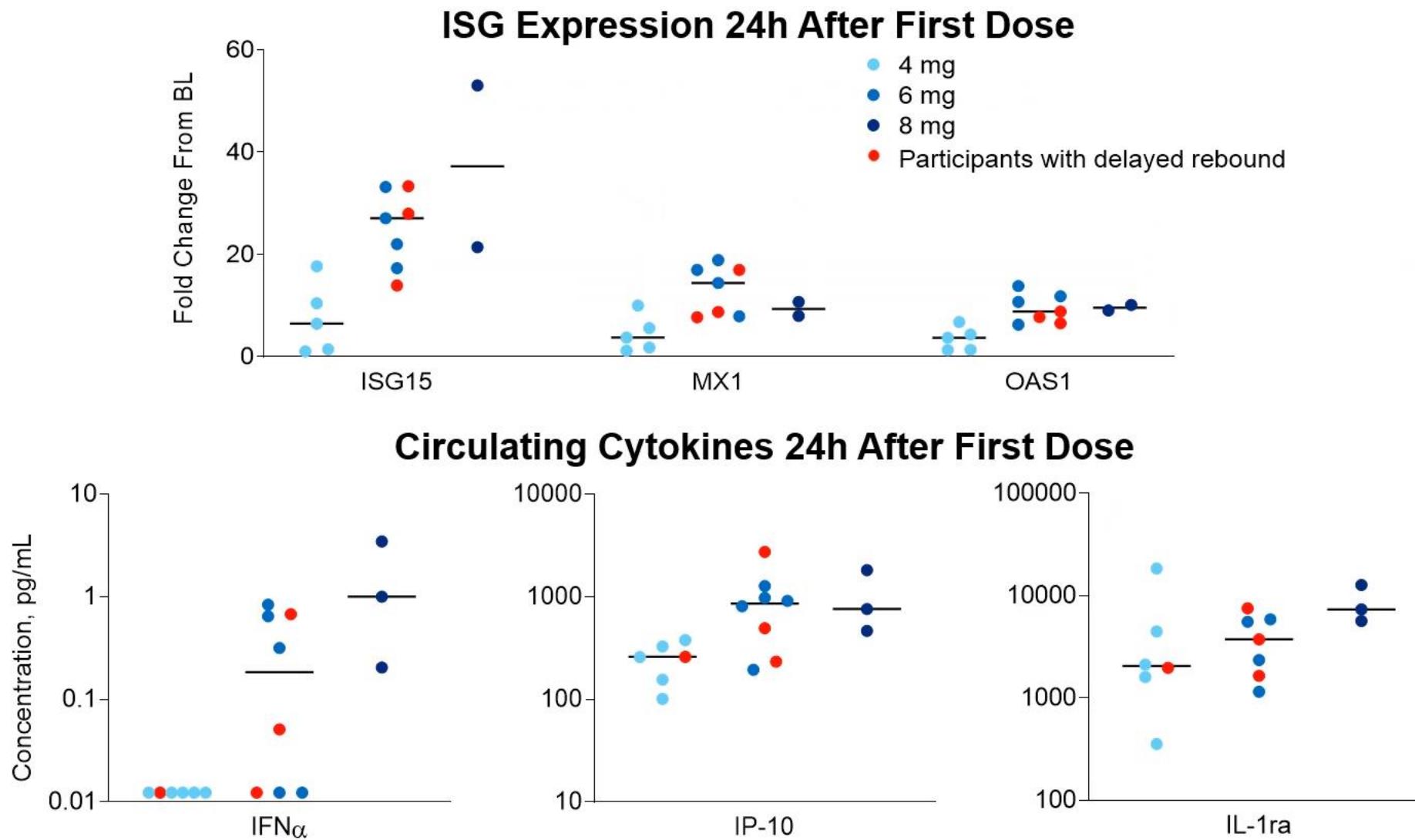
Study Design for Oral Vesatolimod (VES) in HIV Controllers



Biomarker analysis plan:

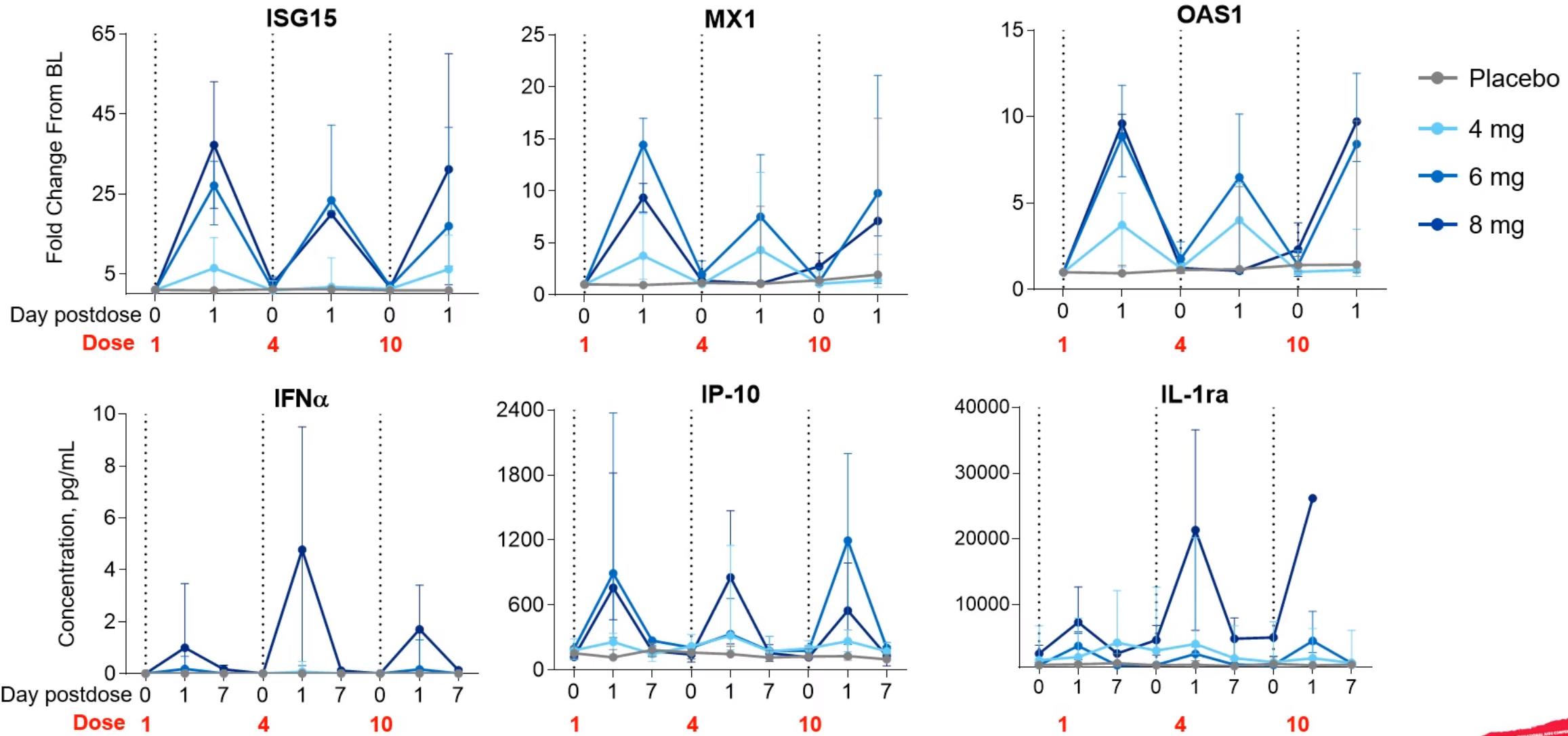
- Interferon stimulated gene (ISG) mRNA levels
- Circulating cytokine levels
- Cellular activation
- HIV-specific immune responses

Interferon Stimulated Genes & Cytokines Increase in a Dose Responsive Manner with Vesatolimod Administration

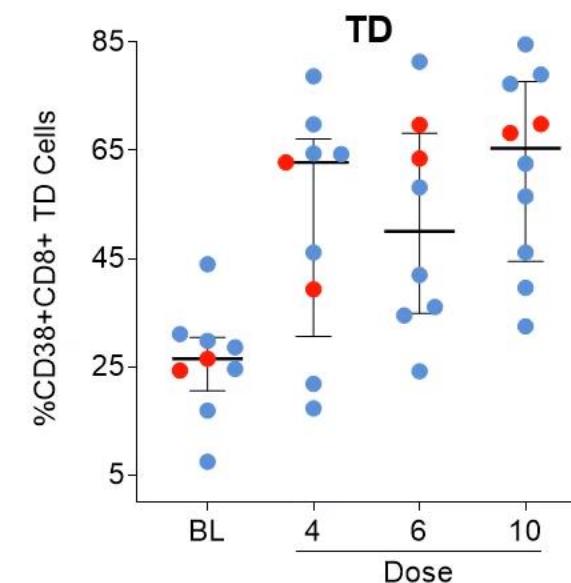
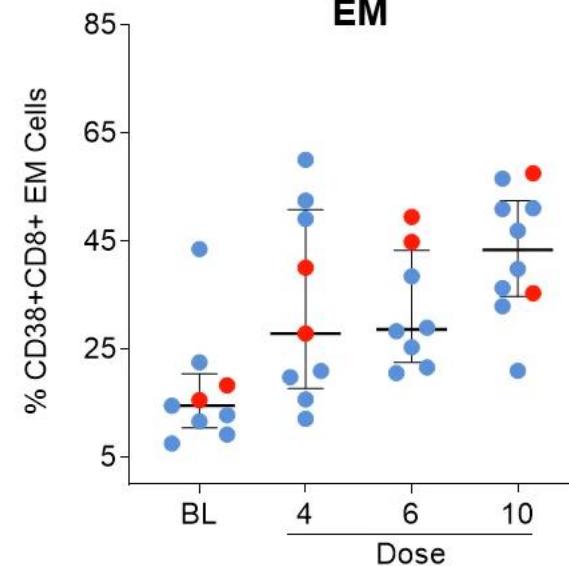
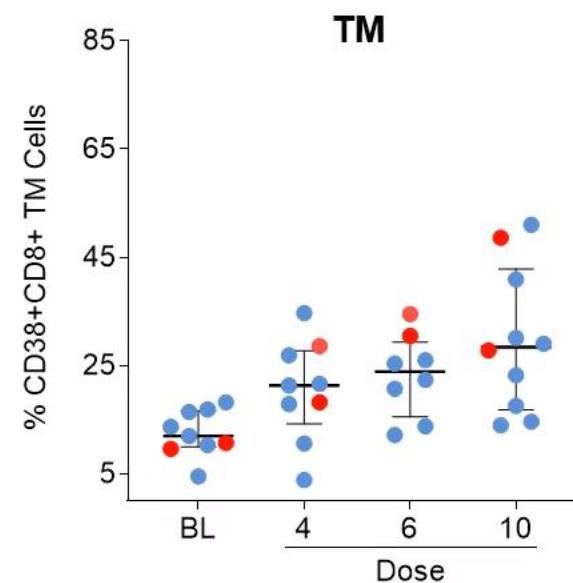
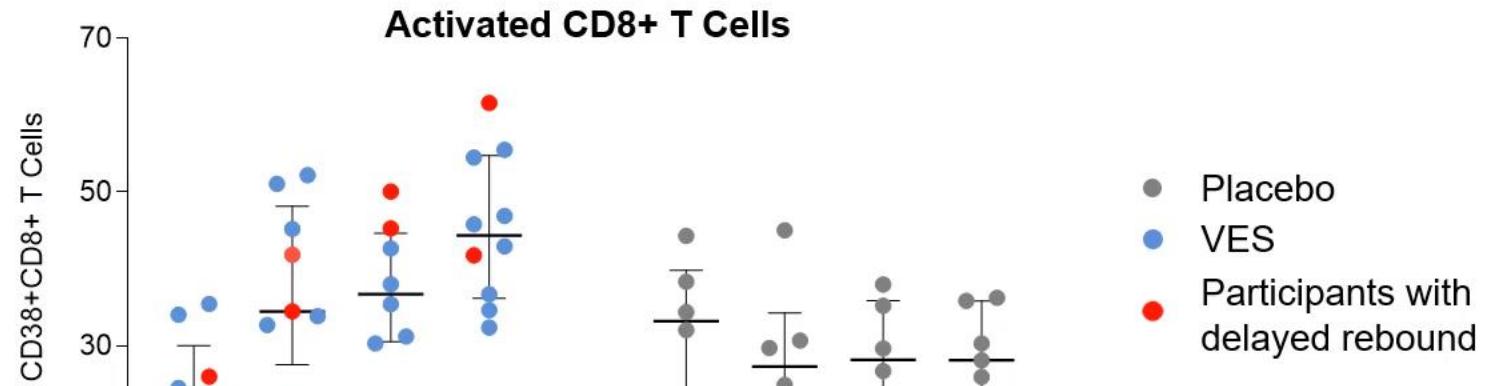
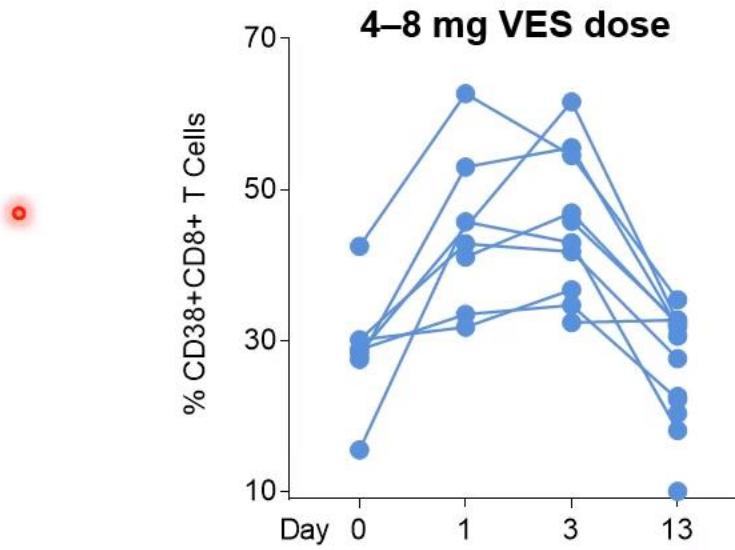


BL, baseline; IL-1ra, interleukin-1 receptor antagonist; IP-10, IFN gamma-induced protein 10; MX1, IFN-induced GTP-binding protein; OAS1, 2'-5' oligoadenylate synthetase 1. Participants with delayed rebound is defined as those with time to viral rebound >6 weeks post ATI

Interferon Stimulated Genes & Cytokine Responses are Consistent Across Doses

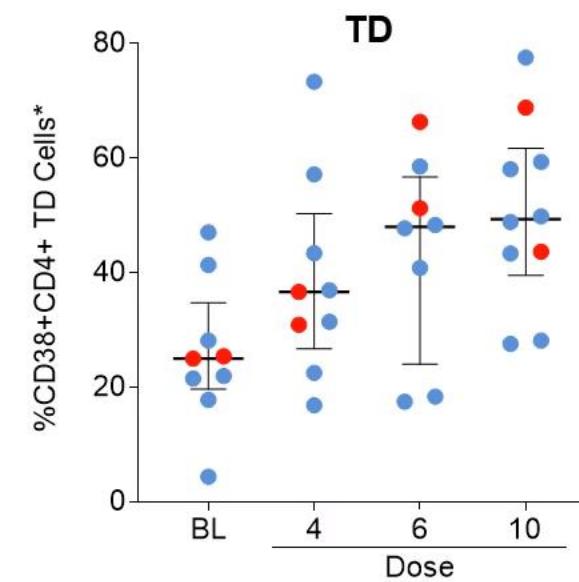
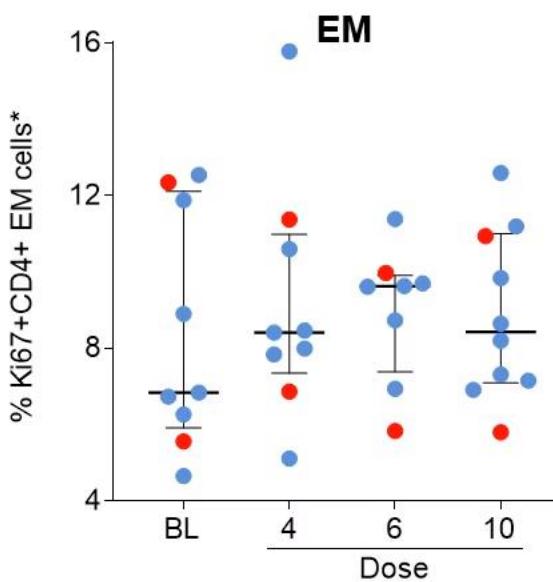
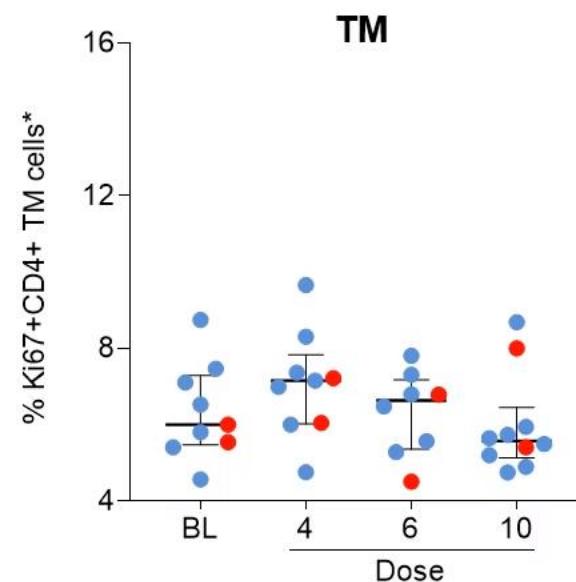
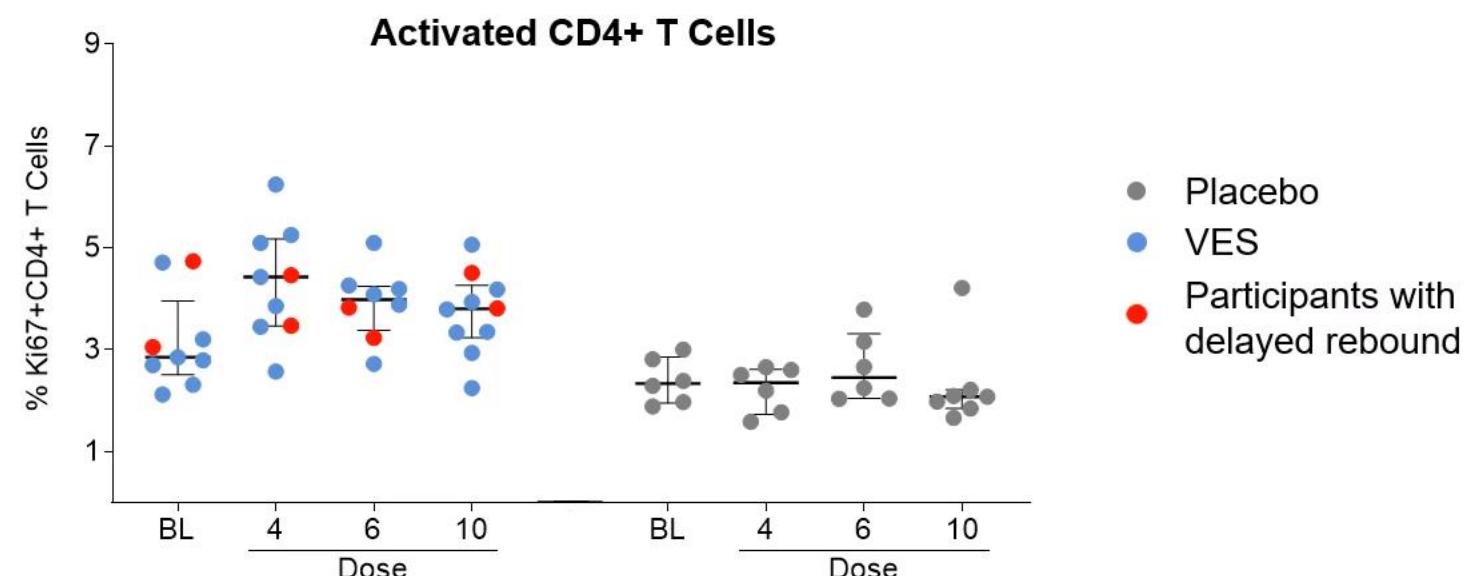
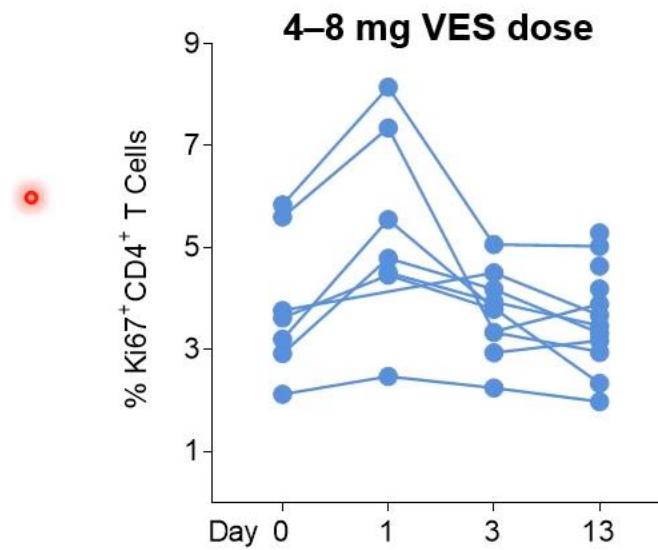


Vesatolimod Increases 24 Hour Activation Markers of CD8+ T Cells

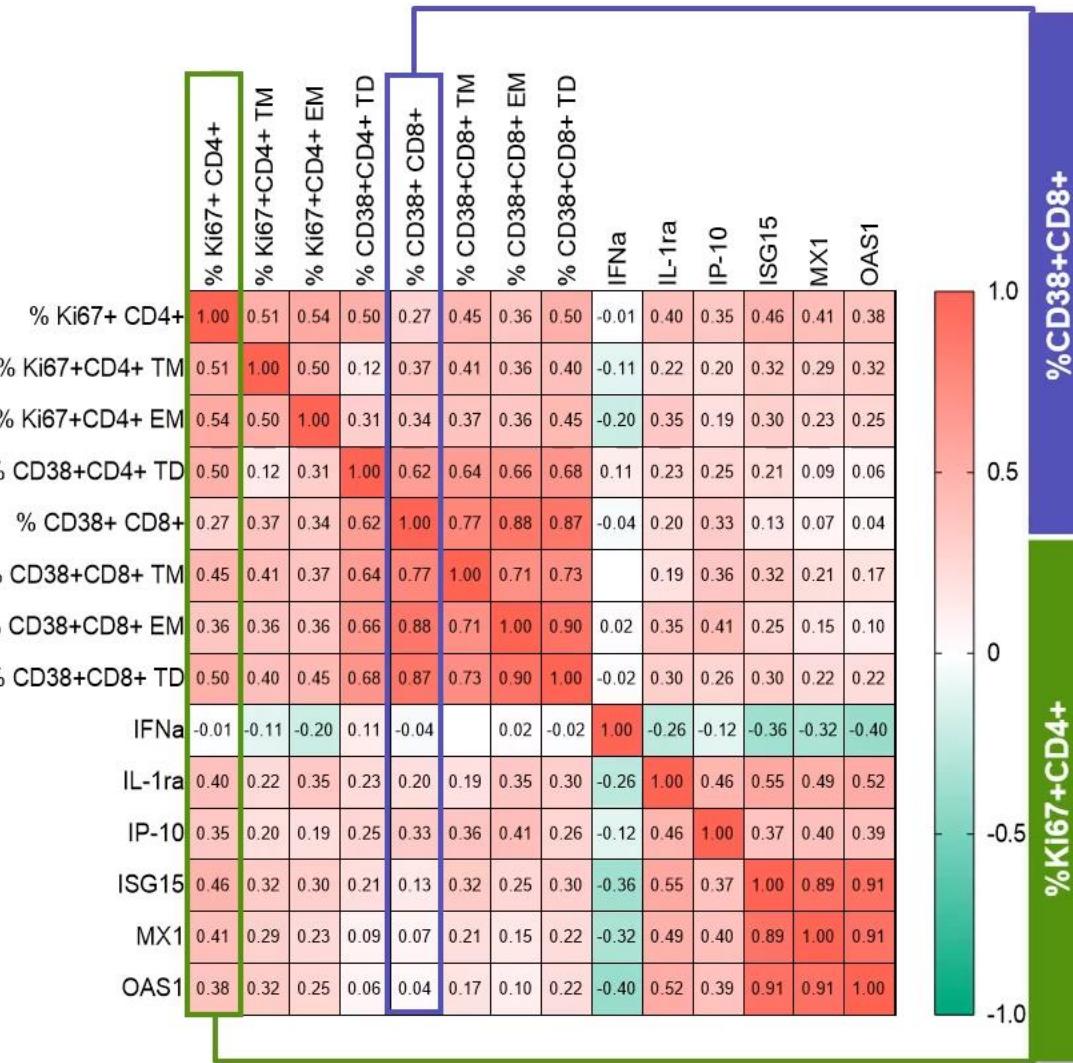


⁶ EM, effector memory; TD, terminally differentiated; TM, memory T cell. Participants with delayed rebound is defined as those with time to viral rebound >6 weeks post ATI

Vesatolimod Increases 24 Hour Activation Markers of CD4+ T Cells

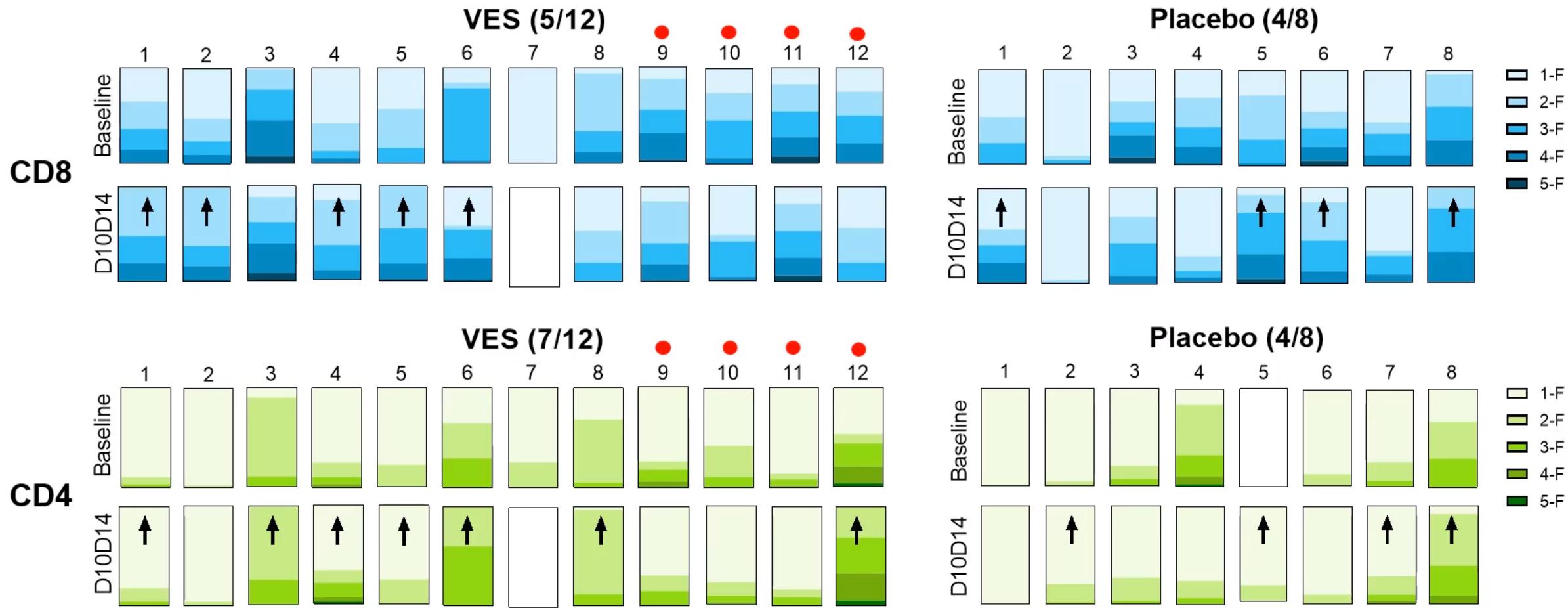


VES-mediated Changes in Interferon Signaling are Positively Correlated with Changes in T Cell Proliferation and Activation



Cell activation ISG or cytokines	Spearman r	p-value (2-tailed)	p-value summary	No. of XY Pairs
% Ki67+CD4+	0.2679	0.0006	***	162
% Ki67+CD4+ TM	0.3669	<0.0001	****	162
% Ki67+CD4+ EM	0.3358	<0.0001	****	162
% CD38+CD4+ TD	0.6199	<0.0001	****	162
% CD38+CD8+ TM	0.7674	<0.0001	****	162
% CD38+CD8+ EM	0.8763	<0.0001	****	162
% CD38+CD8+ TD	0.8714	<0.0001	****	162
IFN α	-0.04127	0.7162	ns	80
IL-1ra	0.2038	0.0905	ns	70
IP-10	0.3342	0.0024	**	80
ISG15	0.1281	0.3561	ns	54
MX1	0.06787	0.6258	ns	54
OAS1	0.03935	0.7776	ns	54
% Ki67+CD4+ TM	0.5143	<0.0001	****	162
% Ki67+CD4+ EM	0.5422	<0.0001	****	162
% CD38+CD4+ TD	0.4973	<0.0001	****	162
% CD38+CD8+	0.2679	0.0006	***	162
% CD38+CD8+ TM	0.4471	<0.0001	****	162
% CD38+CD8+ EM	0.3604	<0.0001	****	162
% CD38+CD8+ TD	0.4987	<0.0001	****	162
IFN α	-0.0092	0.9354	ns	80
IL-1ra	0.3969	0.0007	***	70
IP-10	0.3462	0.0017	**	80
ISG15	0.4648	0.0004	***	54
MX1	0.4067	0.0023	**	54
OAS1	0.3771	0.0049	**	54

Some Vesatolimod Treated Participants Had Increases in T Cell Polyfunctional Responses



- Participants with delayed rebound

Conclusions

- In HIV controllers, oral vesatolimod treatment induces an interferon response that was dose-dependent
- The degree that the interferon pathways were induced was consistently correlated with increases in T cell proliferation and activation
- Increased polyfunctionality of HIV-specific T cell responses observed in some participants
- Participants with delayed viral rebound did not have consistent patterns across biomarkers; further analyses are ongoing
- NK and myeloid readouts are pending and will be correlated with other biomarkers and viral measures
- Vesatolimod may play an important role in HIV cure innovations via combination with CD8+ T cell inducing vaccines or monoclonal antibodies

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