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Vesatolimod Pharmacodynamic Response Associates With Time to HIV Rebound

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Introduction

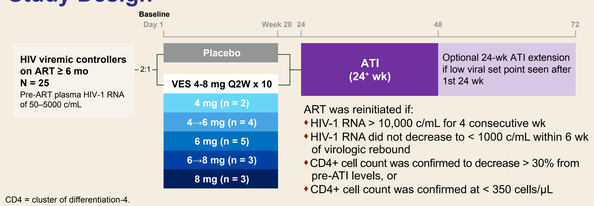
- Vesatolimod (VES) is a toll-like receptor-7 agonist that is being developed as a potential component of combination therapy for HIV cure
- Preclinically, VES in combination with therapeutic vaccine and/or broadly-neutralizing antibodies was shown to delay viral rebound in macaques[1,2]
- Clinically, VES can enhance immune responses in people living with HIV and lead to modest delay in HIV rebound[3,4]
- Study GS-US-382-3961 (NCT03060447) was a randomized, double-blind, placebo-controlled, Phase 1b, clinical trial of VES in antiretroviral therapy (ART)-suppressed "HIV virologic controllers," a subset of people with HIV with history of maintaining low plasma HIV-1 RNA in the absence of ART; in this study, VES treatment resulted in a modest delay in time to HIV rebound

Objective

- To investigate the association between VES pharmacokinetics (PK)/pharmacodynamics (PD) after the 1st dose and viral outcome after ART interruption (ATI)

Methods

Study Design



ART was reinitiated if:
- HIV-1 RNA > 10,000 c/mL for 4 consecutive wk
- HIV-1 RNA did not decrease to < 1000 c/mL within 6 wk of virologic rebound
- CD4+ cell count was confirmed to decrease > 30% from pre-ATI levels, or
- CD4+ cell count was confirmed at < 350 cells/μL

CD4 = cluster of differentiation-4.

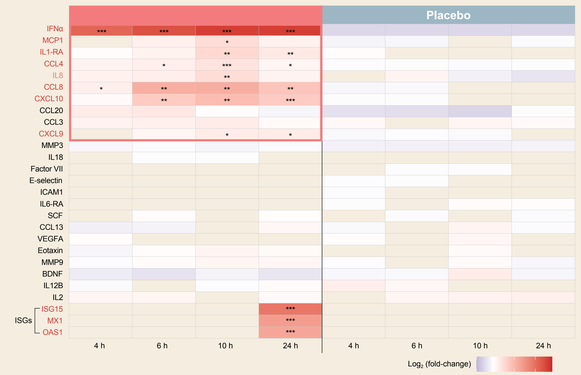
- **Biomarker measurements:**
  - Whole blood samples were collected predose and 24 h after 1st dose to evaluate interferon (IFN)-stimulated genes (ISGs) with real-time quantitative polymerase chain reaction method
  - Plasma samples were collected predose, and 4, 6, 10, and 24 h after 1st dose to evaluate inflammatory markers with multiplex or single-molecule array method
  - Derived biomarker data used for the association analysis included:
    - ISG: fold-change from baseline
    - Plasma proteins: maximal fold-change and area under effect curve of % change from baseline from time 0 to 24 h after 1st dose ($AUEC_{0\text{-}24}$)

$$AUEC = \frac{1}{t}\sum_{i=1}^{t}\frac{1}{2}\,C_{i+1}\,C_i(t_{i+1}-t_i)$$

- **Virologic measurements:**
  - Plasma HIV-1 RNA viral load was assessed by COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test, v2.0 (Roche Diagnostics Corporation, Indianapolis, IN) longitudinally
  - The HIV reservoir in peripheral blood mononuclear cells was assessed by the intact proviral DNA assay (IPDA) at baseline and the start of ATI
  - Viral outcomes: 1st time to plasma HIV RNA ≥ 200 or ≥ 1000 c/mL, cumulative time of plasma RNA ≤ 400 c/mL during ATI, and change from baseline in IPDA at pre-ATI (13 days postdose 10)
- **PK evaluation:**
  - Plasma samples for VES concentrations were collected predose, and 0.5, 1, 2, 4, 6, 8, 10, and 24 h after 1st dose
  - Maximal concentration (C_{max}) and area under the curve from time 0 to 24 h ($AUC_{0\text{-}24}$) after 1st dose were derived for association analysis with PD and viral outcomes
- **Statistical methods:**
  - Both placebo- and VES-treated participants were included in this analysis
  - Cox proportional-hazard model and Spearman's correlation were used to analyze the associations between derived plasma proteins, ISGs or VES PK, and viral outcomes
  - Spearman's correlation was used to analyze the association between plasma proteins or ISGs and VES PK

Results

Significant Elevation in PD Biomarkers After 1st VES Dose Within 24 Hours



Heatmap shows $\log_2$ mean (fold-change); Wilcoxon rank-sum test was used to compare raw values between baseline and other time points: plasma proteins were included in analysis if ≥ 25% of values were quantifiable. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. BDNF = brain-derived neurotrophic factor; CCL = chemokine (C-C motif) ligand; CXCL9 = chemokine (C-X-C motif) ligand-9; ICAM1 = intercellular adhesion molecule-1; IL = interleukin; IP-10 = IFNγ-induced protein 10; MCP1 = monocyte chemotactic protein-1; MMP = matrix metallopeptidase; MX1 = MX dynamin-like guanosine triphosphatase-1; OAS1 = 2′,5′-oligoadenylate synthetase-1; RA = receptor antagonist; SCF = stem cell factor; VEGFA = vascular endothelial growth factor-A.

Immune Biomarkers Significantly Correlated With VES PK

Spearman's Correlation

Biomarker	24-h Measurement	n	VES $AUC_{0\text{-}24}$ R	VES $AUC_{0\text{-}24}$ *P*-Value	VES $AUC_{0\text{-}24}$ FDR	C_{max} R	C_{max} *P*-Value	C_{max} FDR
ISG15	Fold-change	14	0.83	< 0.001	< 0.01	0.84	< 0.001	< 0.01
OAS1	Fold-change	14	0.83	< 0.001	0.01	0.86	< 0.001	< 0.001
MX1	Fold-change	14	0.69	0.01	0.02	0.72	< 0.01	0.013
IFNα	AUEC	23	0.88	< 0.001	< 0.001	0.88	< 0.001	< 0.001
	Max fold-change	23	0.84	< 0.001	< 0.001	0.85	< 0.001	< 0.001
IL1-RA	AUEC	23	0.6	< 0.01	0.01	0.58	< 0.01	0.01
	Max fold-change	23	0.55	0.01	0.02	0.54	0.01	0.03
IP-10	AUEC	23	0.8	< 0.001	< 0.001	0.81	< 0.001	< 0.001
	Max fold-change	23	0.79	< 0.001	< 0.001	0.81	< 0.001	< 0.001
CCL4	AUEC	23	0.77	< 0.001	< 0.001	0.82	< 0.001	< 0.001
	Max fold-change	23	0.78	< 0.001	< 0.001	0.82	< 0.001	< 0.001
CCL8	AUEC	23	0.79	< 0.001	< 0.001	0.80	< 0.001	< 0.001
	Max fold-change	23	0.8	< 0.001	< 0.001	0.82	< 0.001	< 0.001
CXCL9	AUEC	23	0.77	< 0.001	< 0.001	0.79	< 0.001	< 0.001
	Max fold-change	23	0.74	< 0.001	< 0.001	0.78	< 0.001	< 0.001
MCP1	AUEC	23	0.52	0.01	0.03	0.53	0.01	0.03
	Max fold-change	23	0.63	< 0.01	< 0.01	0.66	< 0.01	< 0.01
IL8	AUEC	23	0.52	0.01	0.03	0.52	0.01	0.03

Only included data with nominal $P \le 0.05$; all participants from VES and placebo groups included. FDR = false discovery rate-adjusted *P*-value; Max = maximal; R = rho value.

Lack of Association Between PK and Time to HIV Rebound and Duration of HIV Control During ATI and IPDA

Spearman's Correlation

Measurement	n	Time to 1st Rebound to Plasma HIV-1 RNA of 200 c/mL R	Time to 1st Rebound to Plasma HIV-1 RNA of 200 c/mL *P*-Value	Time to 1st Rebound to Plasma HIV-1 RNA of 1000 c/mL R	Time to 1st Rebound to Plasma HIV-1 RNA of 1000 c/mL *P*-Value	Duration of Plasma HIV-1 RNA ≤ 400 c/mL During ATI R	Duration of Plasma HIV-1 RNA ≤ 400 c/mL During ATI *P*-Value	Change in IPDA From Baseline R	Change in IPDA From Baseline *P*-Value
$AUC_{0\text{-}24h}$	23	0.22	0.32	0.09	0.69	-0.03	0.90	-0.24	0.29
C_{max}	23	0.24	0.27	0.09	0.68	-0.02	0.92	-0.26	0.26

Cox Proportional-Hazards Model

Measurement	n	Time to 1st Rebound to Plasma HIV-1 RNA of 200 c/mL HR (95% CI)	Time to 1st Rebound to Plasma HIV-1 RNA of 200 c/mL *P*-Value	Time to 1st Rebound to Plasma HIV-1 RNA of 1000 c/mL HR (95% CI)	Time to 1st Rebound to Plasma HIV-1 RNA of 1000 c/mL *P*-Value	Duration of Time of Plasma HIV-1 RNA ≤ 400 c/mL During ATI HR (95% CI)	Duration of Time of Plasma HIV-1 RNA ≤ 400 c/mL During ATI *P*-Value
$AUC_{0\text{-}24h}$	23	0.42 (0.16, 1.11)	0.08	0.99 (0.42, 2.30)	0.98	0.59 (0.24, 1.44)	0.25
C_{max}	23	0.42 (0.16, 1.11)	0.08	0.99 (0.42, 2.30)	0.98	0.59 (0.24, 1.44)	0.25

All participants from VES and placebo group included. CI = confidence interval; HR = hazard ratio.

Circulating ISGs and Plasma Proteins Were Associated With Time to HIV Rebound and Duration of HIV Control During ATI

Cox Proportional-Hazards Model

	Biomarkers	Measurement	n	Time to Plasma HIV RNA ≥ 200 c/mL During ATI HR (95% CI)	Time to Plasma HIV RNA ≥ 200 c/mL During ATI *P*-Value	Time to Plasma HIV RNA ≥ 1000 c/mL During ATI HR (95% CI)	Time to Plasma HIV RNA ≥ 1000 c/mL During ATI *P*-Value	Duration of Time of Plasma HIV RNA ≤ 400 c/mL During ATI HR (95% CI)	Duration of Time of Plasma HIV RNA ≤ 400 c/mL During ATI *P*-Value
Positive Association HR < 1	ISG15	24-h fold-change	13	0.16 (0.03, 0.81)	0.03	0.09 (0.01, 0.77)	0.03	0.57 (0.18, 1.84)	0.35
	OAS1	24-h fold-change	13	0.16 (0.03, 0.81)	0.03	0.09 (0.01, 0.77)	0.03	0.57 (0.18, 1.84)	0.35
	ICAM-1	24-h max fold-change	22	0.35 (0.13, 0.92)	0.03	0.53 (0.22, 1.29)	0.16	0.82 (0.34, 1.96)	0.66
	CCL4	24-h max fold-change	22	0.24 (0.08, 0.73)	0.01	0.45 (0.18, 1.15)	0.10	0.74 (0.31, 1.77)	0.50
		24-h AUEC	22	0.24 (0.08, 0.73)	0.01	0.45 (0.18, 1.15)	0.10	0.74 (0.31, 1.77)	0.50
	Factor VII	24-h max fold-change	22	0.38 (0.15, 0.99)	< 0.05	0.53 (0.22, 1.29)	0.16	0.77 (0.32, 1.85)	0.56
		24-h AUEC	22	0.37 (0.14, 0.97)	0.04	0.50 (0.21, 1.21)	0.12	0.76 (0.32, 1.83)	0.55
Negative Association HR < 1	BDNF	24-h max fold-change	22	1.39 (0.57, 3.36)	0.47	2.23 (0.85, 5.82)	0.10	3.31 (1.23, 8.93)	0.02
		24-h AUEC	22	1.39 (0.57, 3.36)	0.47	2.23 (0.85, 5.82)	0.10	3.31 (1.23, 8.93)	0.02
	IL2	24-h max fold-change	22	1.31 (0.55, 3.10)	0.54	1.97 (0.79, 4.93)	0.15	4.68 (1.44, 15.23)	0.01
		24-h AUEC	22	1.68 (0.69, 4.07)	0.25	2.90 (1.16, 7.23)	0.02	5.50 (1.89, 16.01)	< 0.01
	MMP9	24-h max fold-change	22	1.57 (0.66, 3.73)	0.31	2.14 (0.85, 5.36)	0.11	3.29 (1.24, 8.72)	0.02
		24-h AUEC	22	1.15 (0.48, 2.79)	0.76	1.84 (0.74, 4.61)	0.19	3.12 (1.17, 8.29)	0.02

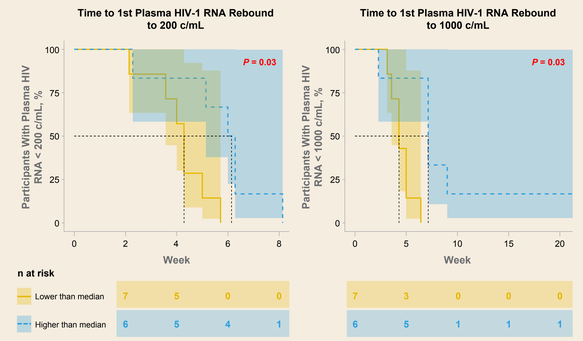
Spearman's Correlation

Biomarkers	Measurement	n	Time to 1st Rebound to Plasma HIV-1 RNA of 200 c/mL R	Time to 1st Rebound to Plasma HIV-1 RNA of 200 c/mL *P*-Value	Time to 1st Rebound to Plasma HIV-1 RNA of 1000 c/mL R	Time to 1st Rebound to Plasma HIV-1 RNA of 1000 c/mL *P*-Value	Duration of Plasma HIV-1 RNA ≤ 400 c/mL During ATI R	Duration of Plasma HIV-1 RNA ≤ 400 c/mL During ATI *P*-Value	Change in IPDA From Baseline R	Change in IPDA From Baseline *P*-Value
ISG15	24-h fold-change	13	0.55	< 0.05	0.51	0.08	0.28	0.35	0.25	0.43
OAS1	24-h fold-change	13	0.58	0.04	0.49	0.09	0.23	0.45	0.34	0.28
MX1	24-h fold-change	22	0.60	0.03	0.57	0.04	0.41	0.17	0.54	0.07
MMP3	24-h AUEC	22	0.43	0.04	0.17	0.45	0.39	0.07	0.20	0.40
	24-h max fold-change	22	0.52	0.01	0.17	0.45	0.32	0.14	0.14	0.55
Factor VII	24-h AUEC	22	0.44	0.04	0.37	0.09	0.29	0.20	0.18	0.45
BDNF	24-h AUEC	22	-0.21	0.35	-0.24	0.29	-0.53	0.01	-0.16	0.51
	24-h max fold-change	22	-0.26	0.24	-0.27	0.23	-0.51	0.02	-0.20	0.40
IL2	24-h AUEC	22	-0.33	0.13	-0.48	0.02	-0.51	0.02	-0.09	0.70
	24-h max fold-change	22	-0.17	0.45	-0.33	0.14	-0.49	0.02	0.09	0.69
MMP9	24-h max fold-change	22	-0.51	0.02	-0.48	0.02	-0.66	< 0.01	-0.31	0.18
	24-h AUEC	22	-0.36	0.10	-0.41	0.06	-0.55	0.01	-0.14	0.54

Only included data with nominal $P \le 0.05$; no significant FDR-adjusted *P*-value; HR < 1 associated with longer time to viral rebound and longer duration of control; HR > 1 associated with shorter time to viral rebound and shorter duration of control; all participants from VES and placebo groups included.

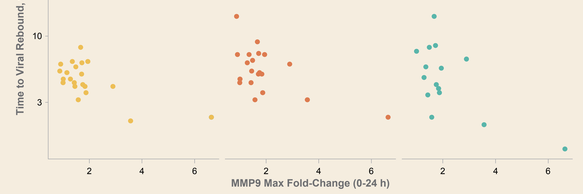
Higher Elevation in ISGs 24 h After 1st Dose Was Associated With Longer Time to HIV Rebound

- Same results were observed for ISG15 and OAS1



Observed significance reported as nominal *P*-values.

Higher Increase in MMP9 24 h After 1st Dose Was Associated With Faster HIV Rebound and Shorter Duration of Control During ATI



Observed significance reported as nominal *P*-values; R derived using Spearman's correlation.

Conclusions

- VES significantly induced PD responses within 24 h after the 1st VES dose in viremic controllers study GS-US-382-3961
- VES-mediated biological effect was associated with viral outcome:
  - Increases in ISGs and CCL4 at 24 h after the 1st dose were associated with longer time to HIV rebound
  - Immune biomarkers correlated with VES PK, including ISG15, MX1, OAS1, IFNα, IP-10, IL-1RA, MCP1, CCL4, CCL8, CXCL9, and IL8
  - No associations were found between VES PK and time to HIV rebound, and duration of HIV control during ATI or IPDA
- Additional biomarkers associated with HIV control during ATI:
  - Longer time to HIV rebound/viral control: factor VII, MMP3, and ICAM1
  - Shorter time to HIV rebound/viral control: BDNF, IL2, and MMP9
  - Higher increase in MMP9 24 h after the 1st dose was associated with faster HIV rebound and shorter duration of control during ATI
- This analysis was limited by the small number of participants and further studies with larger independent cohorts, including those without history of natural pre-ART viral control, are needed to understand and validate the VES PD associated with viral outcomes and their function

References: **1.** Borducchi EN, et al. Nature 2018;563:360-4; **2.** Ventura JD, et al. NPJ Vaccines 2022;7:53; **3.** Riddler SA, et al. Clin Infect Dis 2021;72:e815-24; **4.** SenGupta D, et al. Sci Transl Med 2021;13:eabg3071. **Acknowledgments:** We extend our thanks to the participants, their partners, and families. Special thanks to the study teams. *Principal investigator:* S Deeks; *clinical investigators:* M Ramgopal, C Brinson, E DeJesus, A Mills, P Shalit; *biomarker analysis:* N Jone, V Girling (UCSF–Core Immunology Lab); Y Cai, L Zhang, Y Zheng, M Wire, P Shweh, D Verrill, S Guo, X Liu, L Selzer, L VanderVeen, S Huang, B Downie, B Chen, R Geleziunas, CR de Vries, E Vendrame, D SenGupta, JJ Wallin (Gilead Sciences, Inc.). This study was funded by Gilead. Editorial and production assistance were provided by BioScience Communications, New York, NY, funded by Gilead.
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