

Oral Abstract Session-05

Tuesday, February 24, 2026

137 - CD4-Targeted IL-15 Enhanced bNAb Activity and Improved SHIV Control After Treatment Interruption

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Financial Relationships:

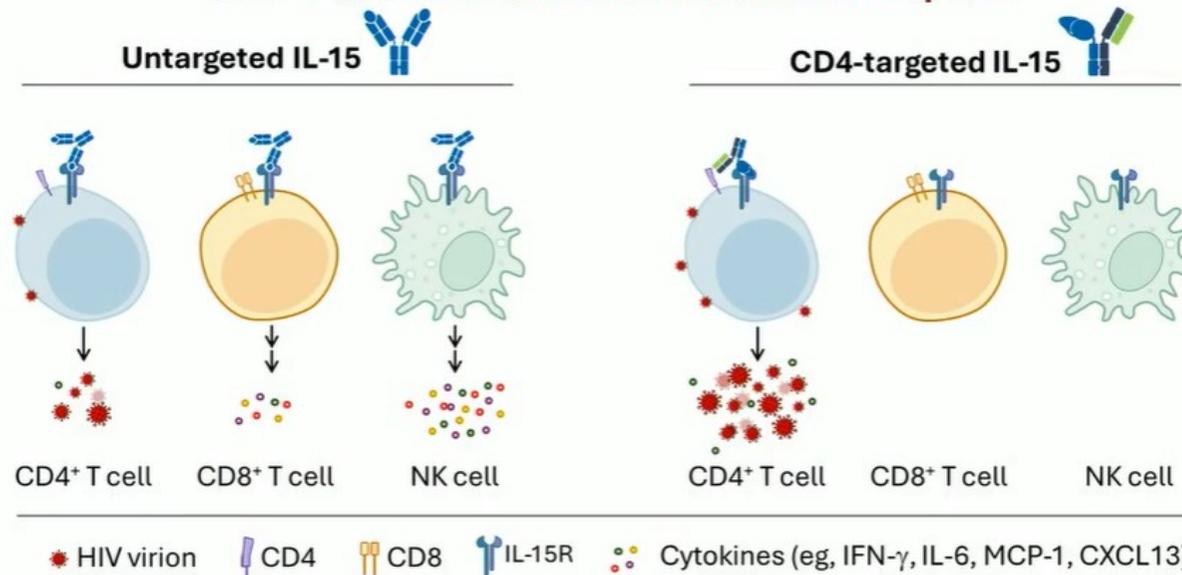
Dr Murry has Self: Employment with Gilead Sciences, Inc. and Self: Stock/stock options with Gilead Sciences, Inc.

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Introduction

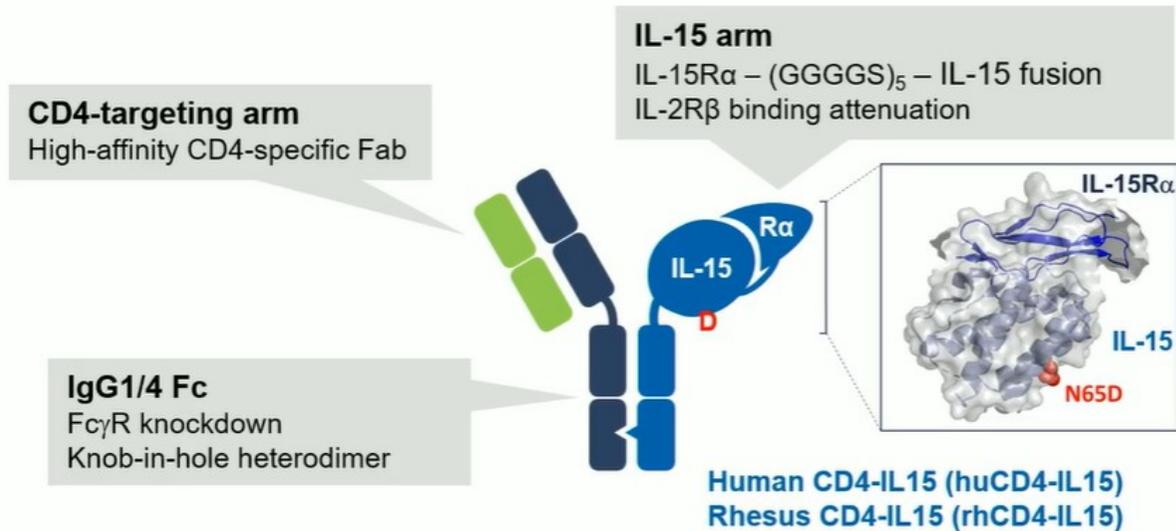
- Primary barrier to HIV cure = latent viral reservoir¹
- IL-15 activates HIV expression from HIV reservoirs^{2,3}

CD4-IL15 is designed to selectively activate CD4⁺ T cells and induce HIV RNA transcription



CD4-IL15, CD4-targeted interleukin 15; CXCL13, C-X-C chemokine ligand 13; IFN- γ , interferon gamma; IL-6, interleukin 6; IL-15, interleukin 15; MCP-1, monocyte chemoattractant protein 1; NK, natural killer.
1. Chun TW, et al. *Proc Natl Acad Sci U S A*. 1997;94:13193-7. 2. Jones RB, et al. *PLoS Pathog*. 2016;12:e1005545. 3. Miller JS, et al. *Nat Med*. 2022;28:392-400.

CD4-Targeted IL-15

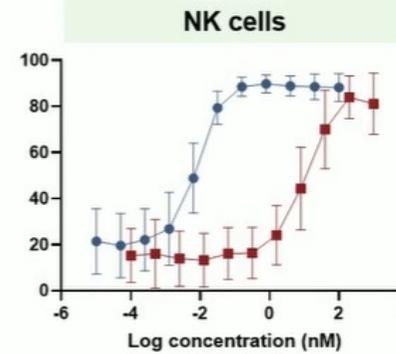
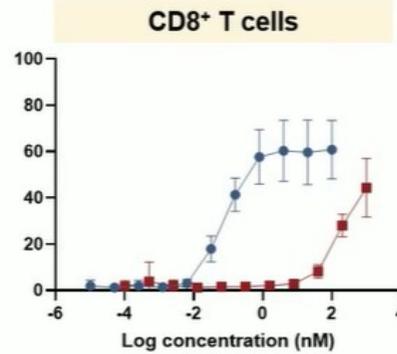
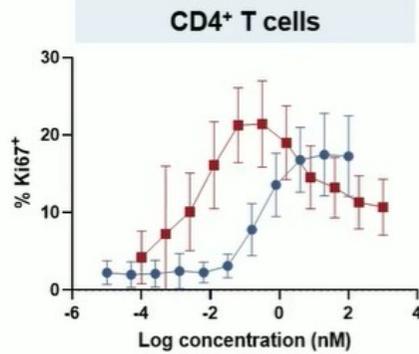
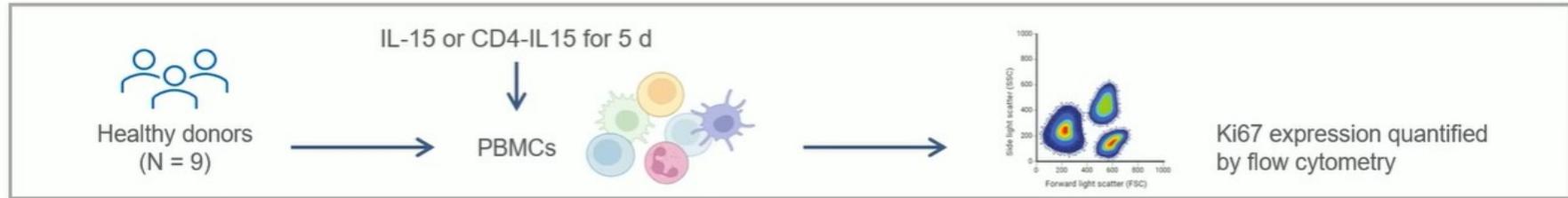


Objectives

- Evaluate the effectiveness of CD4-IL15 to:
 - Selectively activate HIV in CD4⁺ T cells in vitro
 - Enhance reservoir reduction and viral control upon ART interruption when combined with bNAb in an animal model

ART, antiretroviral therapy; bNAb, broadly neutralizing antibody; CD4-IL15, CD4-targeted interleukin 15; Fab, fragment antigen-binding; Fc, fragment crystallizable; Fc γ R, fragment crystallizable gamma receptor; IgG, immunoglobulin G; IL-2R β , interleukin 2 receptor beta subunit; IL-15, interleukin 15; IL-15R α , interleukin 15 receptor alpha subunit.

CD4-IL15 Selectively Induced Proliferation of CD4⁺ T Cells



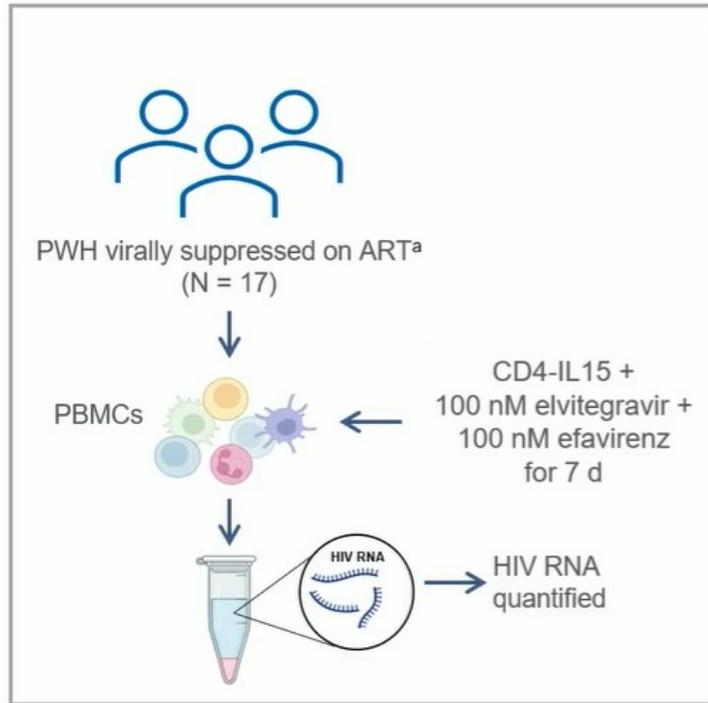
● IL-15
■ CD4-IL15

	EC ₅₀ (nM)			NK/CD4 ⁺ EC ₅₀ Ratio
	CD4 ⁺	CD8 ⁺	NK	
IL-15	0.28	0.080	0.0083	0.030
CD4-IL15	0.0047	170	10	2100

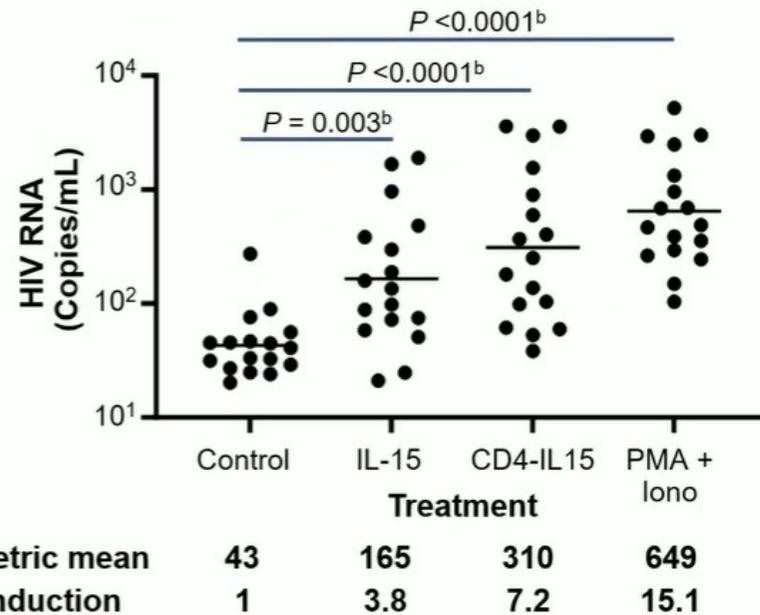
70,000-fold target improvement

CD4-IL15, CD4-targeted interleukin 15; EC₅₀, half-maximal effective concentration; IL-15, interleukin 15; NK, natural killer; PBMC, peripheral blood mononuclear cell.

In PBMCs From PWH, CD4-IL15 Induced HIV Expression



CD4-IL15 showed significant induction of HIV RNA

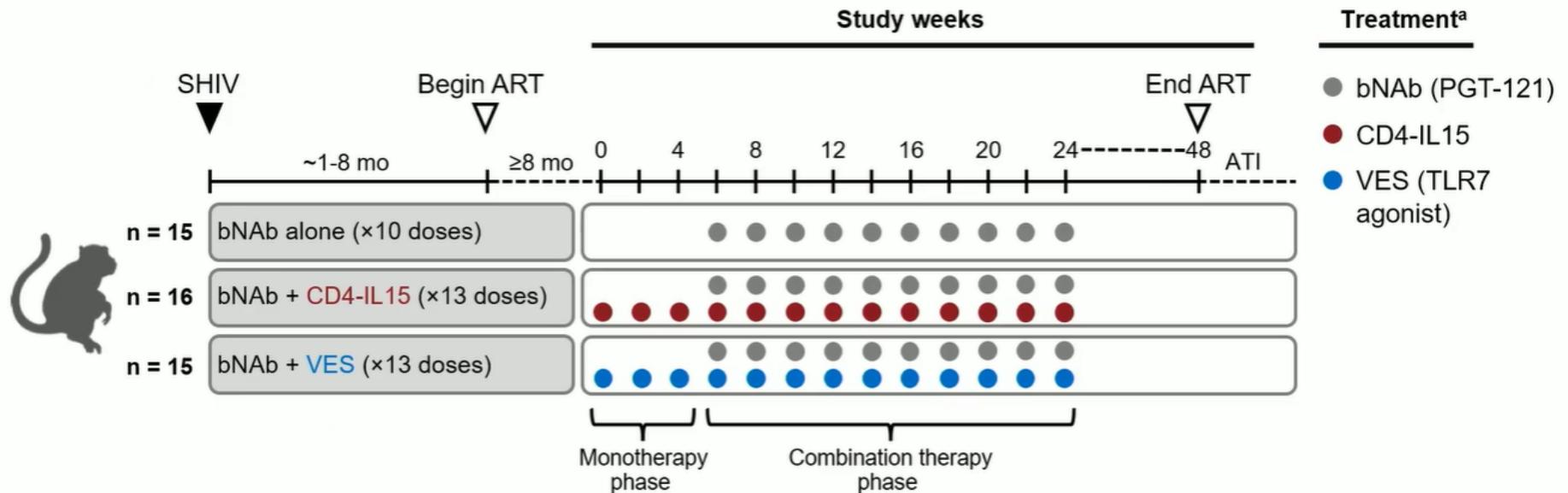


^aDonors with <5-fold induction with PMA + Iono were excluded.

^bP values assessed by the Wilcoxon test.

ART, antiretroviral therapy; CD4-IL15, CD4-targeted interleukin 15; IL-15, interleukin 15; PBMC, peripheral blood mononuclear cell; PMA + Iono, phorbol 12-myristate 13-acetate and ionomycin; PWH, people with HIV.

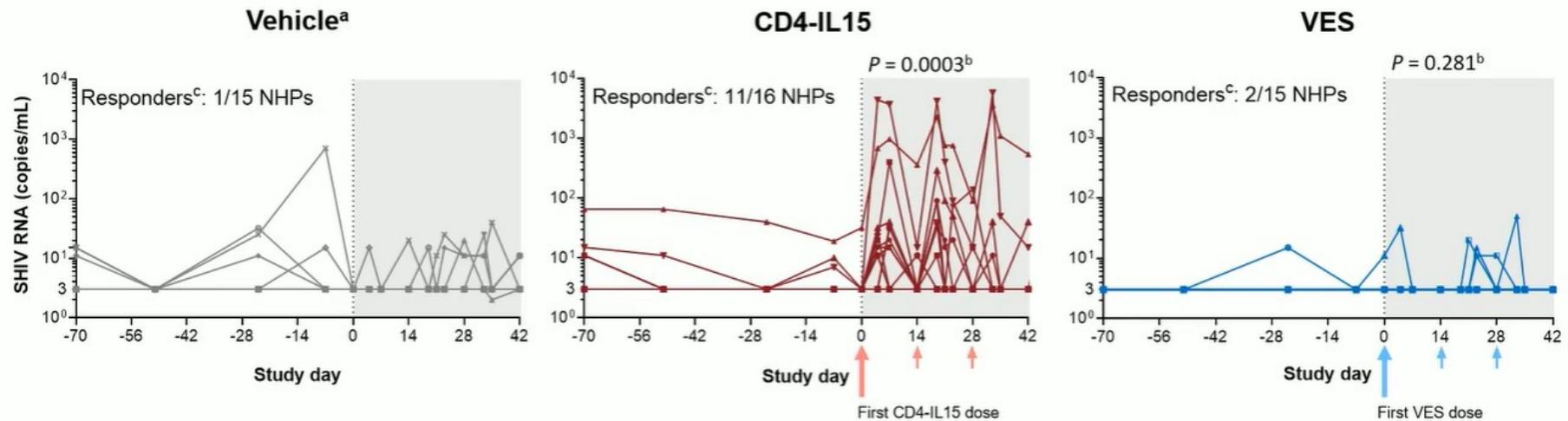
Design of NHP Study Assessing Rhesus CD4-IL15 in Combination With bNAb



^aCD4-IL15 and bNAb were administered via IV infusion; VES was administered by oral gavage. All groups received matched vehicle controls on each dosing day (IV formulation buffer or oral formulation buffer) in accordance with their dosing regimen. ART, antiretroviral therapy; ATI, analytical treatment interruption; bNAb, broadly neutralizing antibody (PGT-121); CD4-IL15, CD4-targeted interleukin 15; IV, intravenous; NHP, nonhuman primate; SHIV, simian-human immunodeficiency virus (SHIV-SF162P3); TLR7, toll-like receptor 7; VES, vesatolimod (toll-like receptor 7 agonist).

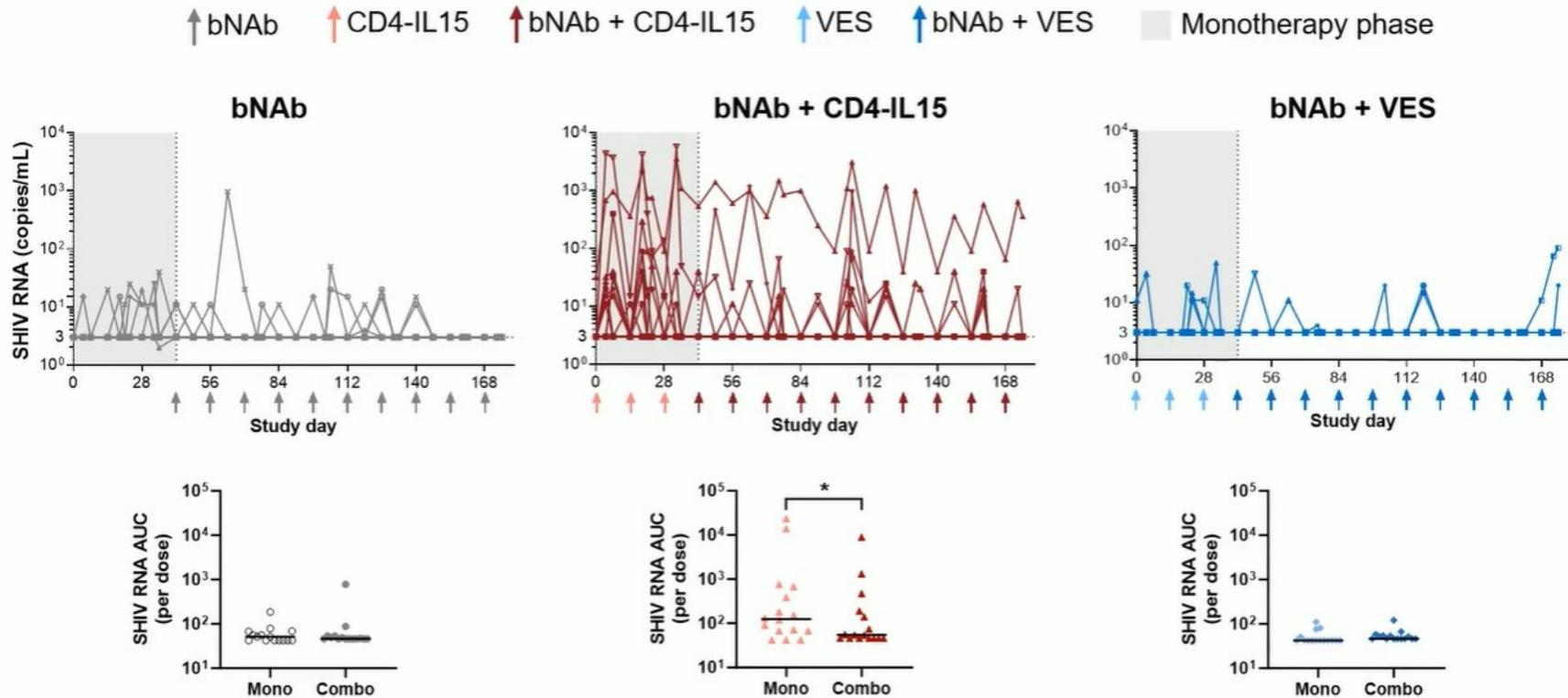
CD4-IL15 Induced Significant Increases in Plasma Viral Blips During the Monotherapy Phase

↑ CD4-IL15 ↑ VES ■ Monotherapy phase



^aCD4-IL15 and bNAb were administered via IV infusion; VES was administered by oral gavage. All groups received matched vehicle controls on each dosing day (IV formulation buffer or oral formulation buffer) in accordance with their dosing regimen. ^bArea under the curve comparisons were made via the Wilcoxon test. ^cResponder defined as ≥ 2 plasma SHIV RNA values above baseline. ^dbNAb, broadly neutralizing antibody (PGT-121); CD4-IL15, CD4-targeted interleukin 15; IV, intravenous; NHP, nonhuman primate; SHIV, simian-human immunodeficiency virus (SHIV-SF162P3); VES, vesatolimod (toll-like receptor 7 agonist).

Viral Blips Significantly Reduced After Addition of bNAb in CD4-IL15 Group

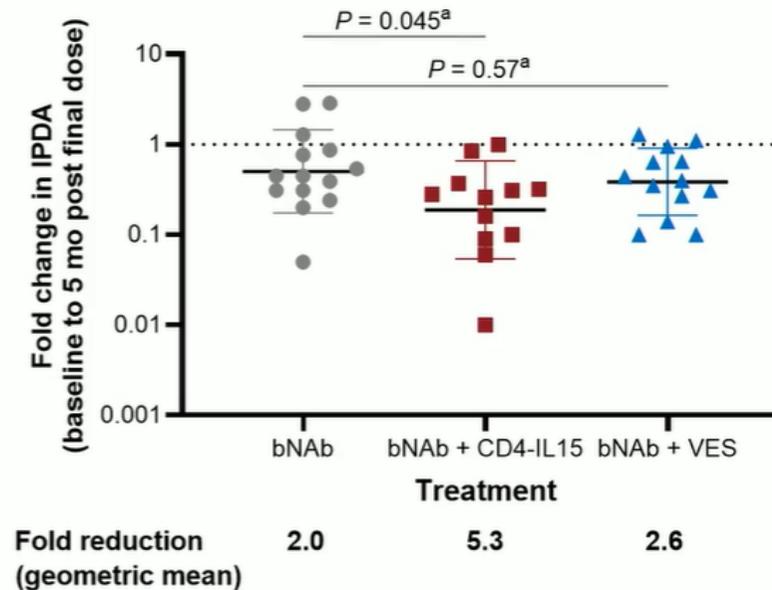


^aArea under the curve comparisons were made via the Wilcoxon test. * P < 0.05

bNAb, broadly neutralizing antibody (PGT-121); CD4-IL15, CD4-targeted interleukin 15; SHIV, simian-human immunodeficiency virus (SHIV-SF162P3); VES, vesatolimod (toll-like receptor 7 agonist).

bNAb + CD4-IL15 Showed the Greatest Reservoir Reduction of the 3 Groups

- Significant increases in cellular SHIV RNA were seen in lymph nodes with bNAb + CD4-IL15 treatment
- Five months after the final dose, bNAb + CD4-IL15 significantly reduced intact proviral DNA in lymph nodes relative to bNAb alone
- No changes in cellular SHIV RNA or proviral DNA were observed in PBMCs

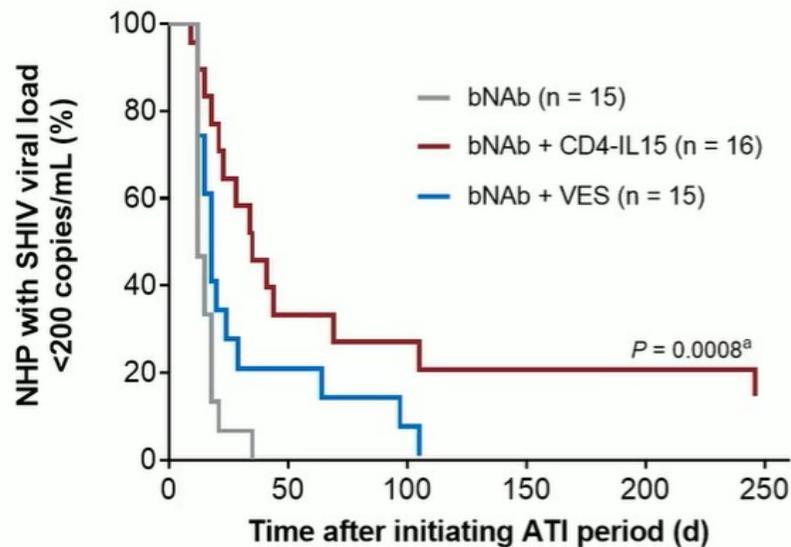


^a*P* values assessed by the Mann-Whitney test.

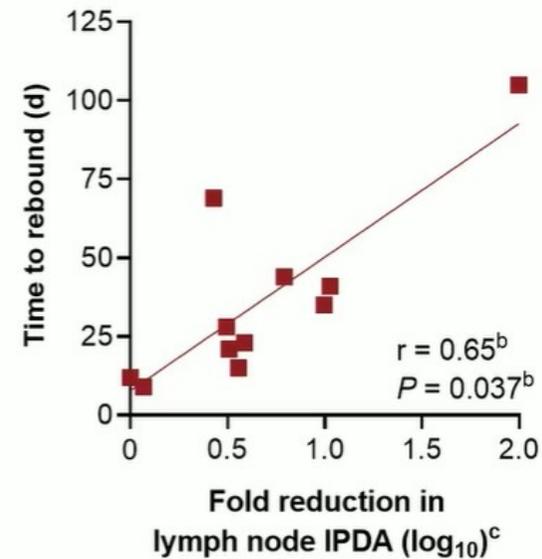
bNAb, broadly neutralizing antibody (PGT-121); **CD4-IL15**, CD4-targeted interleukin 15; **IPDA**, intact proviral DNA assay; **PBMC**, peripheral blood mononuclear cell; **SHIV**, simian-human immunodeficiency virus (SHIV-SF162P3); **VES**, vesatolimod (toll-like receptor 7 agonist).

bNAb + CD4-IL15 Significantly Delayed Rebound Relative to bNAb Alone

bNAb + CD4-IL15 significantly delayed viral rebound after initiating ATI period



Time to rebound correlated with reductions in lymph node intact SHIV DNA



^a P value assessed by Mantel-Cox log-rank test. ^bValue derived by Spearman correlation. ^cFold reduction assessed post final dose (baseline to 5 months); animals with undetectable IPDA were excluded from the correlation analysis. ATI, analytical treatment interruption; bNAb, broadly neutralizing antibody (PGT-121); CD4-IL15, CD4-targeted interleukin 15; IPDA, intact proviral DNA assay; NHP, nonhuman primate; SHIV, simian-human immunodeficiency virus (SHIV-SF162P3); VES, vesatolimod (toll-like receptor 7 agonist).

Summary

- Conclusions
 - CD4-IL15 is highly selective for CD4⁺ T cells and activates HIV expression
 - In an NHP model, CD4-IL15 increased SHIV expression
 - The combination of CD4-IL15 with bNAb reduced proviral reservoirs and enhanced viral control during ATI
 - These findings support further evaluation of CD4-IL15 in potential HIV cure strategies

Plain language summary

- In people with well-controlled HIV, the virus can hide in some cells; for the immune system to find and clear cells with hidden virus, the virus must first “wake up”
- In our study, we found that an engineered protein called CD4-IL15 was able to wake up hidden virus in cells from people with HIV and in an animal model of HIV infection; using CD4-IL15 together with antibodies that work against many versions of HIV helped reduce the amount of hidden virus and delay the virus from returning after HIV medicines were stopped in an animal model

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