

11TH EDITION

DECEMBER 10-13, 2024

HIV PERSISTENCE DURING THERAPY

Reservoirs & Eradication Strategies Workshop

Fort
Lauderdale

Short-term combination immunotherapy with broadly neutralizing antibodies and CCR5 blockade mediates ART-free viral control in infant rhesus macaques

Gabriela Webb

Jonah B. Sacha Laboratory
Division of Pathobiology & Immunology
Oregon National Primate Research Center
Portland, OR



www.hiv-persistence.com

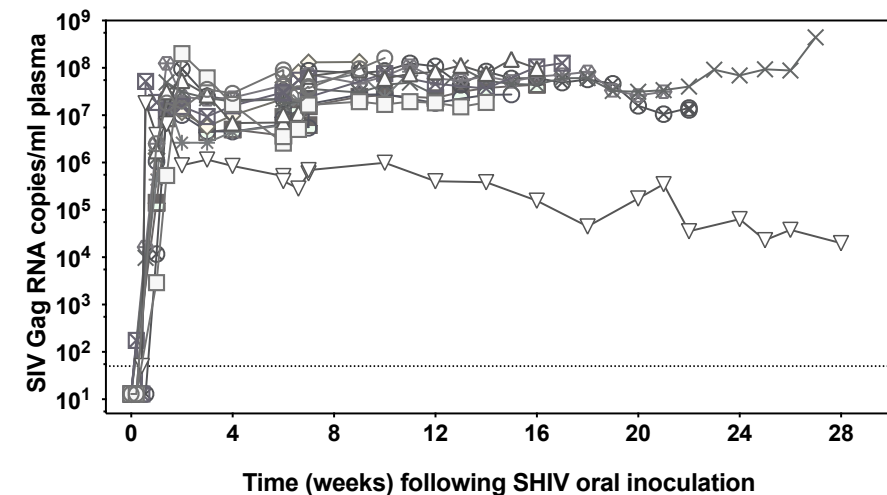
CONFLICTS OF INTEREST

No conflicts of interest

Infant macaques

a model for human pediatric HIV infection

- Born in a natural setting and allowed to suckle up to 7 days
- Oral high dose SHIV_{SF162P3}
 - 100% infection rate (4×10^4 TCID₅₀)
 - Rapid pathogenesis
- 75% mortality by 6 months w/o treatment
- Rapid disease due to high persistent viremia



Defining the window of opportunity for treatment

nature medicine

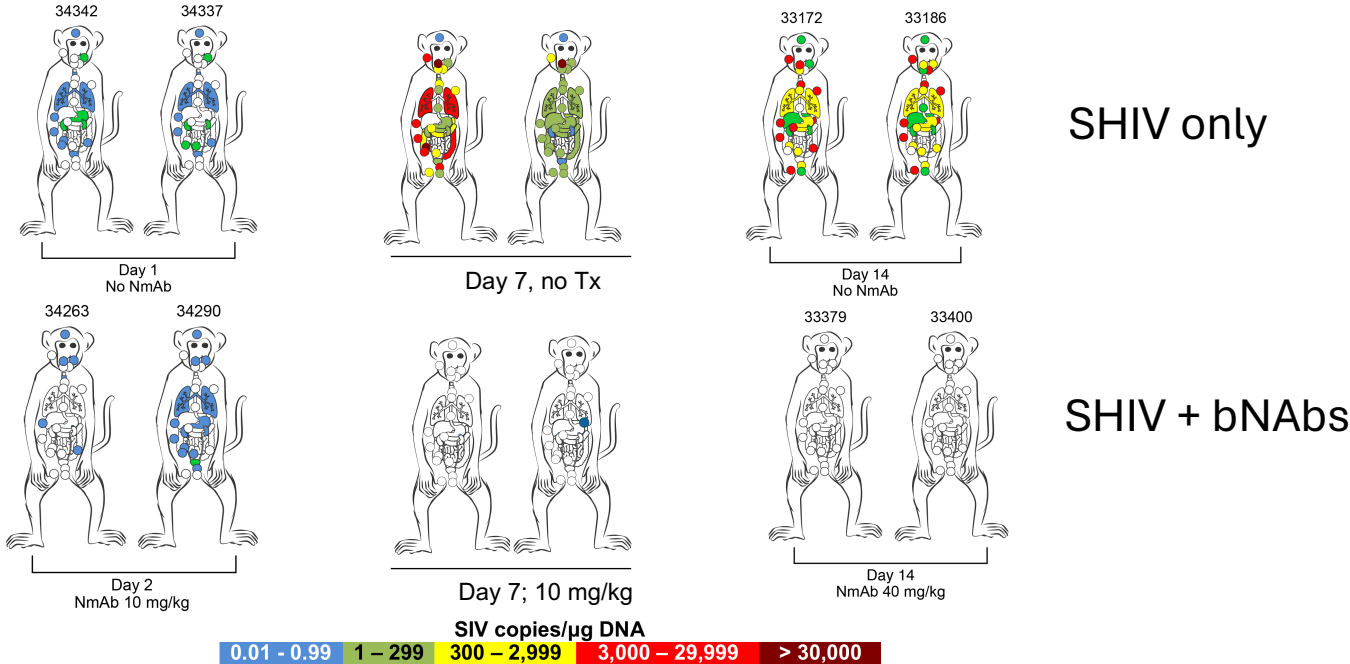
Early short-term treatment with neutralizing human monoclonal antibodies halts SHIV infection in infant macaques

Ann J Hessel^{1,2}, J Pablo Jaworski¹, Erin Epton¹, Kenta Matsuda³, Shilpi Pandey¹, Christoph Kahl¹, Jason Reed², William F Sutton¹, Katherine B Hammond², Tracy A Cheever¹, Philip T Barnette¹, Alfred W Legasse¹, Shannon Planer¹, Jeffrey J Stanton¹, Amarendra Pegu⁴, Xuejun Chen⁴, Keyun Wang⁴, Don Siess¹, David Burke¹, Byung S Park¹, Michael K Axthelm^{1,2}, Anne Lewis¹, Vanessa M Hirsch³, Barney S Graham⁴, John R Mascola⁴, Jonah B Sacha^{1,2} & Nancy L Haigwood^{1,2}

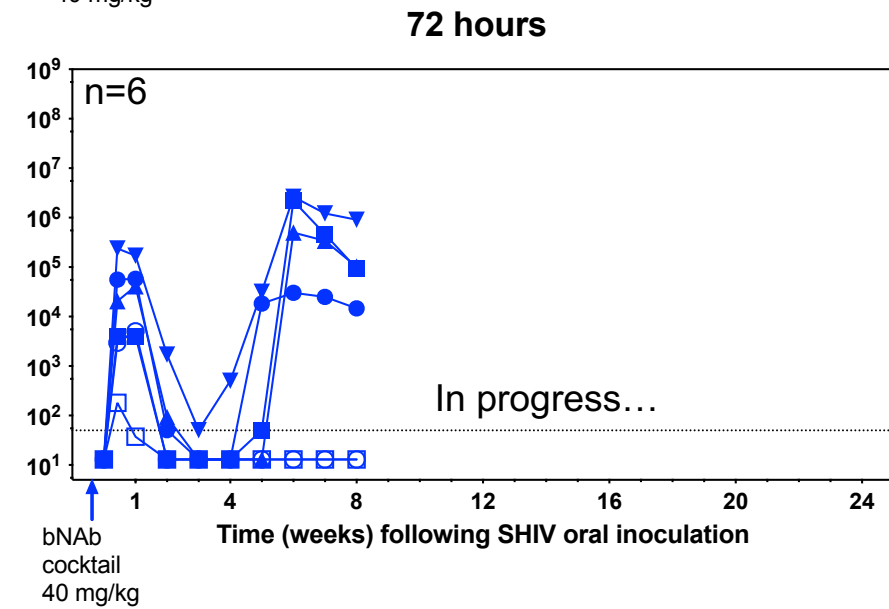
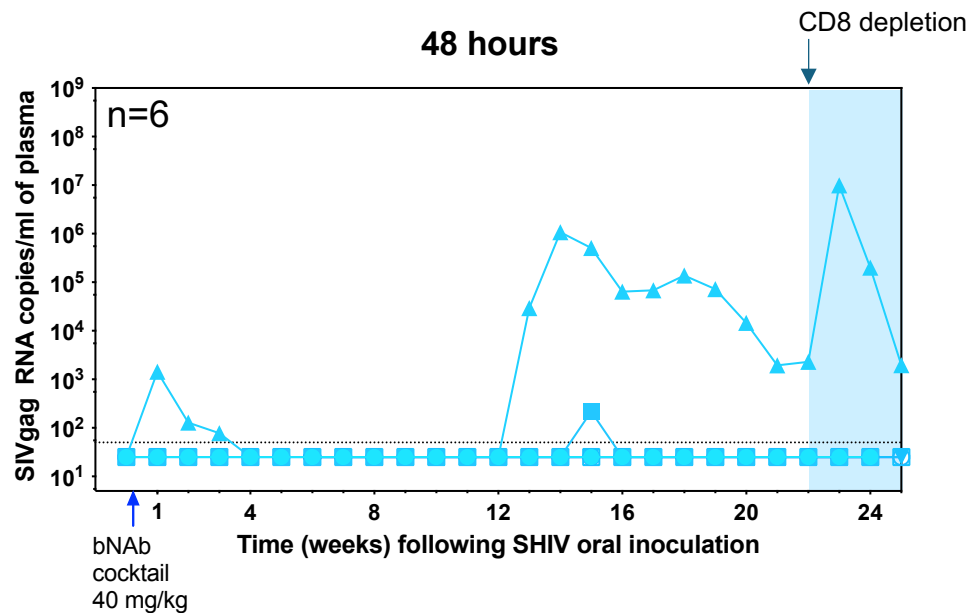
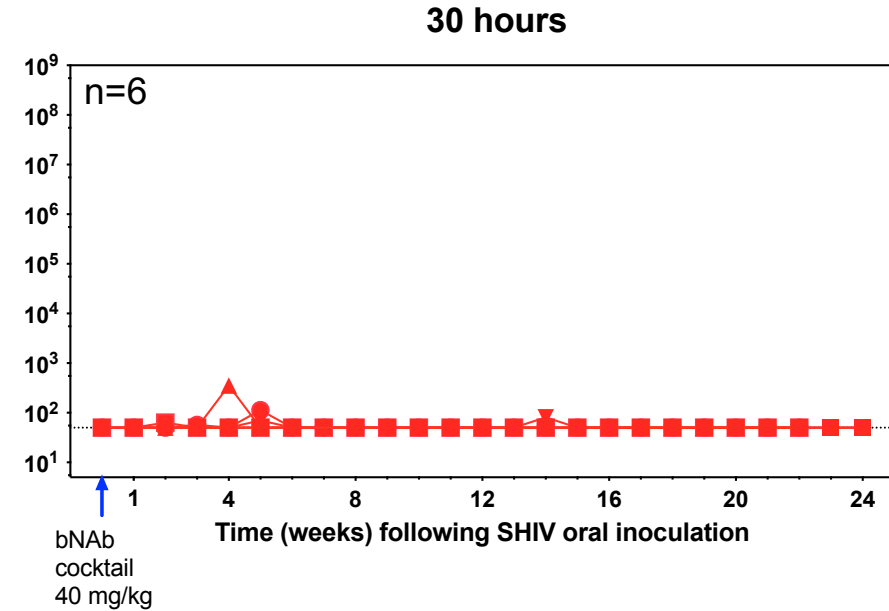
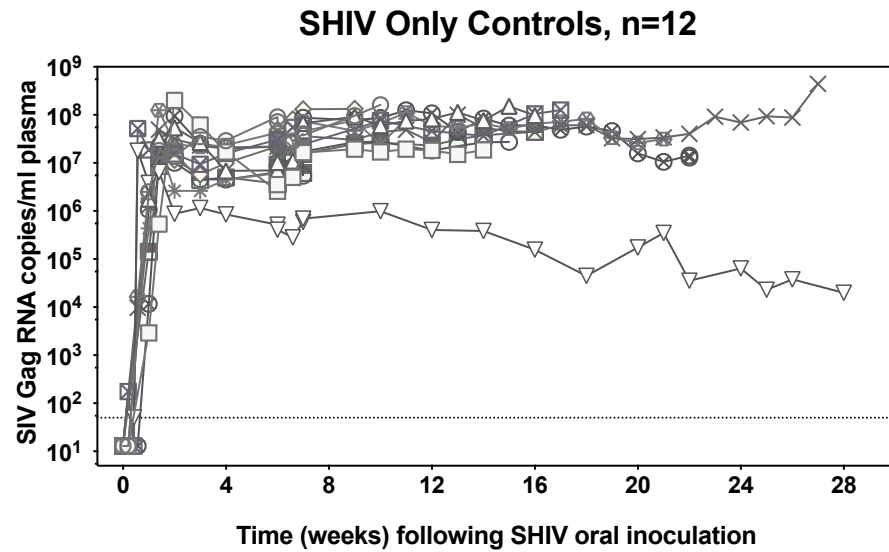


Single-dose bNAbs cocktail or abbreviated ART post-exposure regimens achieve tight SHIV control without adaptive immunity

Mariya B. Shapiro¹, Tracy Cheever², Delphine C. Malherbe^{2,8}, Shilpi Pandey², Jason Reed³, Eun Sung Yang⁴, Keyun Wang⁴, Amarendra Pegu⁴, Xuejun Chen⁴, Don Siess⁵, David Burke⁵, Heidi Henderson², Rebecca Lewinsohn², Miranda Fischer², Jeffrey J. Stanton⁶, Michael K. Axthelm², Christoph Kahl^{5,9}, Byung Park⁷, Anne D. Lewis⁶, Jonah B. Sacha^{1,2,3}, John R. Mascola⁴, Ann J. Hessel² & Nancy L. Haigwood^{1,2*}

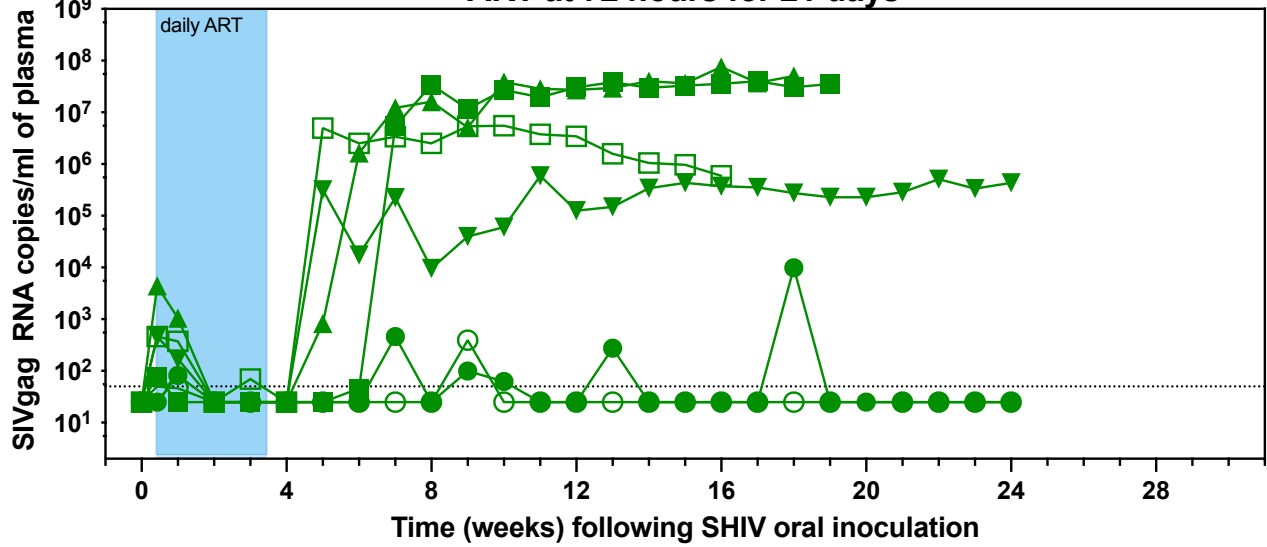


Window of opportunity for bNAb treatment <72 hrs

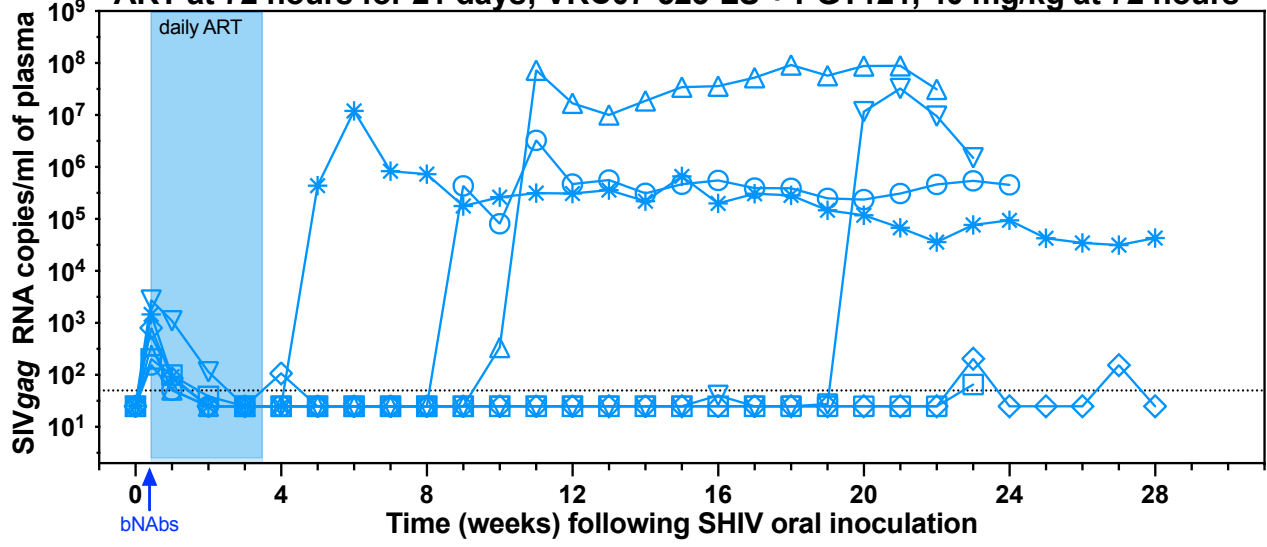


Short-term ART +/- bNAb at 72hrs results in rebound

ART at 72 hours for 21 days

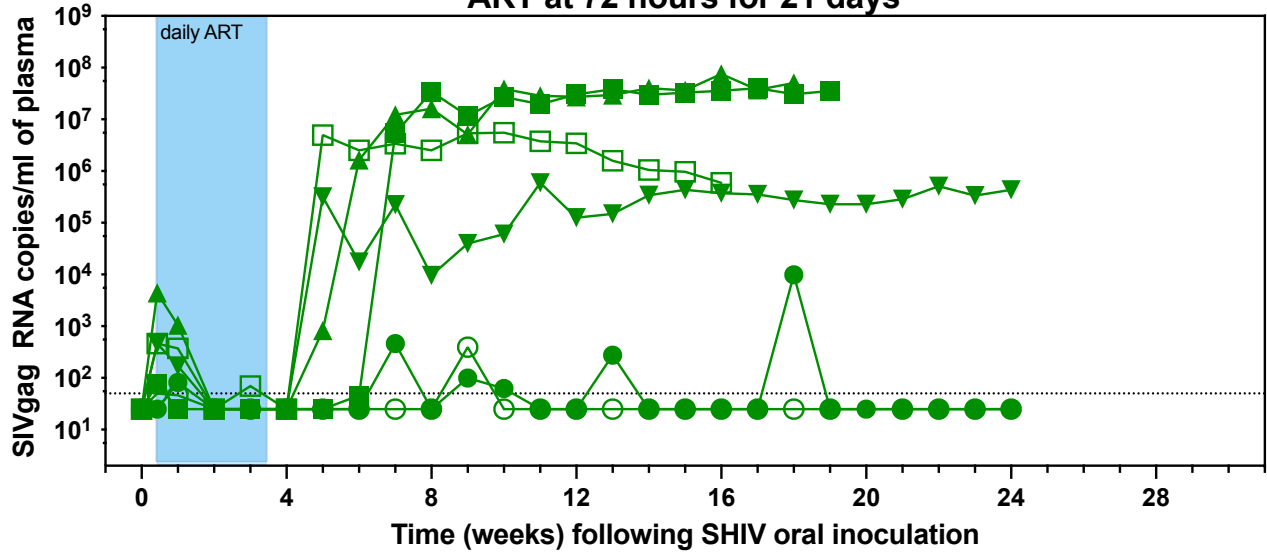


ART at 72 hours for 21 days; VRC07-523-LS + PGT121, 40 mg/kg at 72 hours

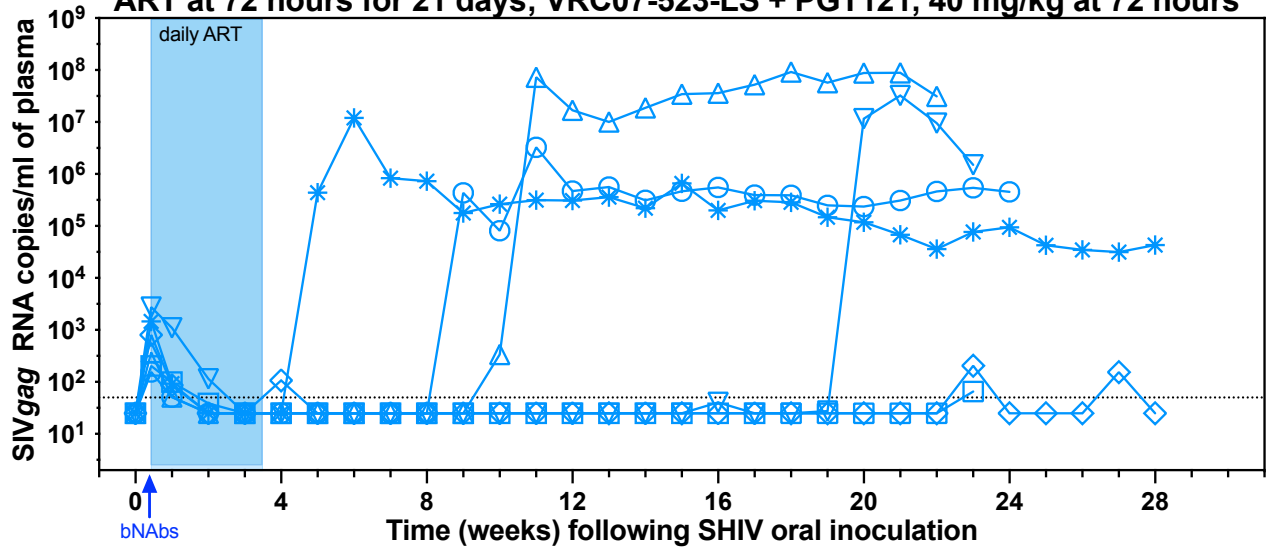


Short-term ART +/- bNAb at 72hrs results in rebound

ART at 72 hours for 21 days

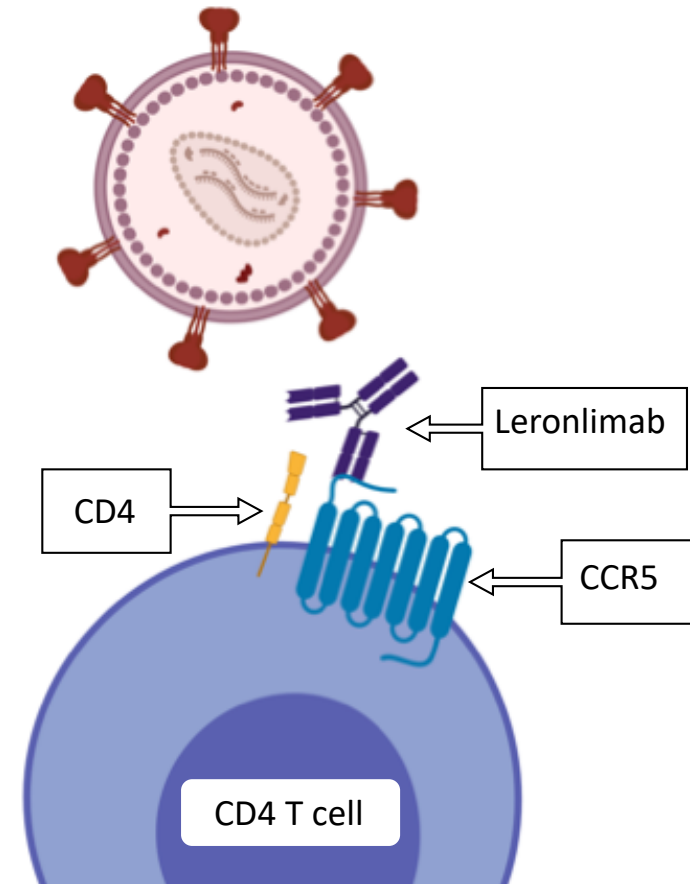


ART at 72 hours for 21 days; VRC07-523-LS + PGT121, 40 mg/kg at 72 hours



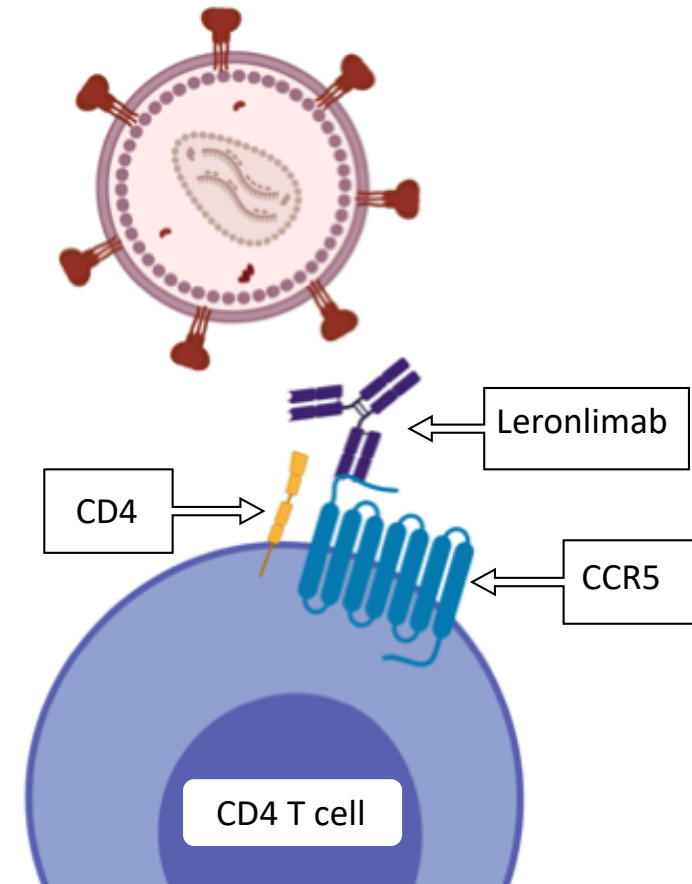
Would CCR5 blockade alone, or in combination, be effective at 72 hours post infection in infants?

Leronlimab (formerly PRO140)



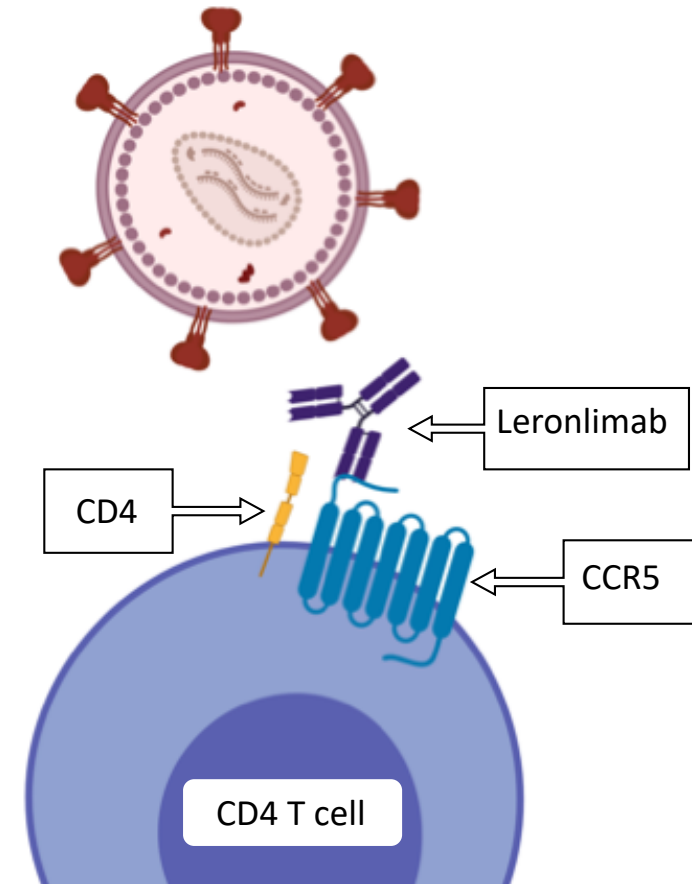
Leronlimab (formerly PRO140)

- Humanized monoclonal IgG4 antibody



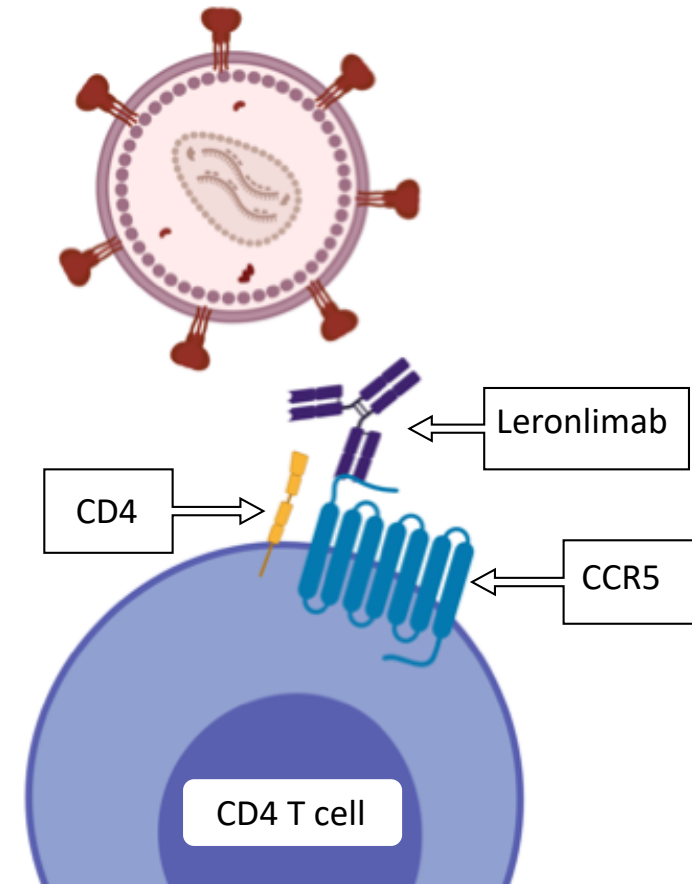
Leronlimab (formerly PRO140)

- Humanized monoclonal IgG4 antibody
- Binds to N-terminus and ECL2 of CCR5



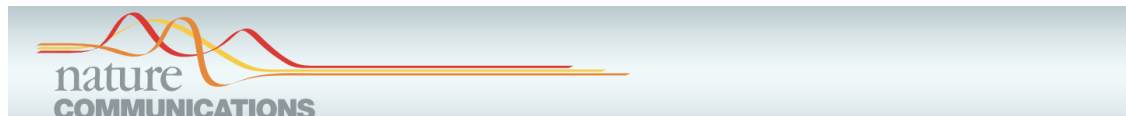
Leronlimab (formerly PRO140)

- Humanized monoclonal IgG4 antibody
- Binds to N-terminus and ECL2 of CCR5
- In clinical trials
 - High safety profile - tested in over 1,000 PLWH



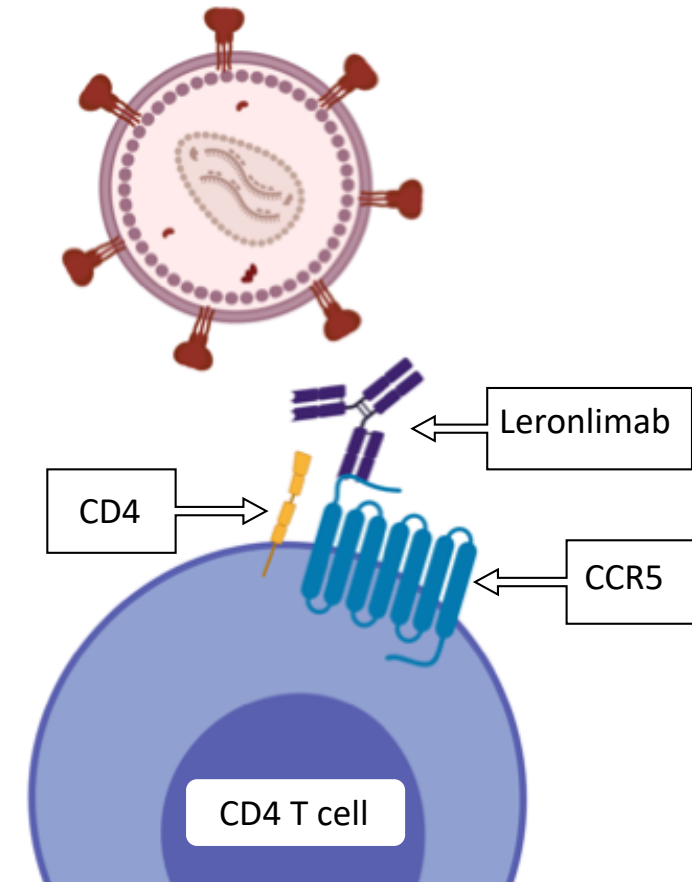
Leronlimab (formerly PRO140)

- Humanized monoclonal IgG4 antibody
- Binds to N-terminus and ECL2 of CCR5
- In clinical trials
 - High safety profile - tested in over 1,000 PLWH
 - Successfully used as PrEP to protect from mucosal SHIV acquisition



Antibody-based CCR5 blockade protects Macaques from mucosal SHIV transmission

Xiao L. Chang^{1,2,10}, Gabriela M. Webb^{1,2,10}, Helen L. Wu^{1,2}, Justin M. Greene¹, Shaheed Abdulhaqq¹, Katherine B. Bateman¹, Jason S. Reed¹, Cleiton Pessoa¹, Whitney C. Weber¹, Nicholas Maier¹, Glen M. Chew³, Roxanne M. Gilbride¹, Lina Gao², Rebecca Agnor², Travis Giobbi², Jeffrey Torgerson², Don Siess², Nicole Burnett², Miranda Fischer², Oriene Shiel², Cassandra Moats², Bruce Patterson⁴, Kush Dhody⁵, Scott Kelly⁶, Nader Pourhassan⁶, Diogo M. Magnani⁷, Jeremy Smedley², Benjamin N. Bimber^{1,2}, Nancy L. Haigwood¹, Scott G. Hansen¹, Timothy R. Brown⁸, Lishomwa C. Ndhlovu^{9,11} & Jonah B. Sacha^{1,2,11}



Combining ART, bNAbs, and LRM for cure



Control (n=2)

high dose oral
SHIV_{SF162P3}



day 3

week 8

week 27

...

Combining ART, bNAbs, and LRM for cure



Control (n=2)



ART + bNAbs (n=2)

high dose oral
SHIV_{SF162P3}

PGT121 + VRC07
(40 mg/kg)

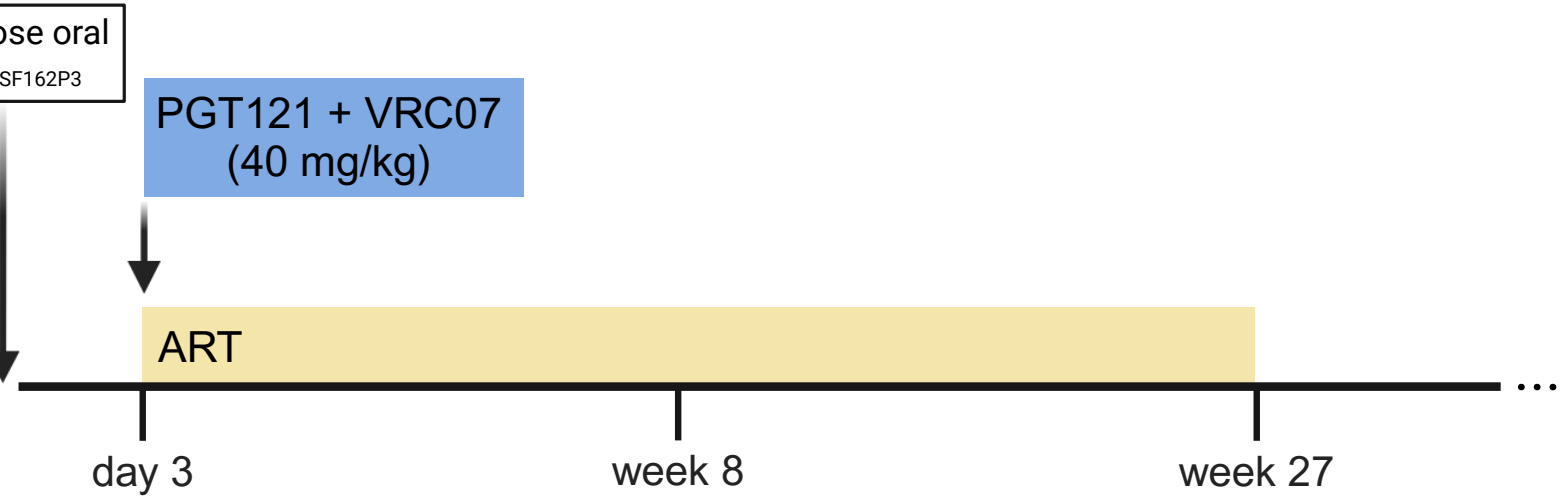
ART

day 3

week 8

week 27

...



Combining ART, bNAbs, and LRM for cure



Control (n=2)

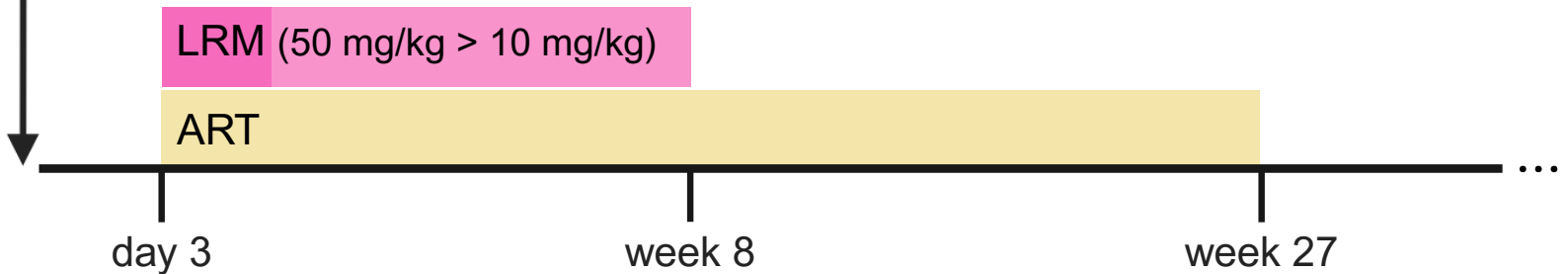


ART + bNAbs (n=2)



ART + LRM (n=6)

high dose oral
SHIV_{SF162P3}



Combining ART, bNAbs, and LRM for cure



Control (n=2)



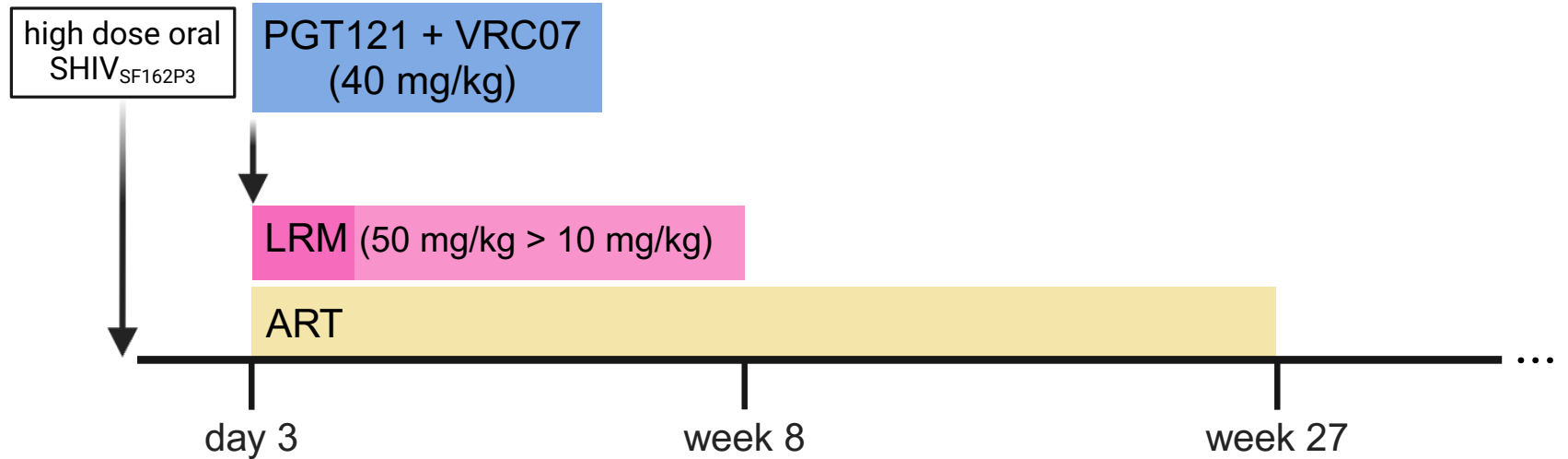
ART + bNAbs (n=2)



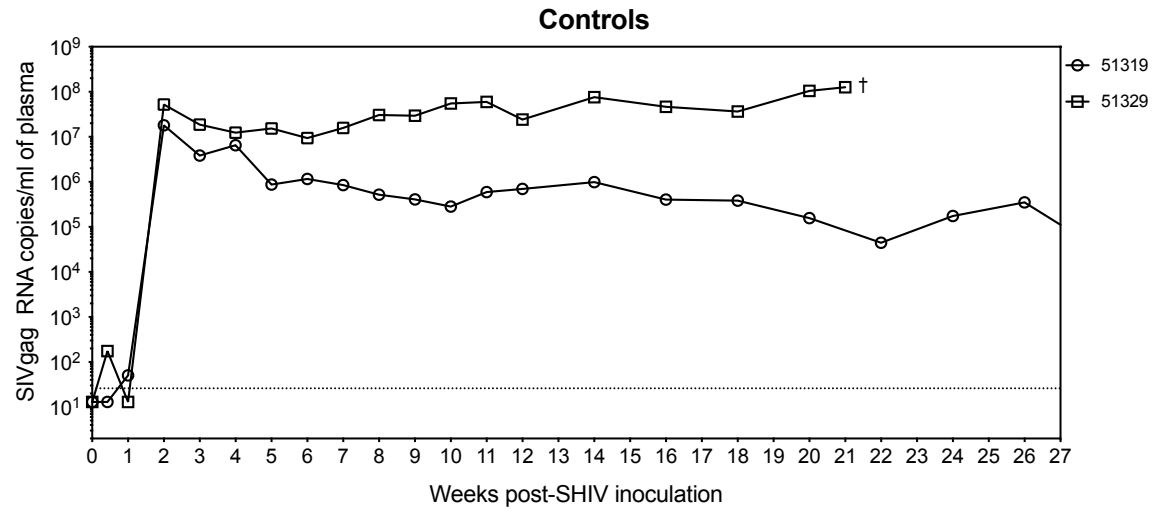
ART + LRM (n=6)



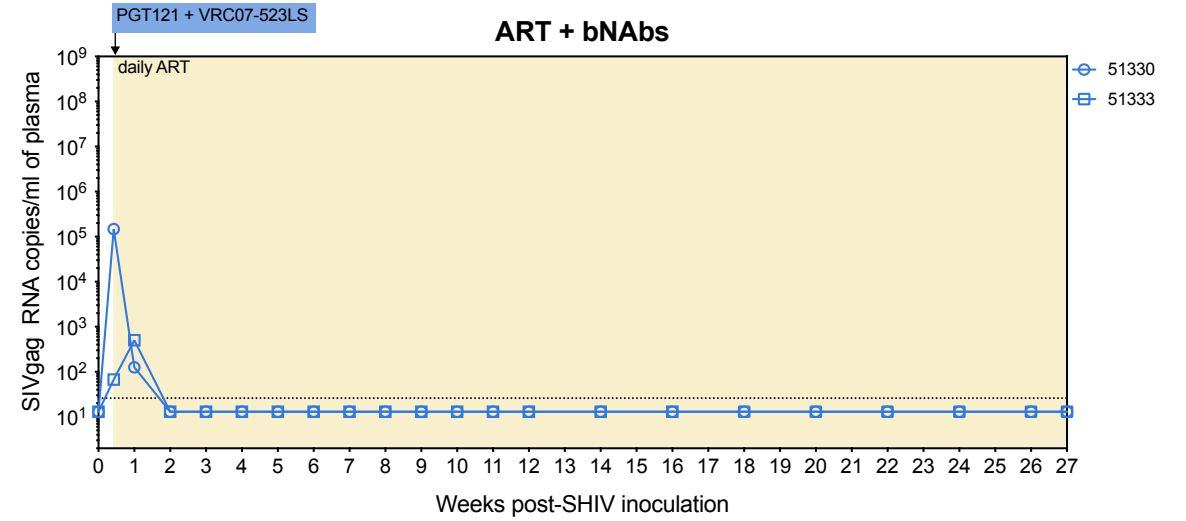
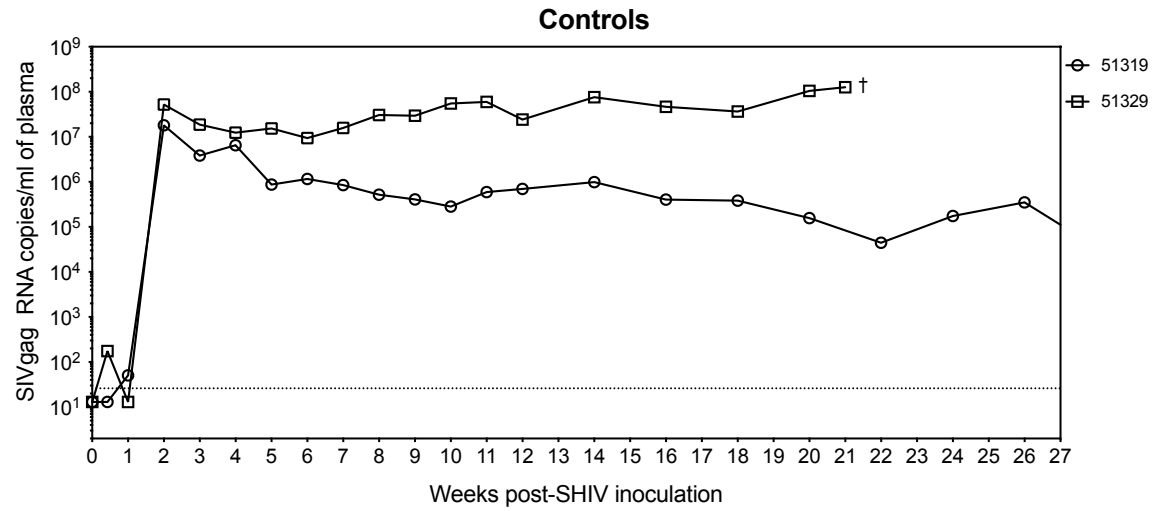
ART + bNAbs + LRM (n=8)



Plasma viral load monitoring

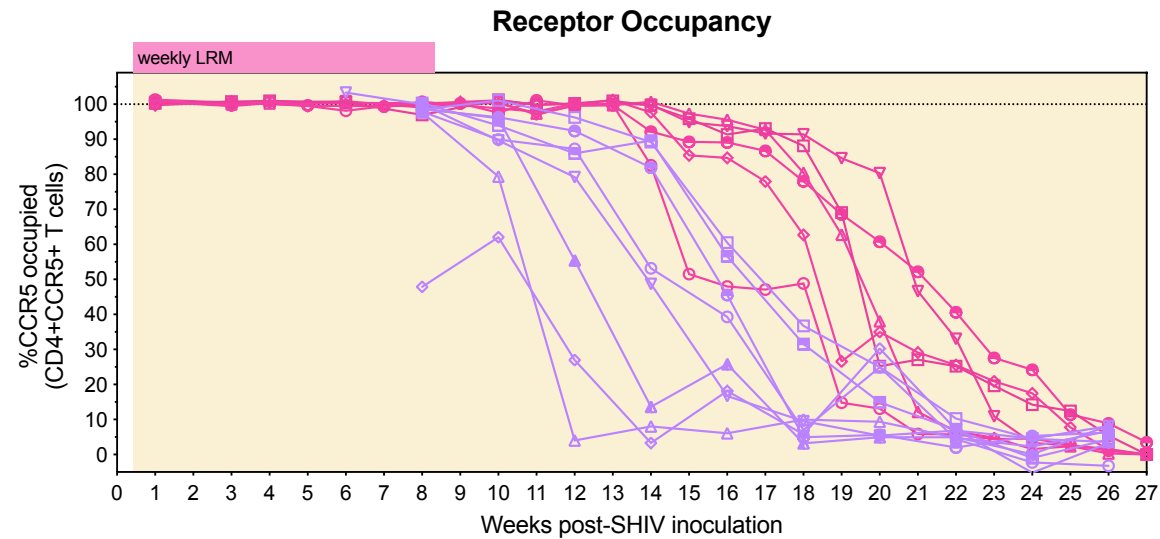
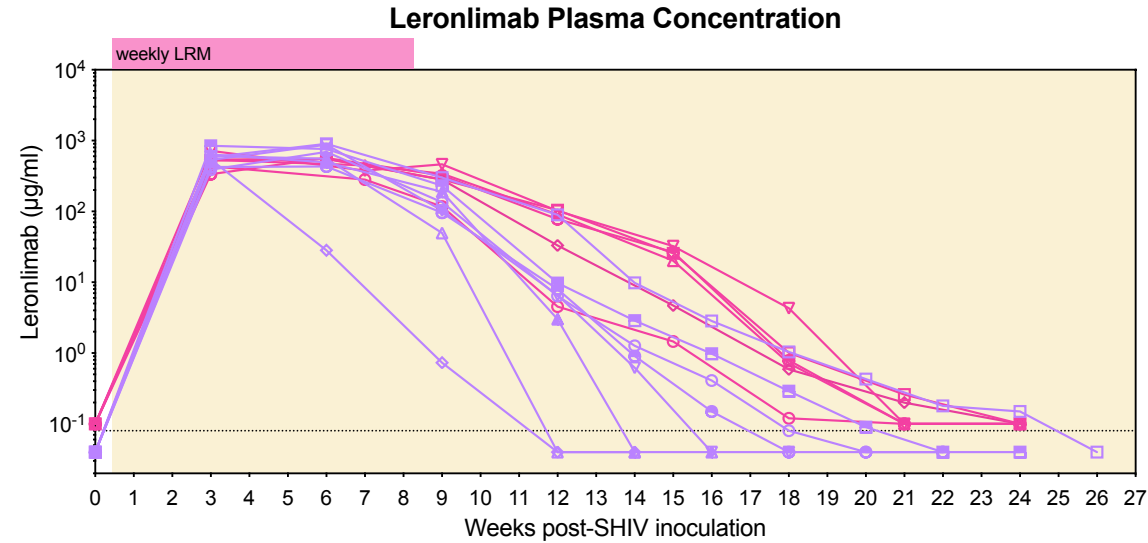


Plasma viral load monitoring



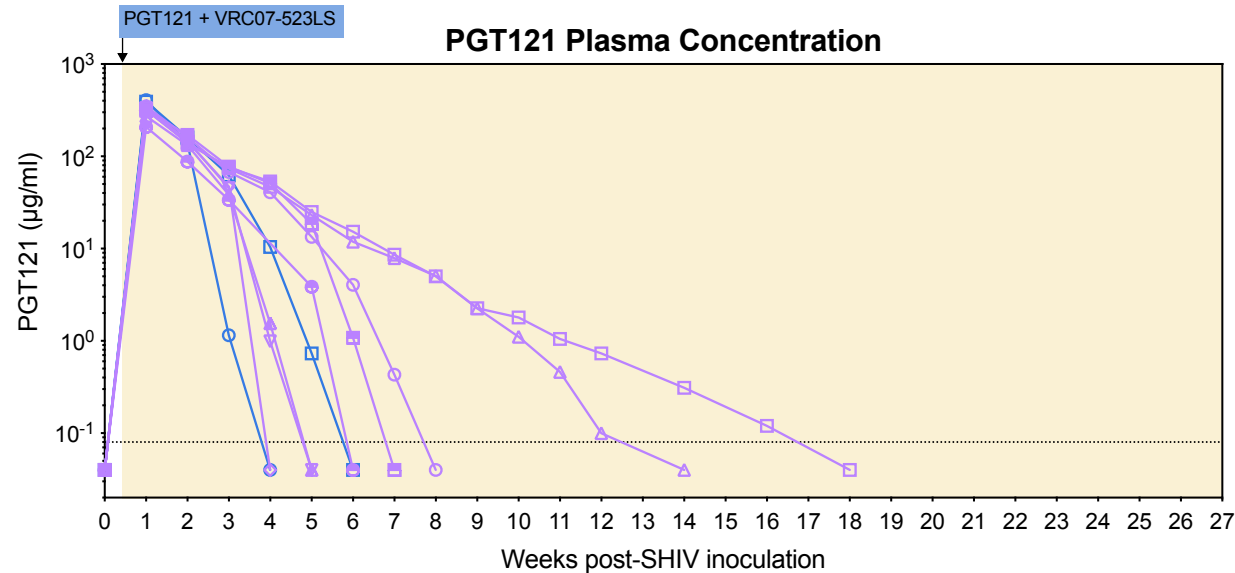
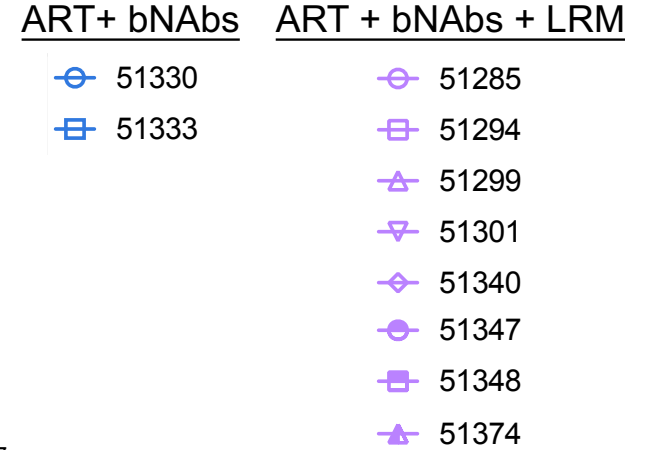
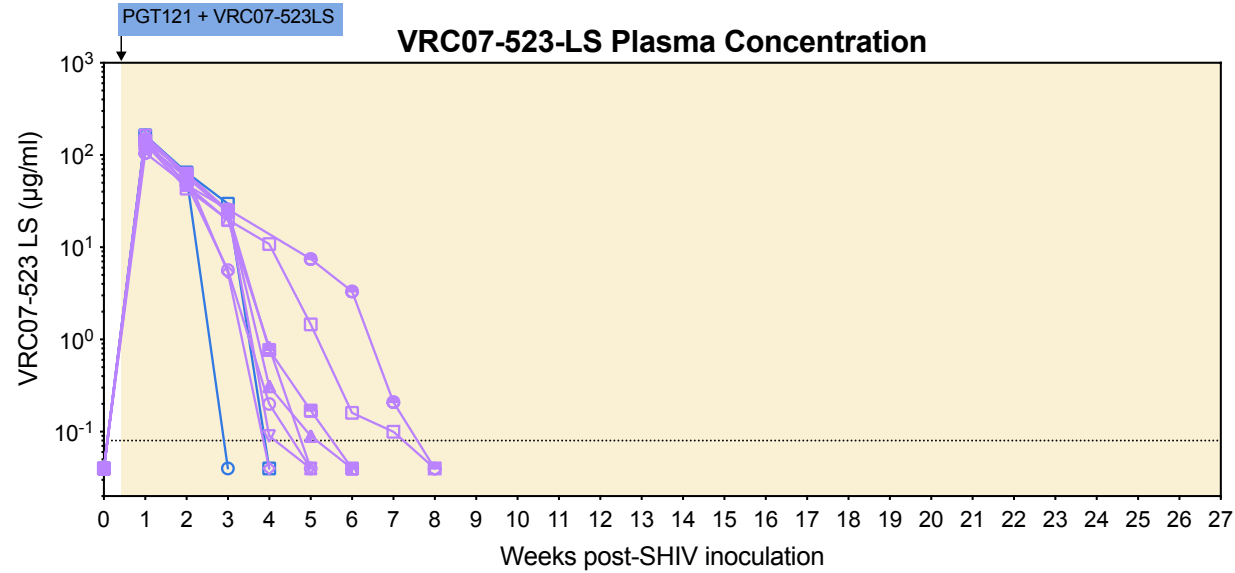
Leronlimab

Plasma concentration and receptor occupancy

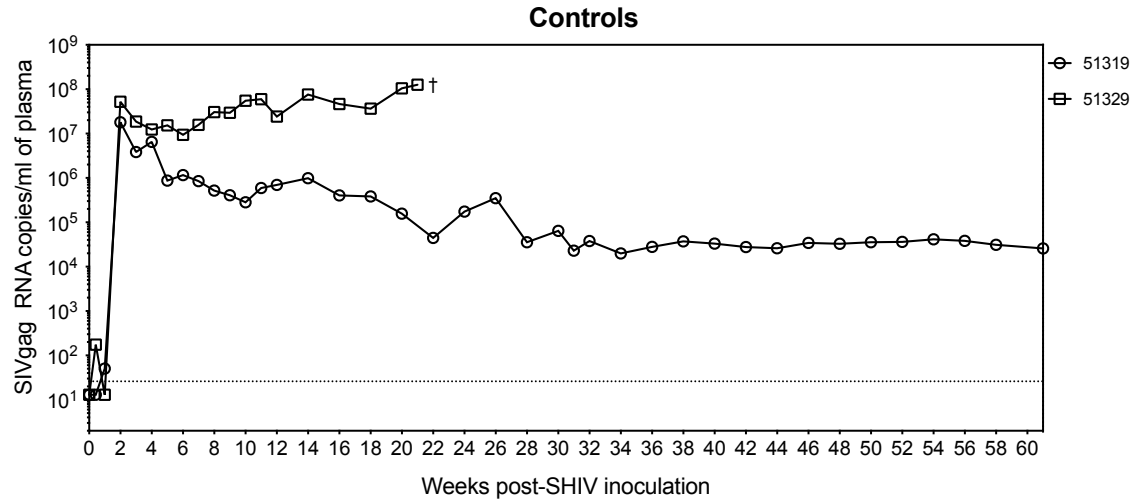


bNAbs (VRC07-523LS & PGT121)

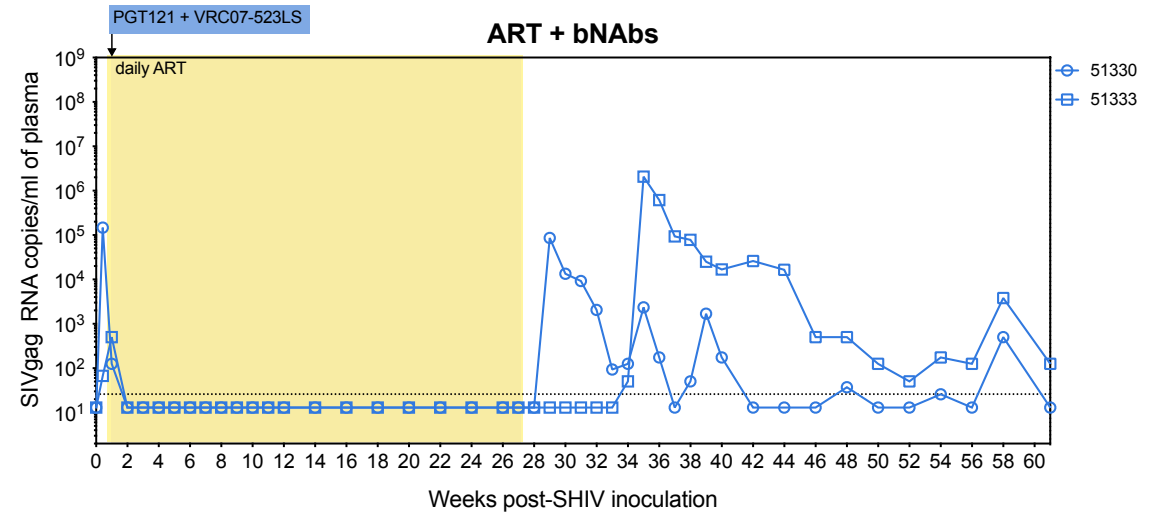
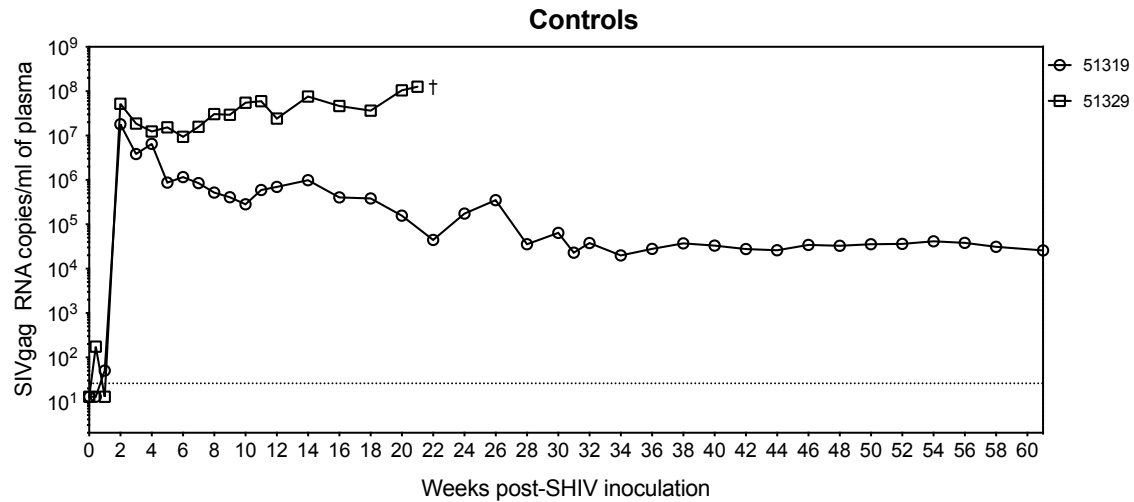
Plasma concentrations



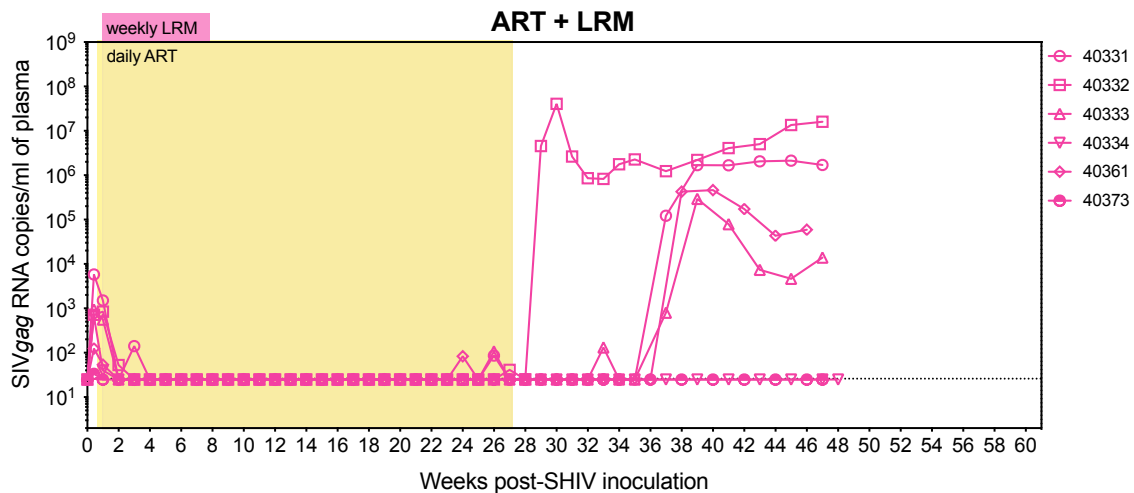
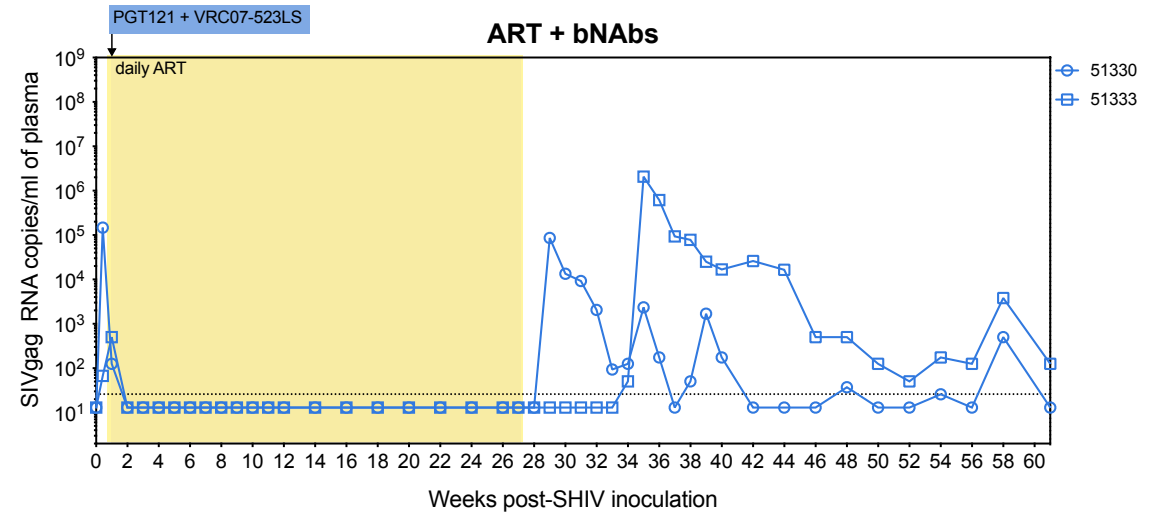
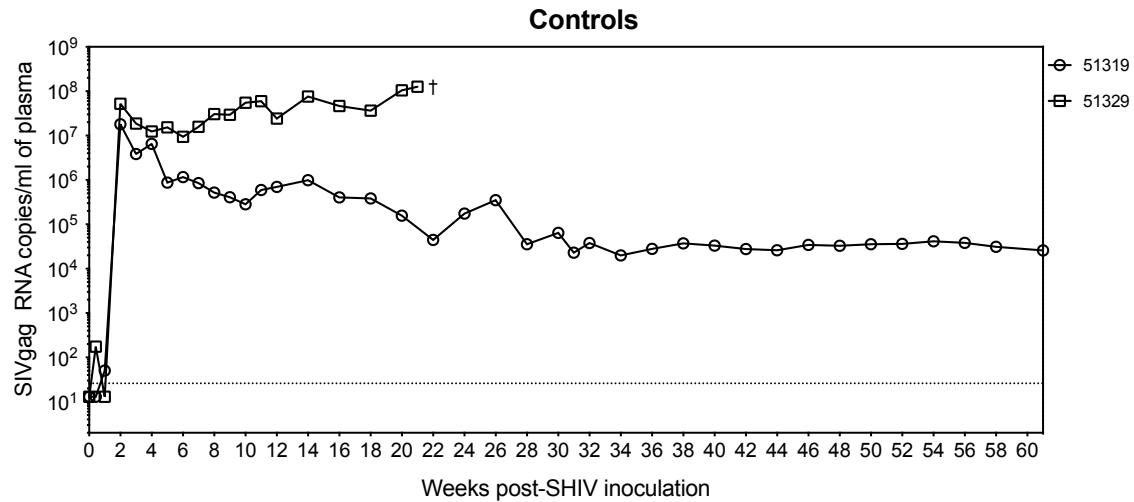
Plasma viral load monitoring *post-ART release*



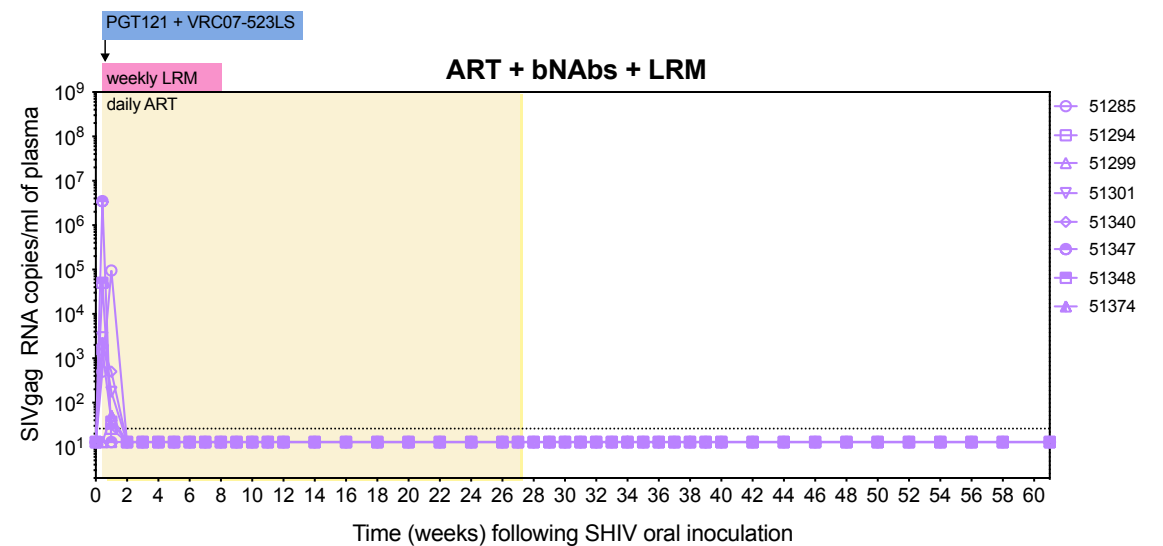
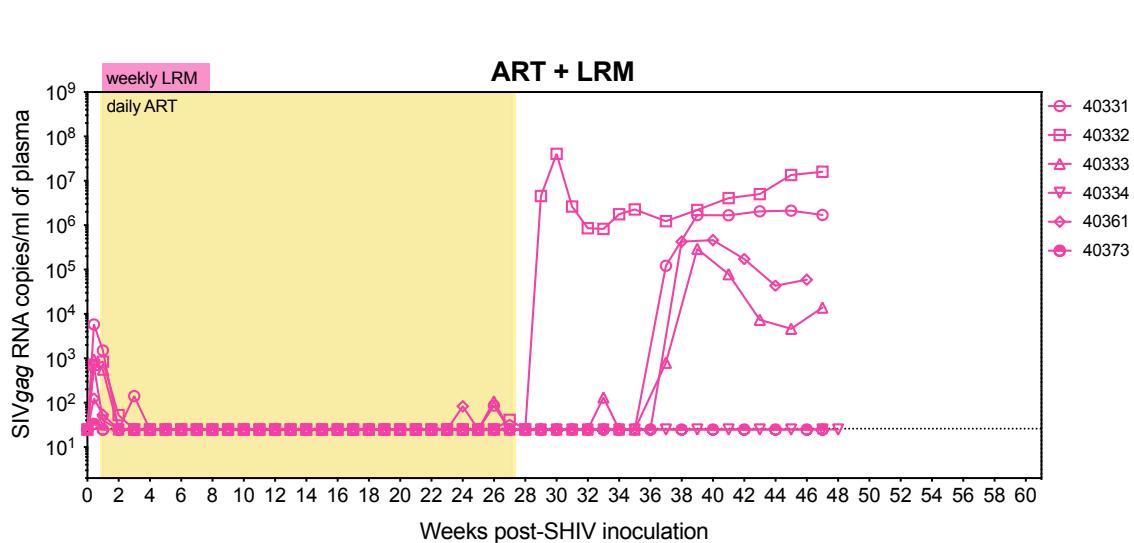
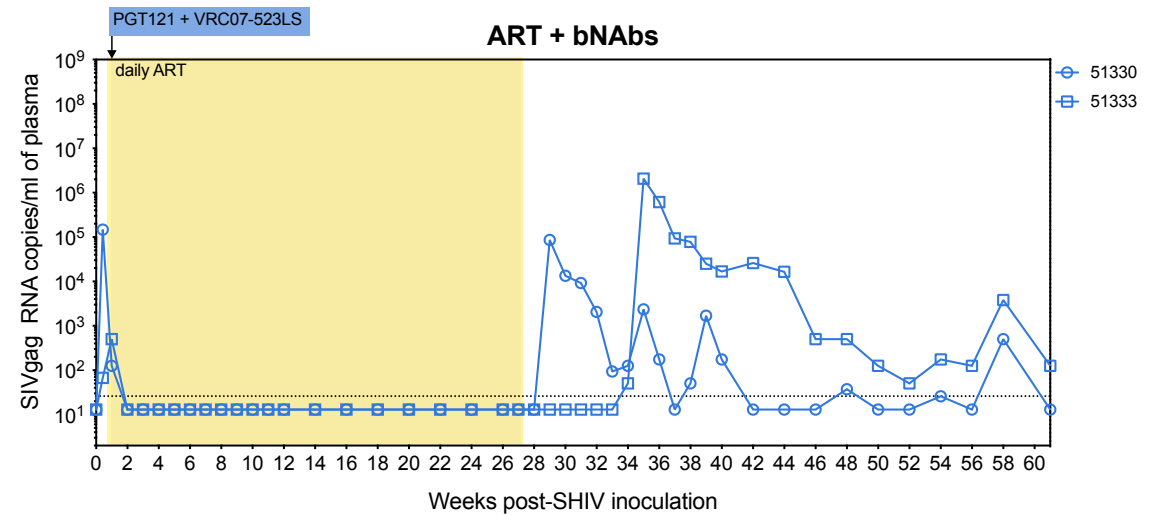
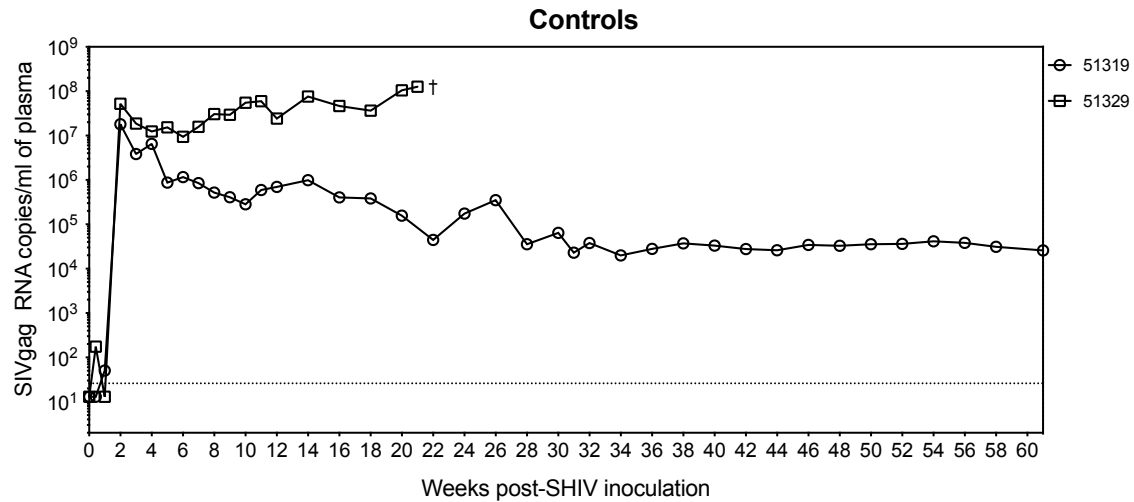
Plasma viral load monitoring *post-ART release*



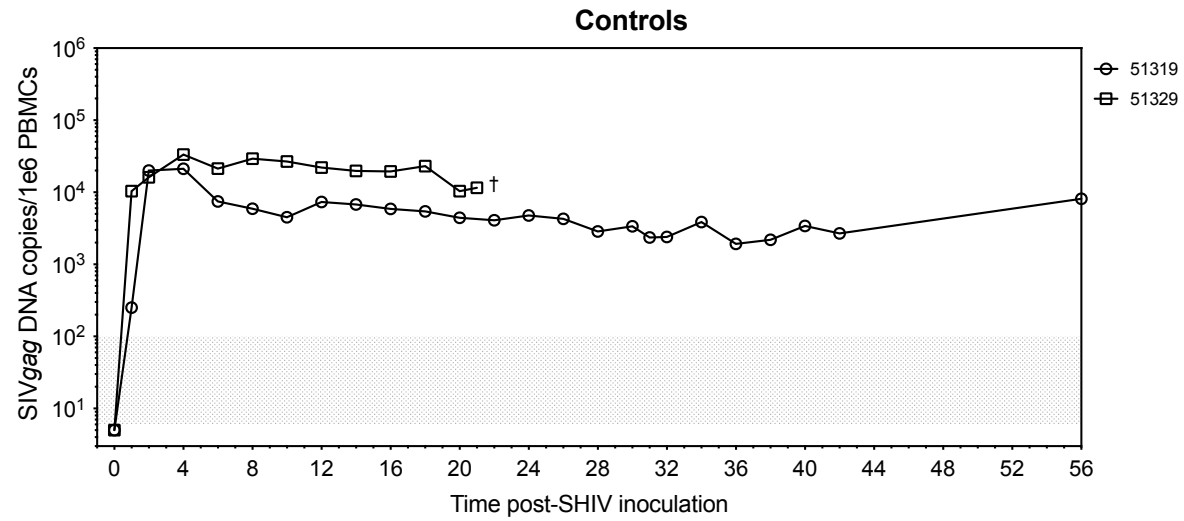
Plasma viral load monitoring *post-ART release*



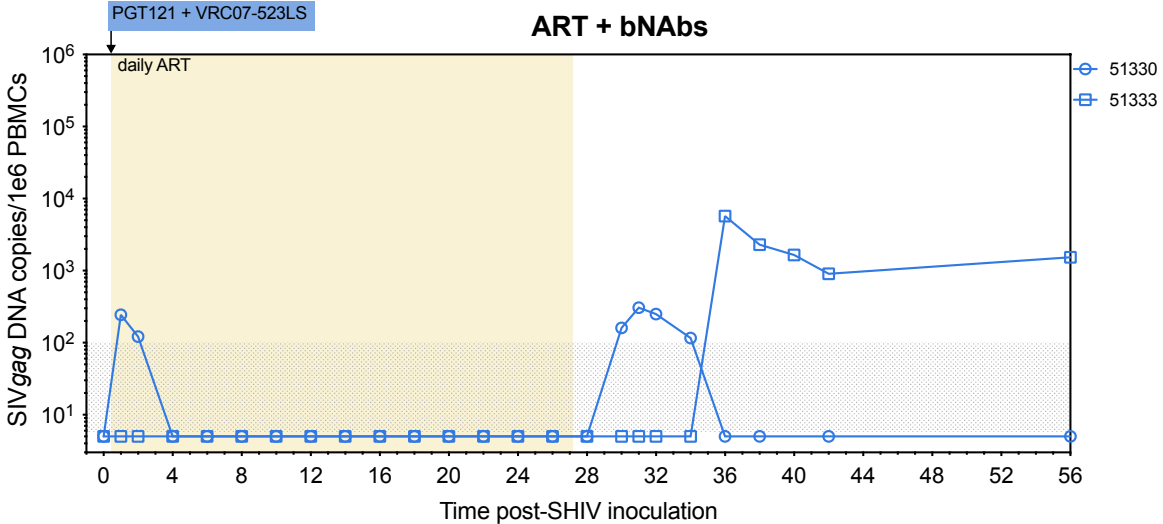
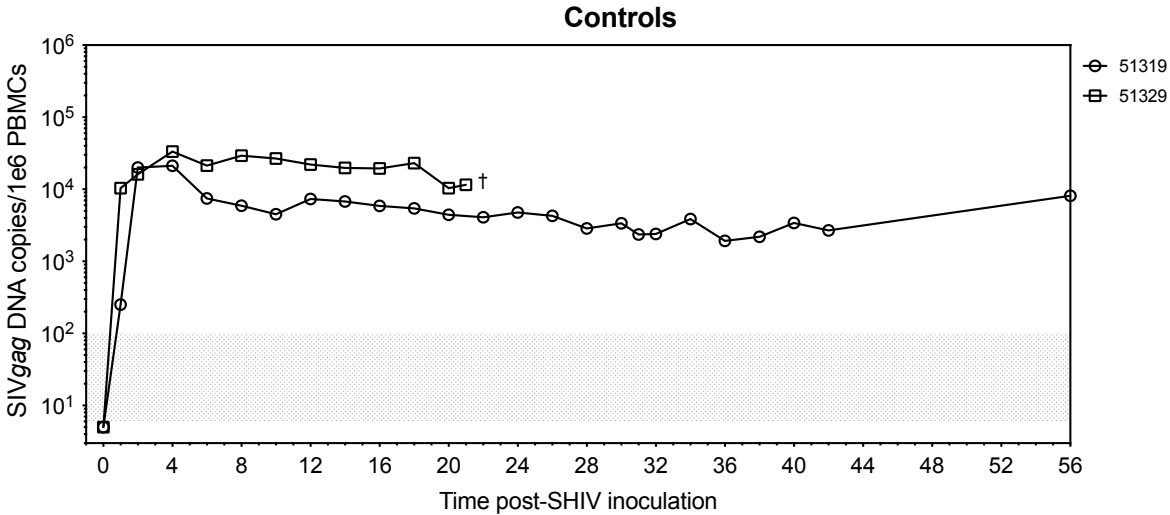
Plasma viral load monitoring *post-ART release*



Cell-associated viral DNA monitoring

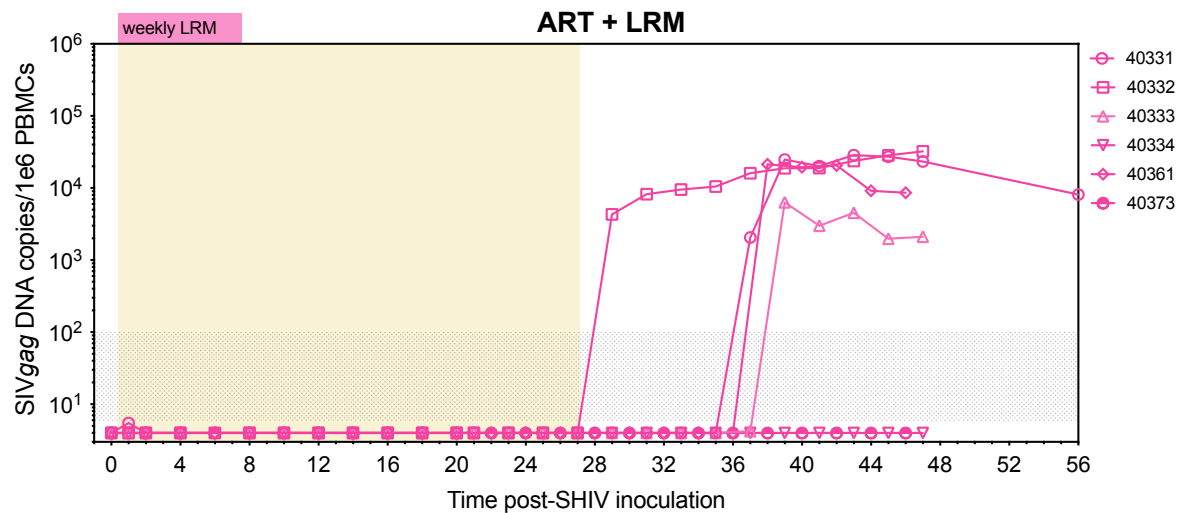
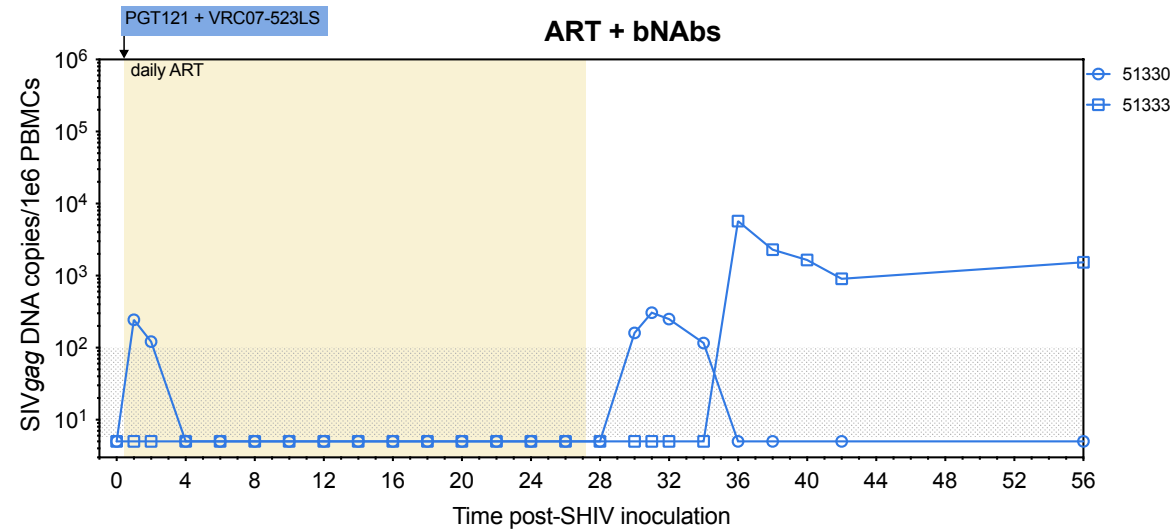
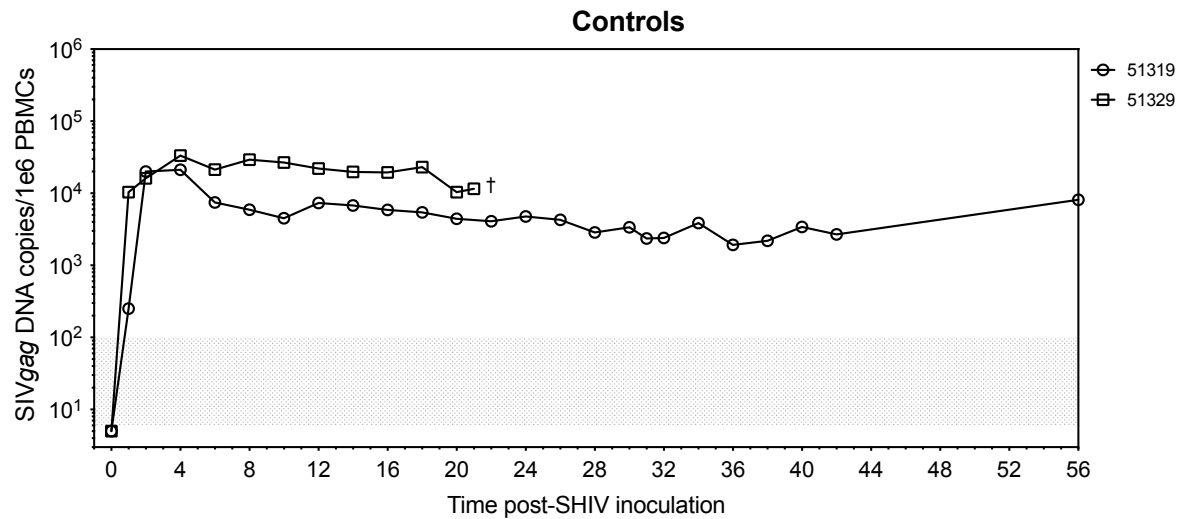


Cell-associated viral DNA monitoring

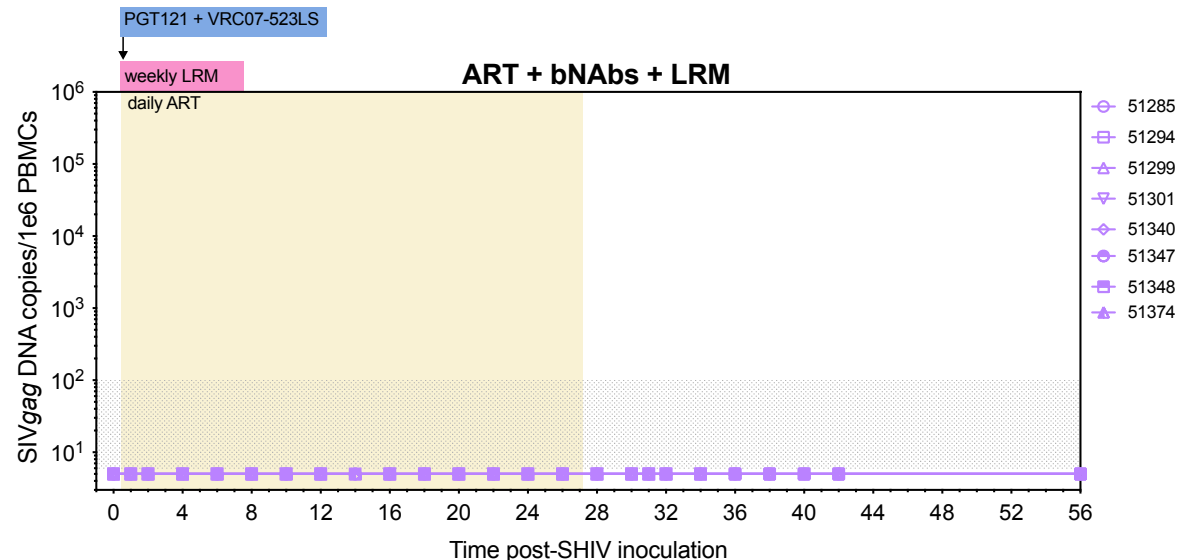
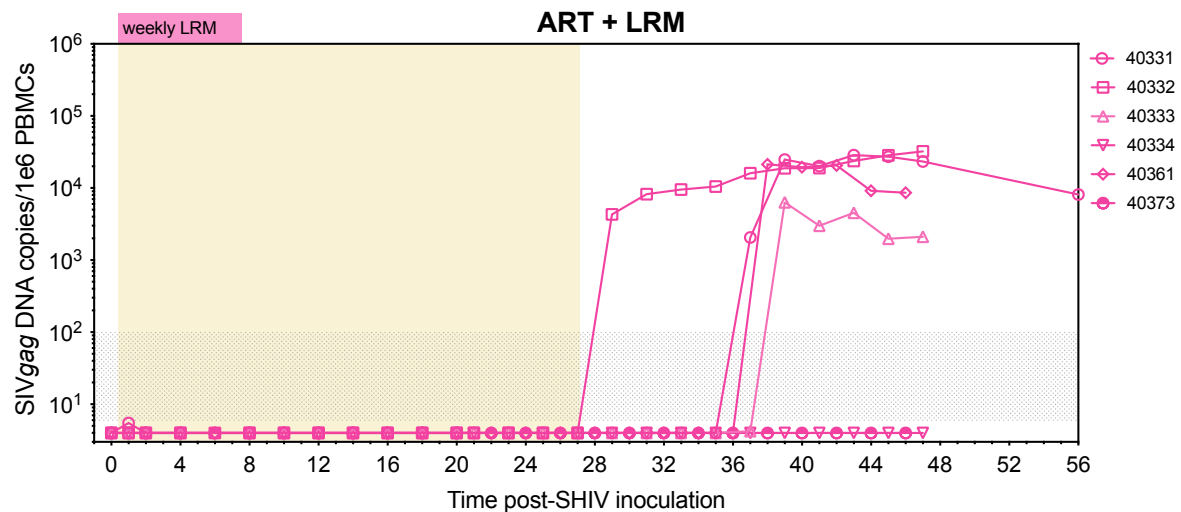
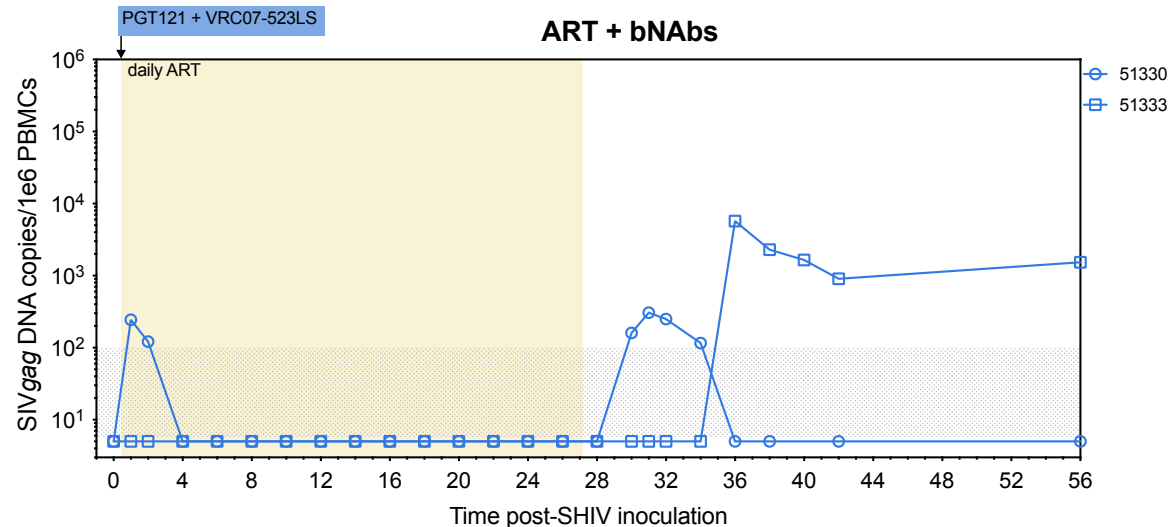
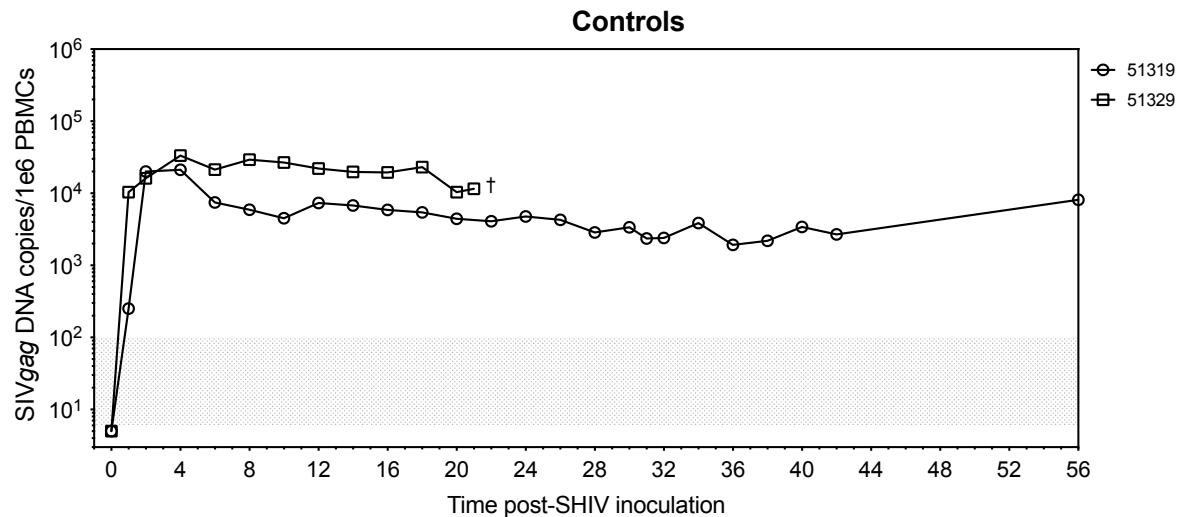


Shaded area indicated LOD range

Cell-associated viral DNA monitoring



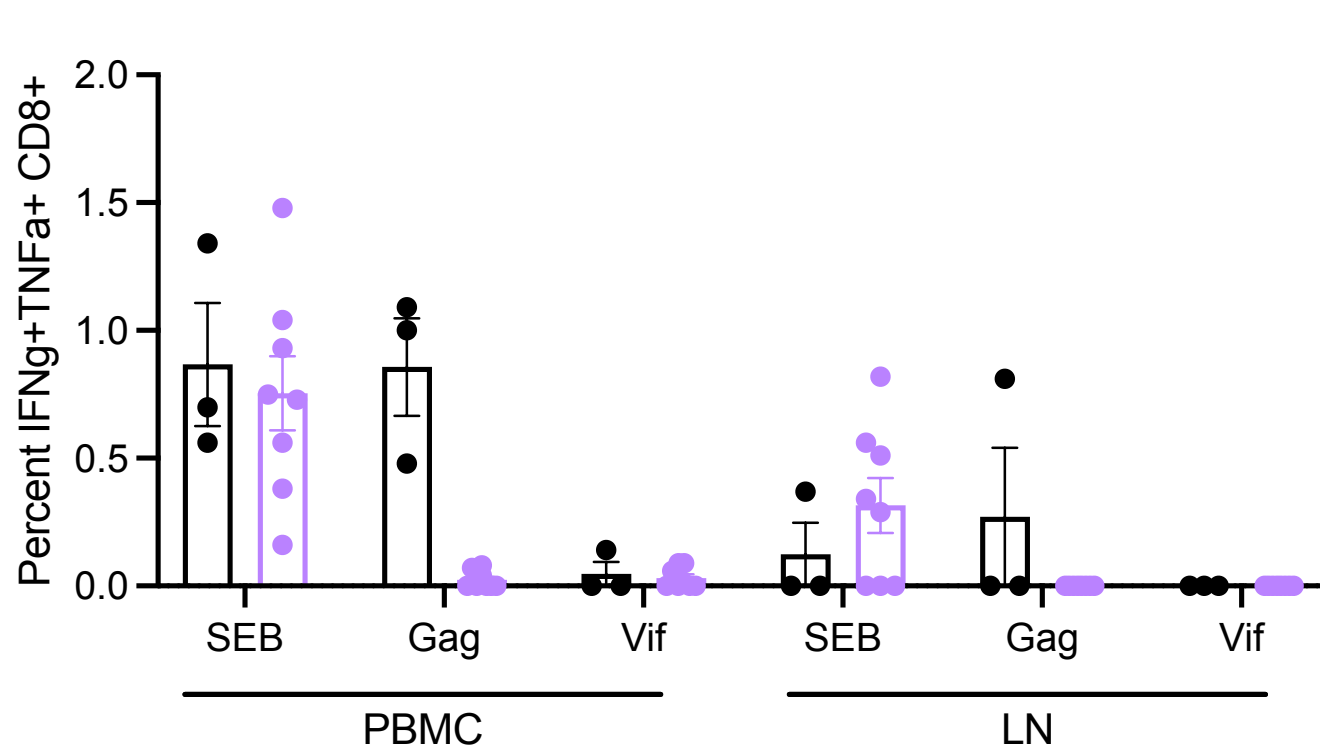
Cell-associated viral DNA monitoring



Shaded area indicated LOD range

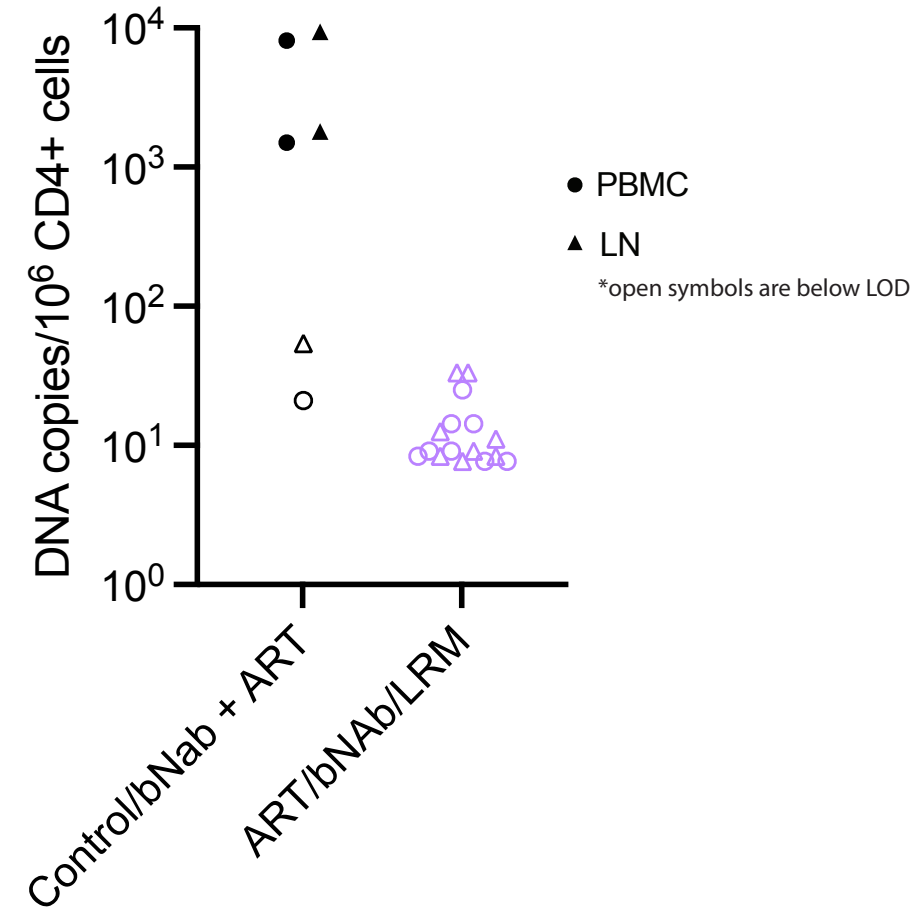
Immunological analysis and viral reservoir

Week 56 PBMC & LN



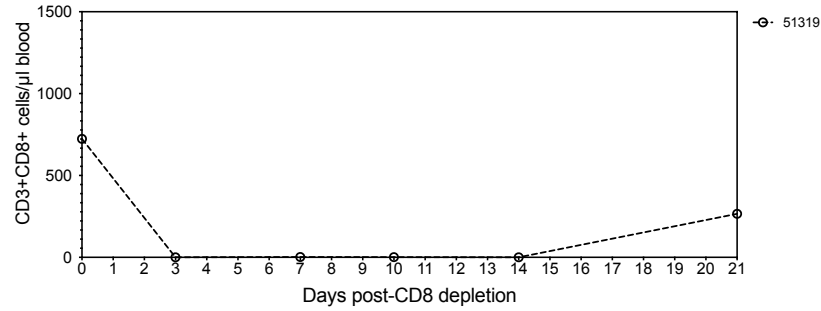
● controls (control/bNAB + ART)

● ART + bNAbs + LRM

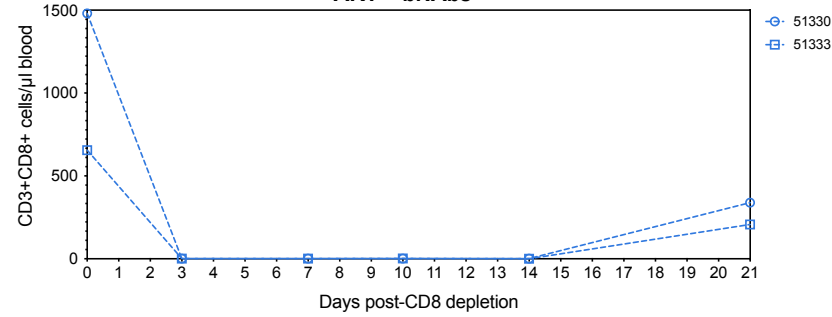


CD8 depletion at week 60

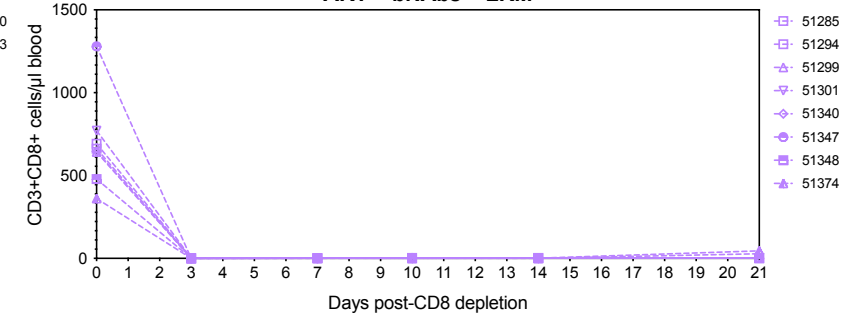
Controls



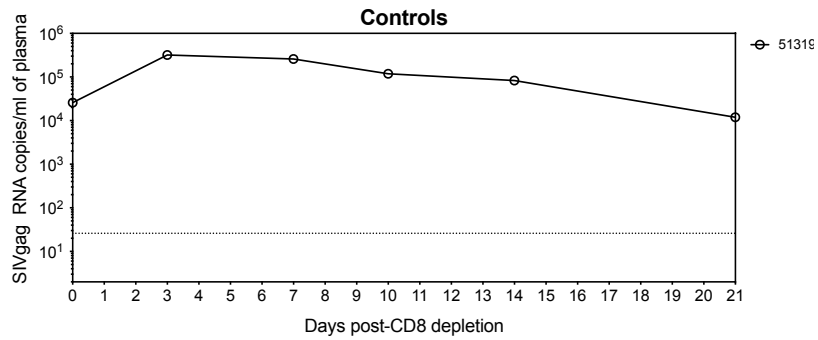
ART + bNAbs



ART + bNAbs + LRM

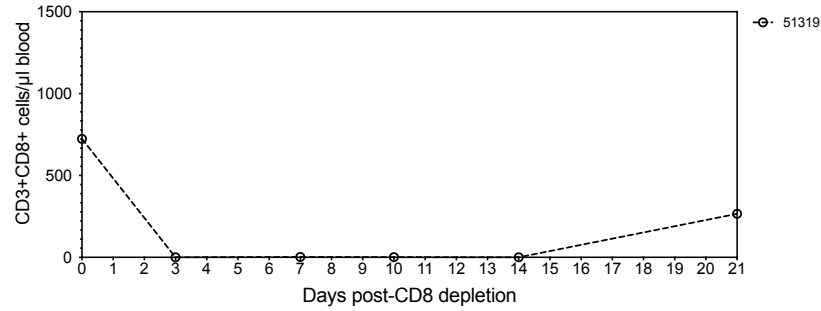


Controls

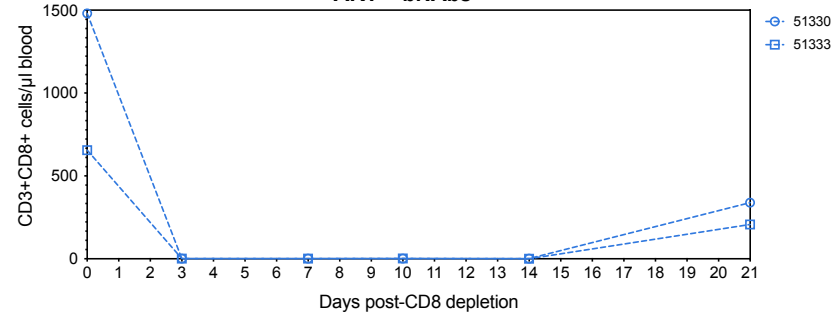


CD8 depletion at week 60

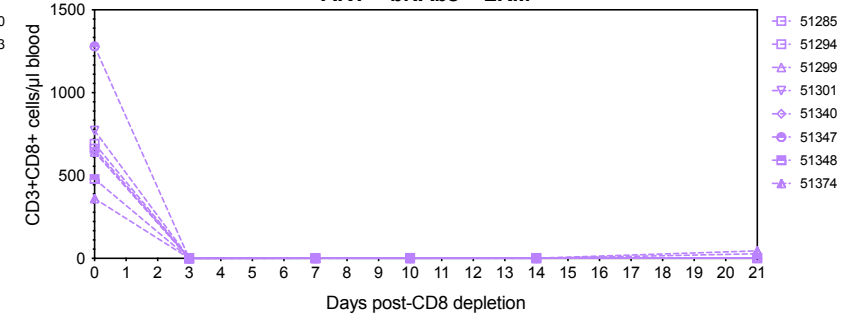
Controls



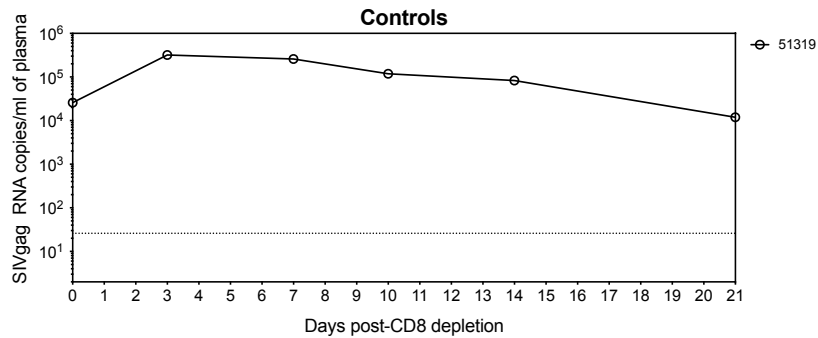
ART + bNAbs



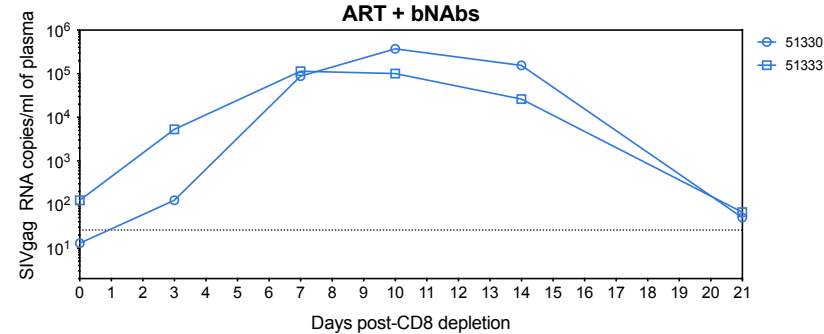
ART + bNAbs + LRM



Controls

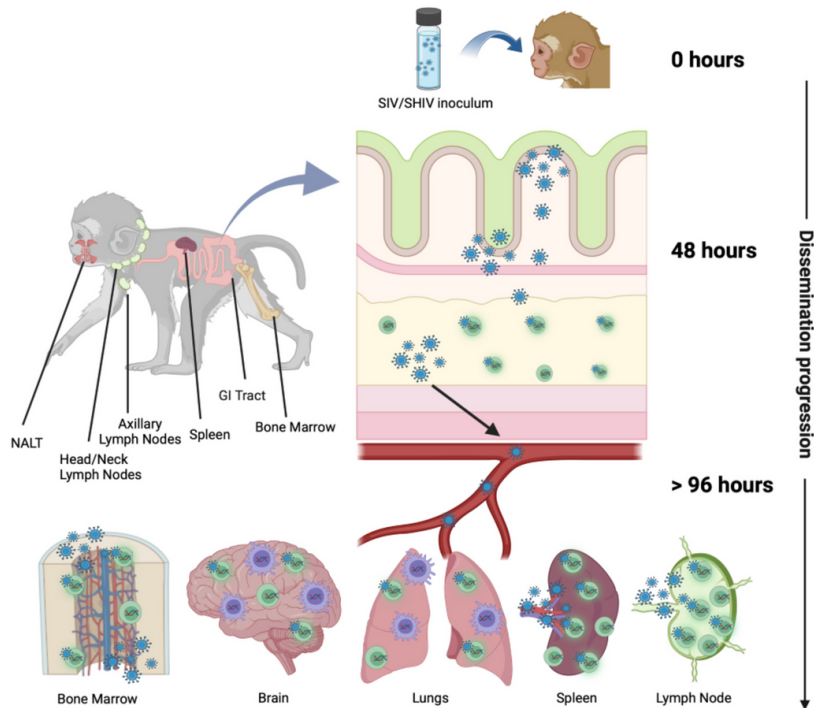


ART + bNAbs

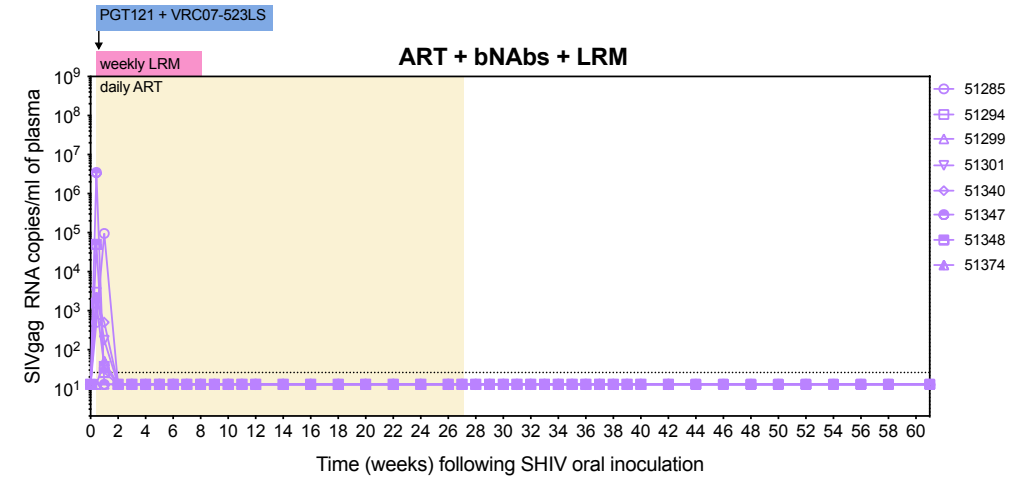


Conclusions & Future Directions

- CCR5 blockade synergizes with bNAbs to prevent reservoir establishment in SHIV-infected infant macaques



Fonseca et al. Current HIV/AIDS Report. 2024.



- Mechanism of synergy remains unclear –
 - Combinatorial antiviral efficacy?
 - Alteration in trafficking of infected cells?
 - Preventing reseeding of virus?
 - Other mechanisms?

Acknowledgements

Haigwood Laboratory

Nancy Haigwood

Tracy Ordonez

Shilpi Pandey

Ann Hessell

NIH/VRC

John Mascola

Xuejun Chen

Amar Pegu

Sacha Laboratory

Jonah Sacha

Jason Reed

Cleiton Pessoa

Hannah Fisher

Matthew Humkey

ONPRC

Scott Hansen

Kim Armantrout

Rachele

Bochart

Jeremy

Smedley

Tonya Swanson

Bree Fischer

Ann Lewis

UC Davis

Koen Van Rompay

Jennifer Watanabe

Jodie Usachenko

CNPRC husbandry staff



National Institutes
of Health

NIH P51 OD001092 and U42 (ONPRC);
R01-HD 080459 and R01-AI133712

