Strategies to Achieve ART-free HIV Remission: An Industry Perspective

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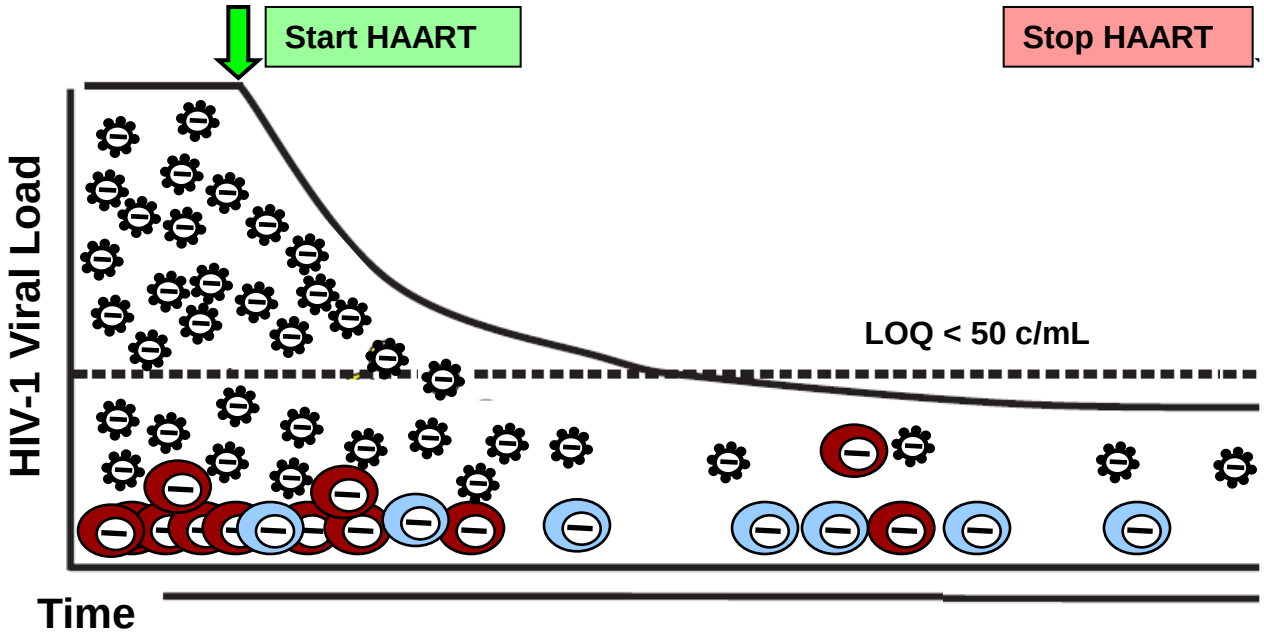
May 8, 2015
UCLA Grand Rounds

Barrier to HIV Eradication



Productive infection / Active reservoir

Latent infection / Latent Reservoir

Latent reservoir of replication-competent HIV-1 persists in resting memory CD4+ T-cells during ART (1 per million) with a half-life of ~44 months

Kick and Kill Strategy to Eliminate Reservoirs of Latent HIV

KICK

Activate expression of HIV

KILL

Kill cells expressing HIV proteins

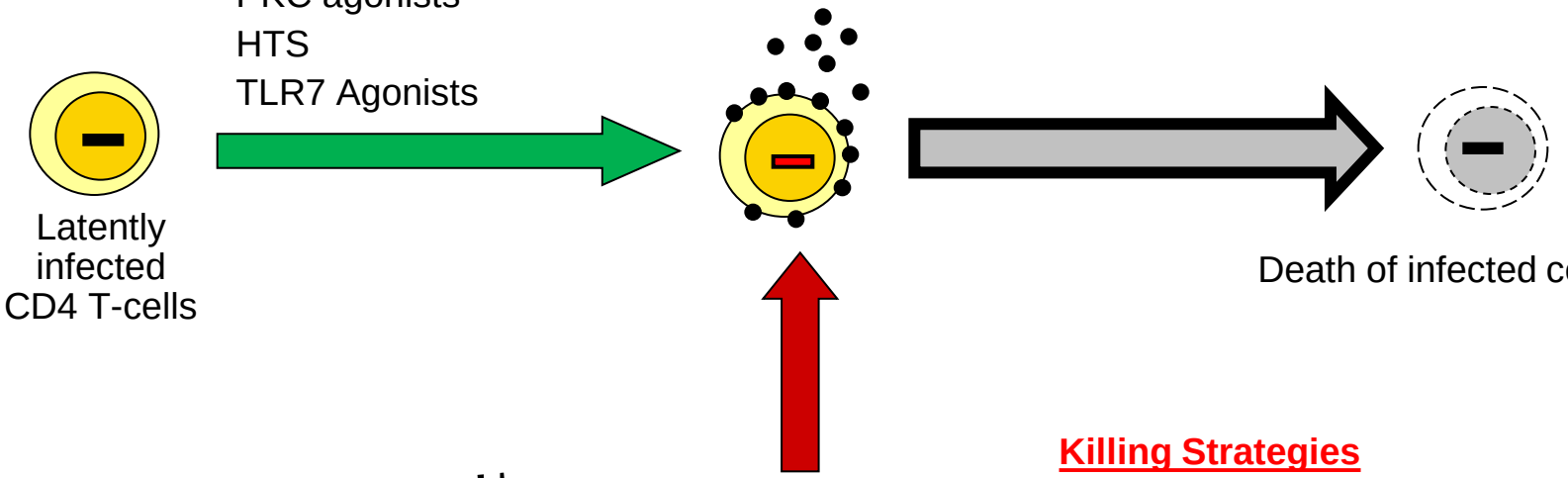
Latency Reversal Agents

HDACis

PKC agonists

HTS

TLR7 Agonists



Latently infected CD4 T-cells

Death of infected cells

Macrophages

CD8 T-cells

NK cells

Killing Strategies

Therapeutic vaccines

Anti-gp120/gp41 antibodies

Immune check point inhibitors

Immune modulators (TLR7 agonists)

Can current in vitro assays and analytical methods help select LRAs for clinical testing?

- Cost
- Borrowing from years of experience with ARVs
- Criteria for other classes of agents will be different

Criteria for Selecting LRAs for Clinical Testing

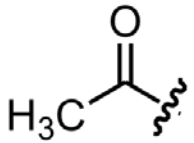
- **Activity in primary latency assays or cell lines not sufficient**

- **LRA must activate HIV expression in patient cells (ex vivo)**
  - Expression of cell-associated vRNA not sufficient
  - Must induce vRNA in culture supernatants (pelletable)

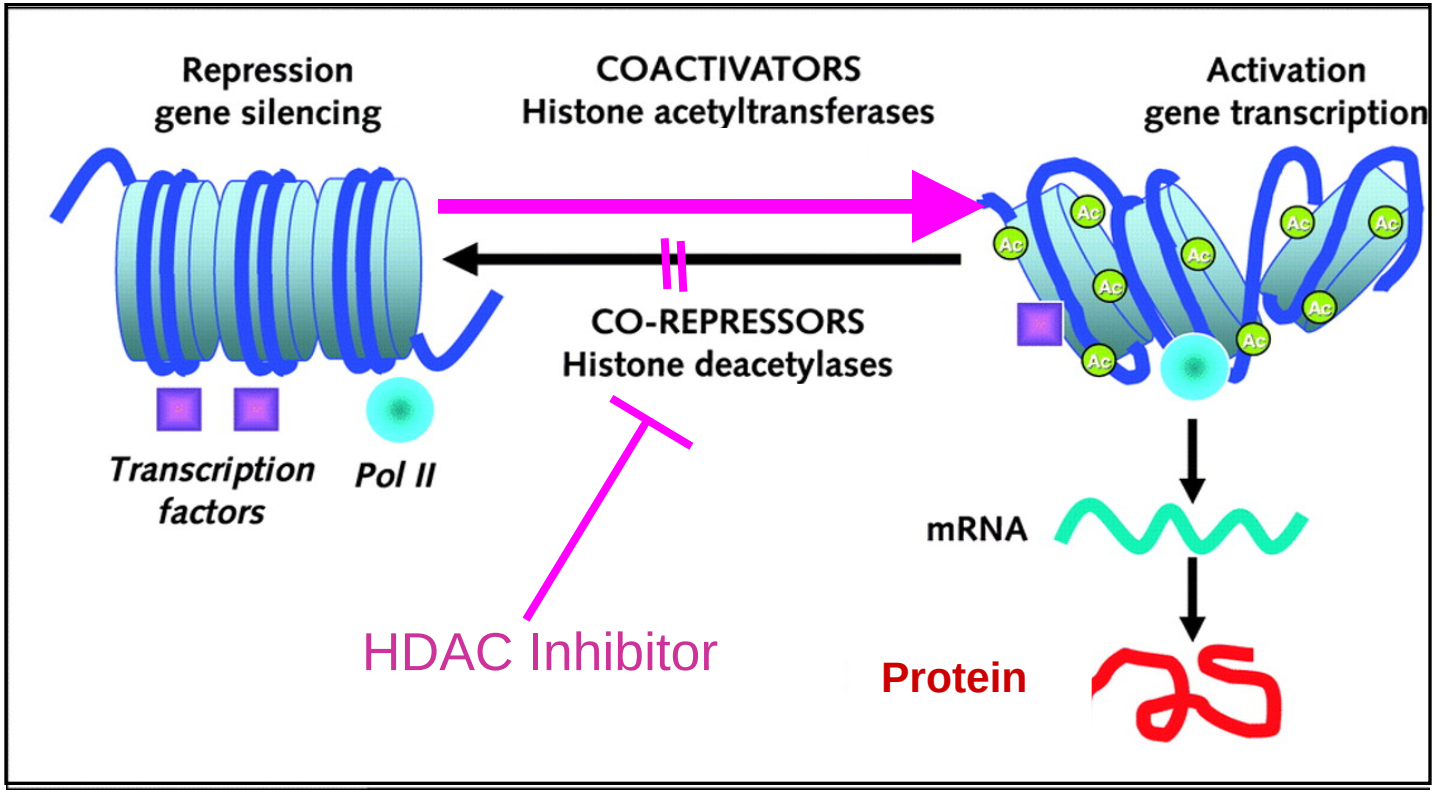
- **LRA concentrations that activate HIV expression in vitro**
  - Achievable in plasma/tissues in animals or clinically (safety margin)
  - Cmax equal or greater than EC50 (Adjust. for plasma prot. Binding)

HDAC Inhibitors

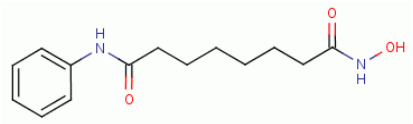
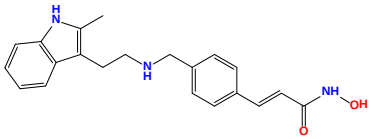
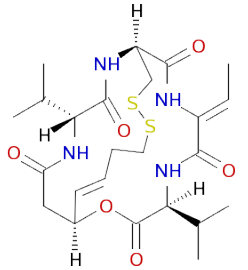
Histone Deacetylases (HDACs) and Latent HIV



- Remove chemical moieties called acetyl groups from Lysine
- Act on proteins: Histones, Tubulin, Transcription factors
- Suppress Gene Expression (including HIV expression)
- HDAC inhibitors activate latent HIV
- HDAC inhibitors: FDA approved (CTCL, PTL) and in development



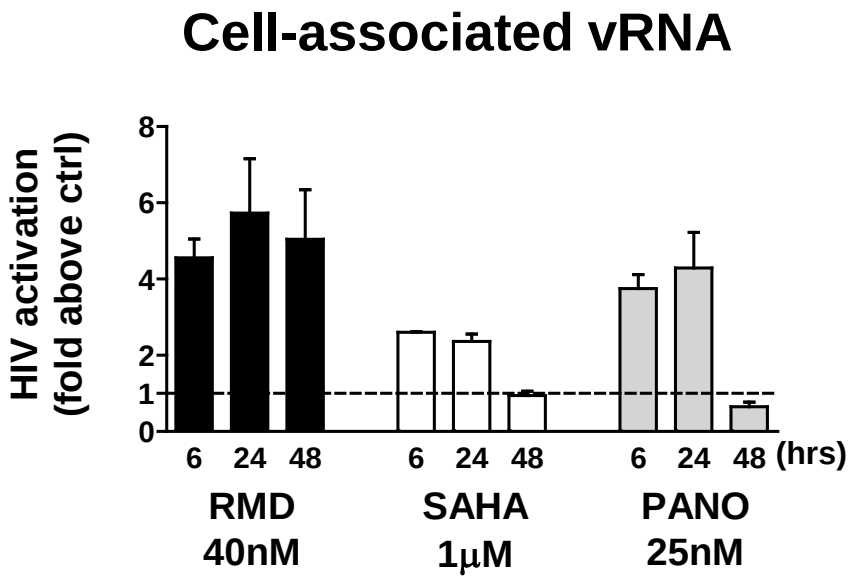
HDACis Tested in HIV+ Subjects on cART

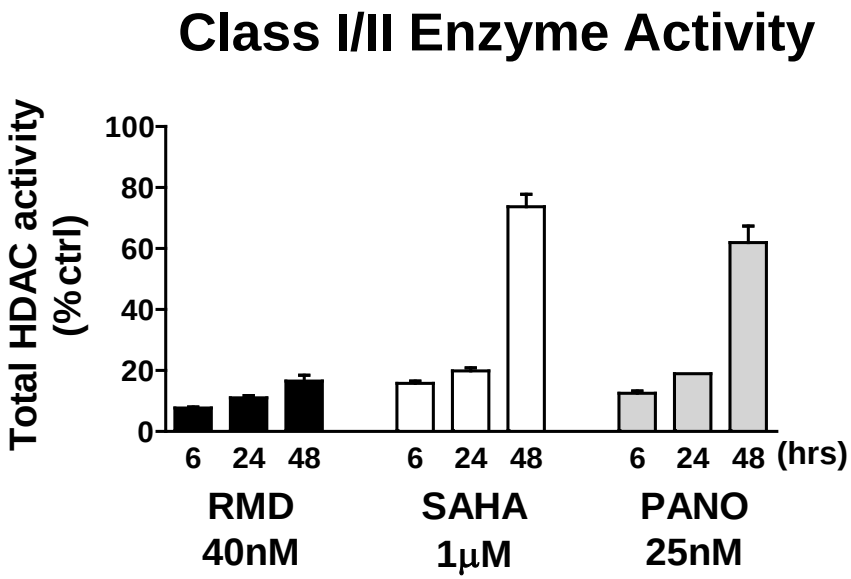
	Vorinostat SAHA (Merck)	**Panobinostat** (Novartis)	**Romidepsin** (Celgene)
Structure			
Regulatory Status	FDA Approved	FDA Approved	FDA Approved
Indication	CTCL	MM	CTCL
Clinical studies in HIV+ Subjects on cART	Margolis (US) Lewin (AUS)	Aarhus team (DEN) CLEAR	A5315 (ACTG) Bionor / Aarhus REDUC (DEN)
Potency to activate HIV in vitro (EC_{50})*	3,950 nM	10 nM	4.5 nM
Human Cmax / HIV Activation (EC_{50})	**0.1**	**2**	**11**

*Modification of Bosque and Planelles assay (2009)

HIV Activation Correlates with Inhibition of Cellular HDAC Activity

Memory CD4+ T-cells from ART-suppressed Subjects Pulse Treatment Mimicking Clinical Dosing



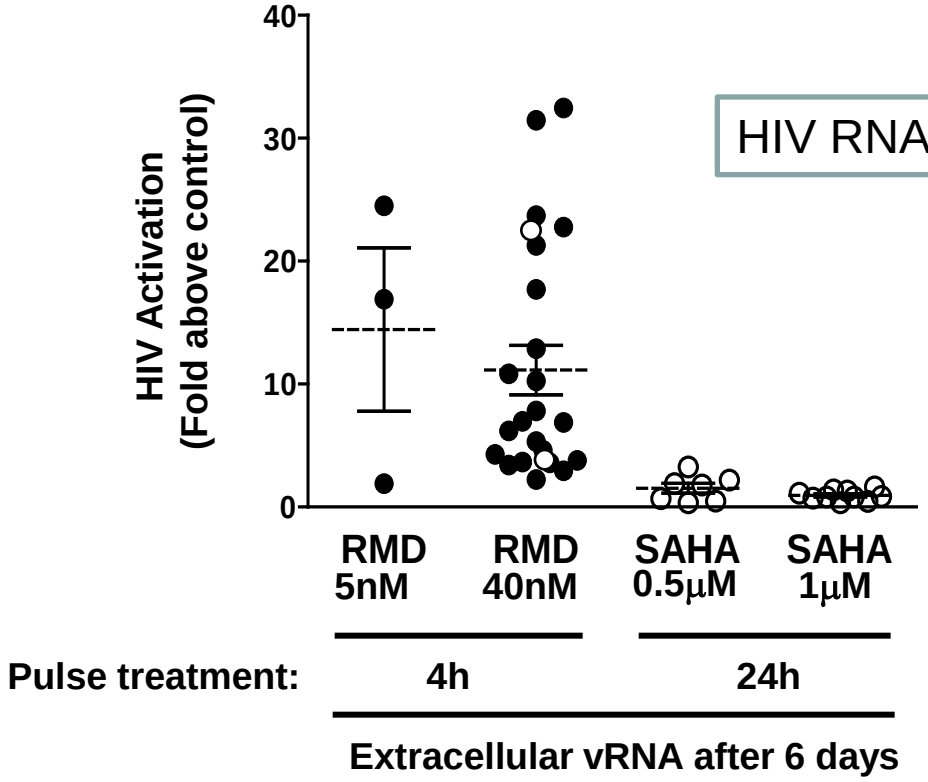


Does HDACi-mediated activation of HIV RNA lead to protein and virion production?

Wei et al, PLoS Pathogens, 2014

RMD Induces Extracellular HIV RNA Production

- Memory CD4+ T-cells from ART Suppressed Subjects
- Pulse treatments with concentrations achieved clinically
- Measure HIV RNA levels in culture supernatants after 6 days

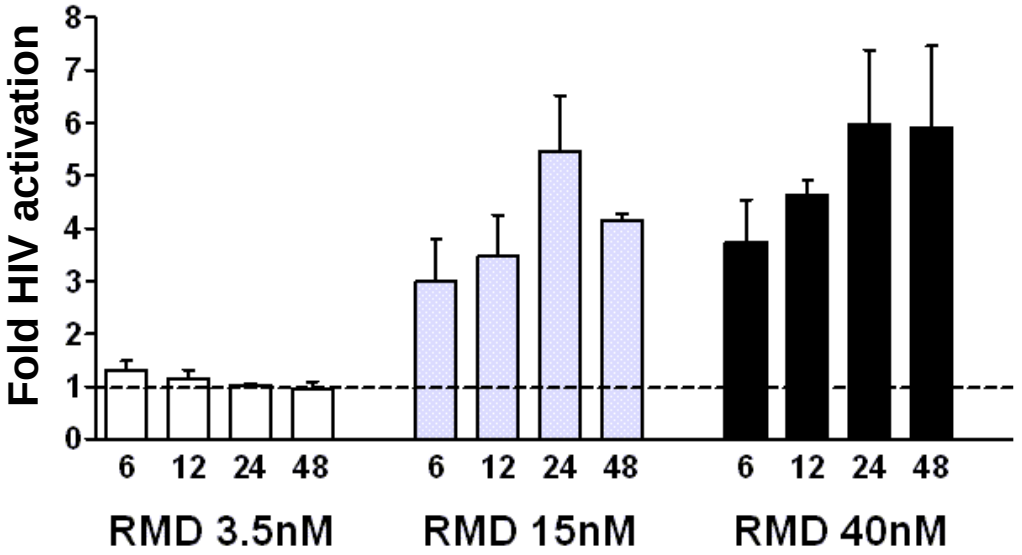


HIV RNA can be pelleted (21,000g / 60 min)

Wei et al, PLoS Pathogens, 2014

Selecting RMD Doses for Clinical Testing

Resting CD4+ T-cells from HIV+ subjects on cART (n=3)



Percent clinically achievable exposure	4%	15%	40%	100%
Equivalent dose	0.5 mg/m^2	2.0 mg/m^2	5.0 mg/m^2	14 mg/m^2

Doses selected for

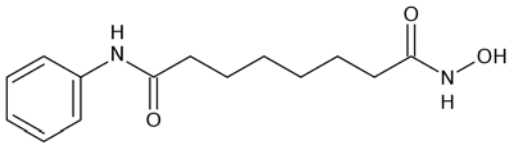
- **ACTG-A5315**
- **REDUC**

CTCL Dose

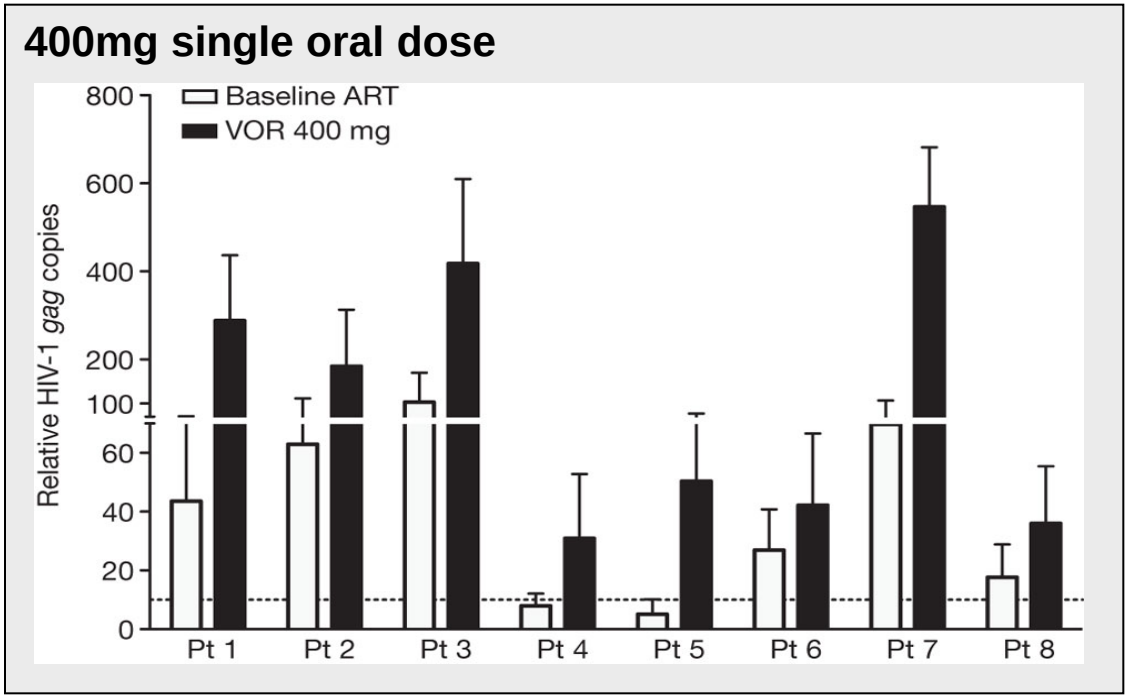
Wei et al, PLoS Pathogens, 2014

SAHA Phase I: Activation of HIV Expression

- Patients on fully suppressive HAART (n=8)
- Pre-screened ex vivo for SAHA effect
- HIV RNA in CD4+ cells after single dose of SAHA



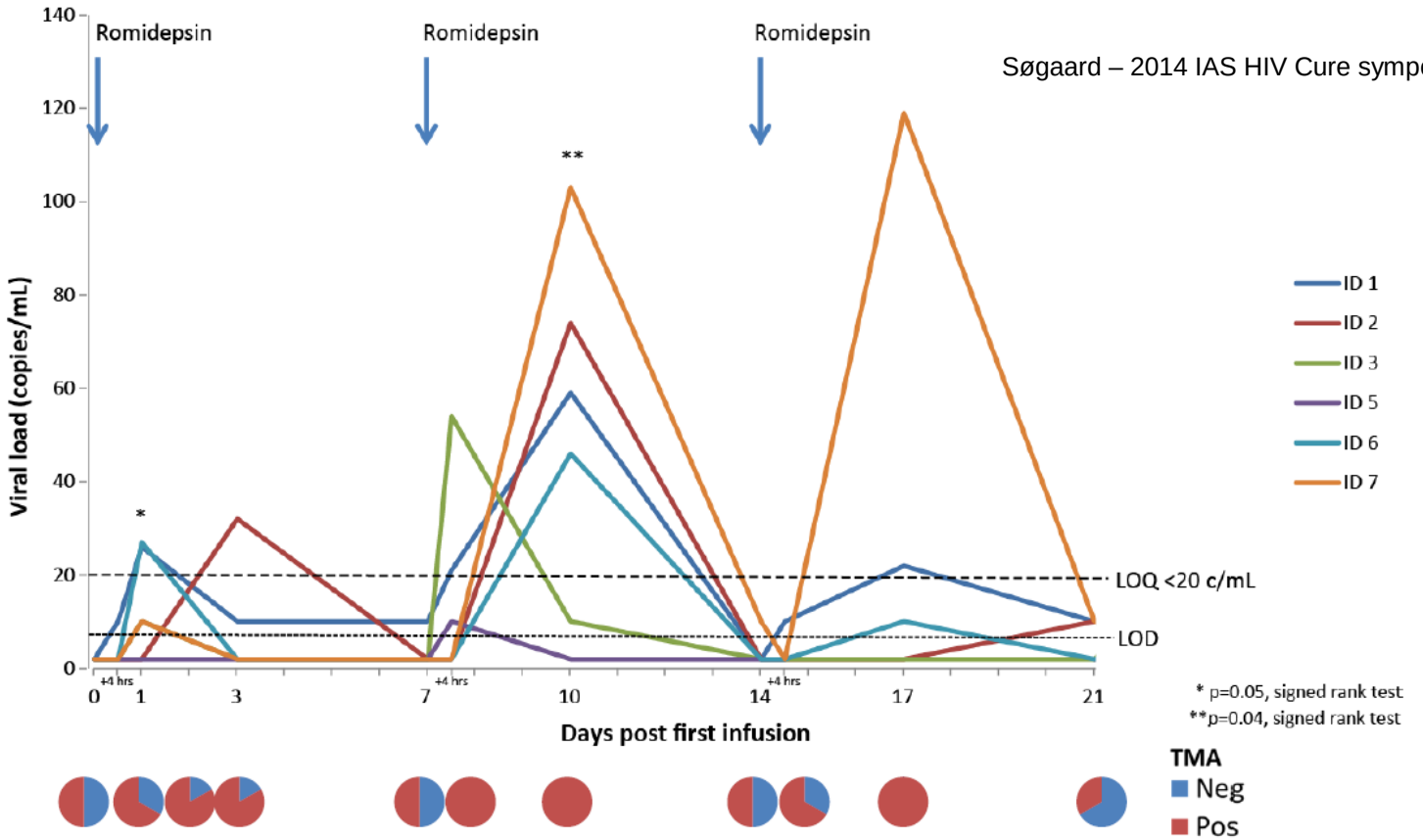
SAHA (Vorinostat)
Merck, Inc.
Approved for CTCL



Mean 5-fold increase in vRNA but multiple dose study ~2-fold increase and NO increase in plasma viremia

Archin et al, Nature, 2012

REDUC Trial: Romidepsin-Induced Plasma HIV-1 RNA in 5 of 6 Patients



Søgaard – 2014 IAS HIV Cure symposium (Melbourne)

Viral load: COBAS® TaqMan® HIV-1 Test, v2.0
TMA: Qualitative NAT screening system (PROCLEIX ULTRIO Plus, Genprobe)

Summary of HDACis in Clinical Testing

	Vorinostat SAHA (Merck)	**Panobinostat** (Novartis)	**Romidepsin** (Celgene)
Potency to Reactivate HIV (*in vitro*)	**Low**	**High**	**High**
Human Cmax / HIV Activation (EC_{50})	**0.1**	**2**	**11**
***Ex vivo* HIV activation (cell-associated vRNA)**	**Yes**	**Yes**	**Yes**
***Ex vivo* HIV activation (supernatant vRNA)**	**No**	**???**	**Yes**
***In vivo* HIV activation (plasma vRNA blips)**	**No**	**Maybe**	**Yes**

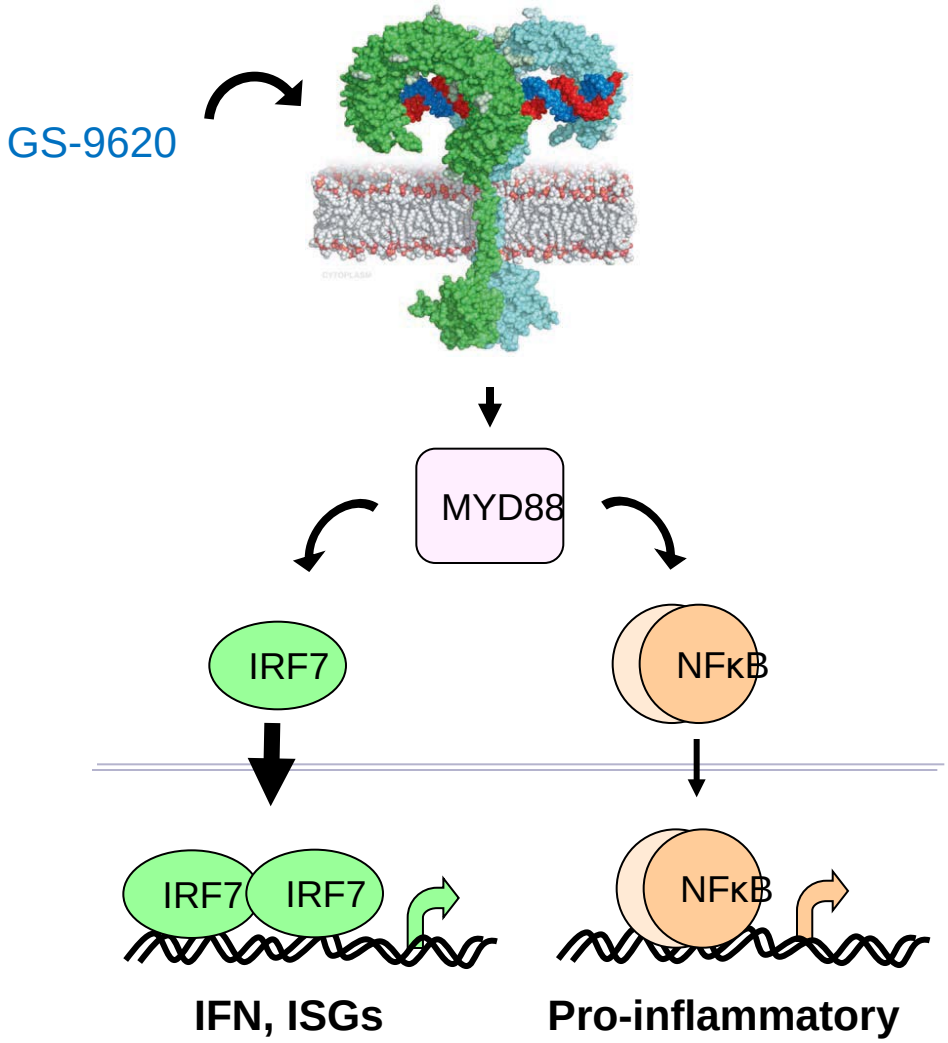
Can in vitro assays and analytical methods help select LRAs for clinical testing?

TLR7 Agonists for HIV

A 7 Year Journey

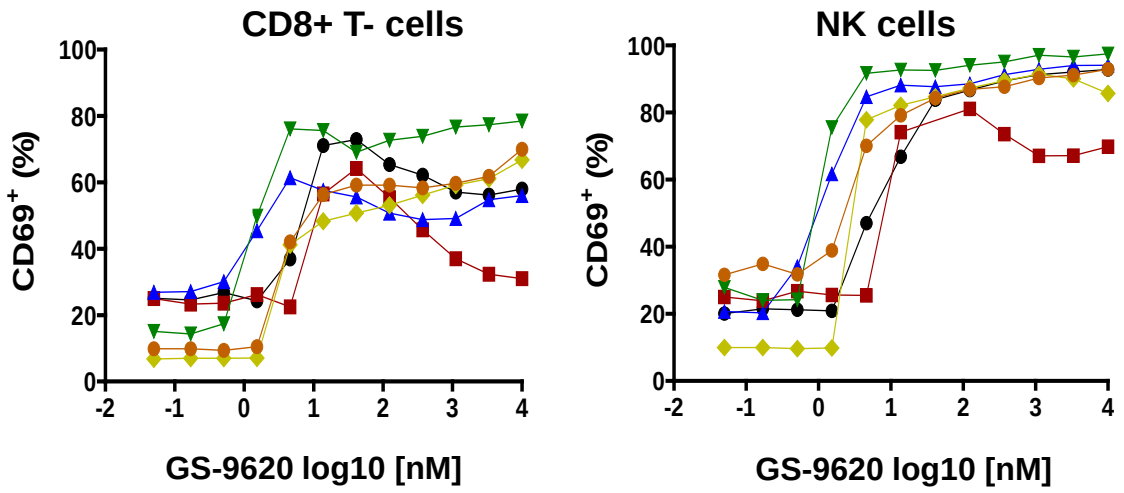
GS-9620: A Potent and Selective TLR7 Agonist

- Administered orally
- Potent and selective for TLR7
  - TLR7 in pDCs and B-cells
- Reduces sAg and viral DNA in woodchucks (WHV) and chimpanzees (HBV)
- Phase 1 completed and Phase 2 study in HBV subjects at doses that do not induce systemic IFNα under way



Rationale for TRL7 Agonist in Kick and Kill

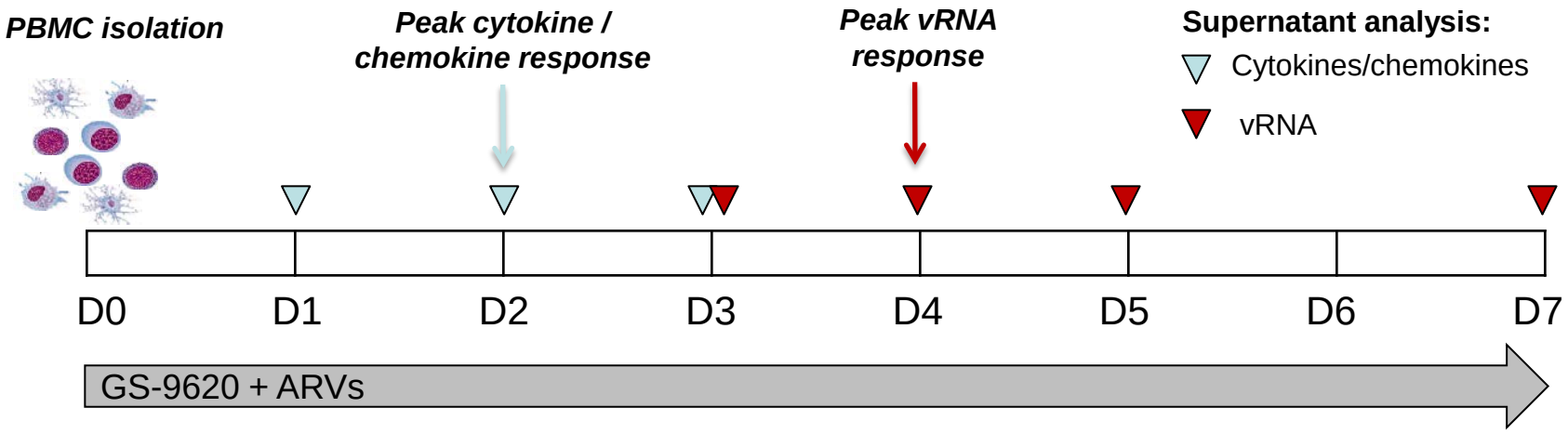
- **Kick**
  - **GS-9620 induces HIV-1 RNA in PBMCs from HIV+ subjects on cART**
  - **TLR7 agonists activate CD4+ T-cells (small fraction and indirectly)**
- **Kill**
  - **TLR7 agonists enhance antigen presentation by pDC**
  - **TLR7 agonists activate CD8+ T-cells and NK cells (enhance ADCC)**



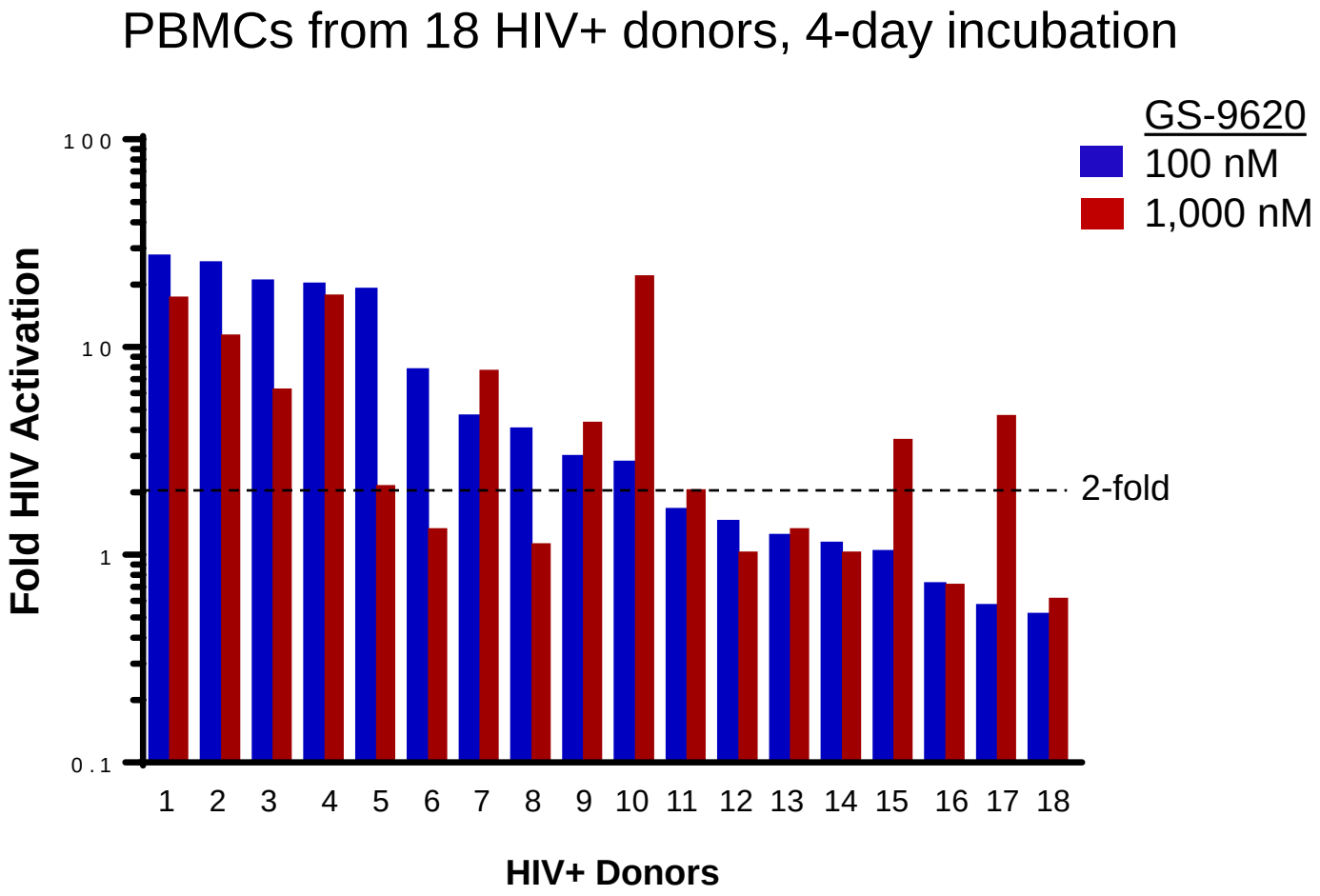
- **PBMCs from HIV+ donors on cART (n=6) treated with GS-9620**
- **Confirmed in Phase I – Healthy Volunteers**

Testing TLR7 agonists Ex vivo in cultures of PBMCs derived from HIV+ subjects on cART

- HIV-infected donors on cART (plasma vRNA <50 copies/mL for > 1 yr)
- PBMCs from donors' leukapheresis were treated with DMSO or GS-9620 (100 or 1,000 nM) in the presence of ARVs (EFV + EVG, 100 nM each)
- Cytokines/chemokines in culture supernatants were analyzed using 34-plex Luminex panel for type I IFNs and IFN-inducible cytokines
- HIV-1 RNA in cell-free culture supernatants was quantified by real-time qRT-PCR using the AmpliPrep/COBAS® TaqMan® assay



GS-9620 Activates HIV Ex Vivo in PBMCs from HIV+ Donors on cART



- Cells from 72% of donors responded (≥ 2-fold activation) at 100 or 1,000 nM GS-9620
- Mean fold activation : 9x (range 2 – 27x)

Test-of-concept in Rhesus Monkeys

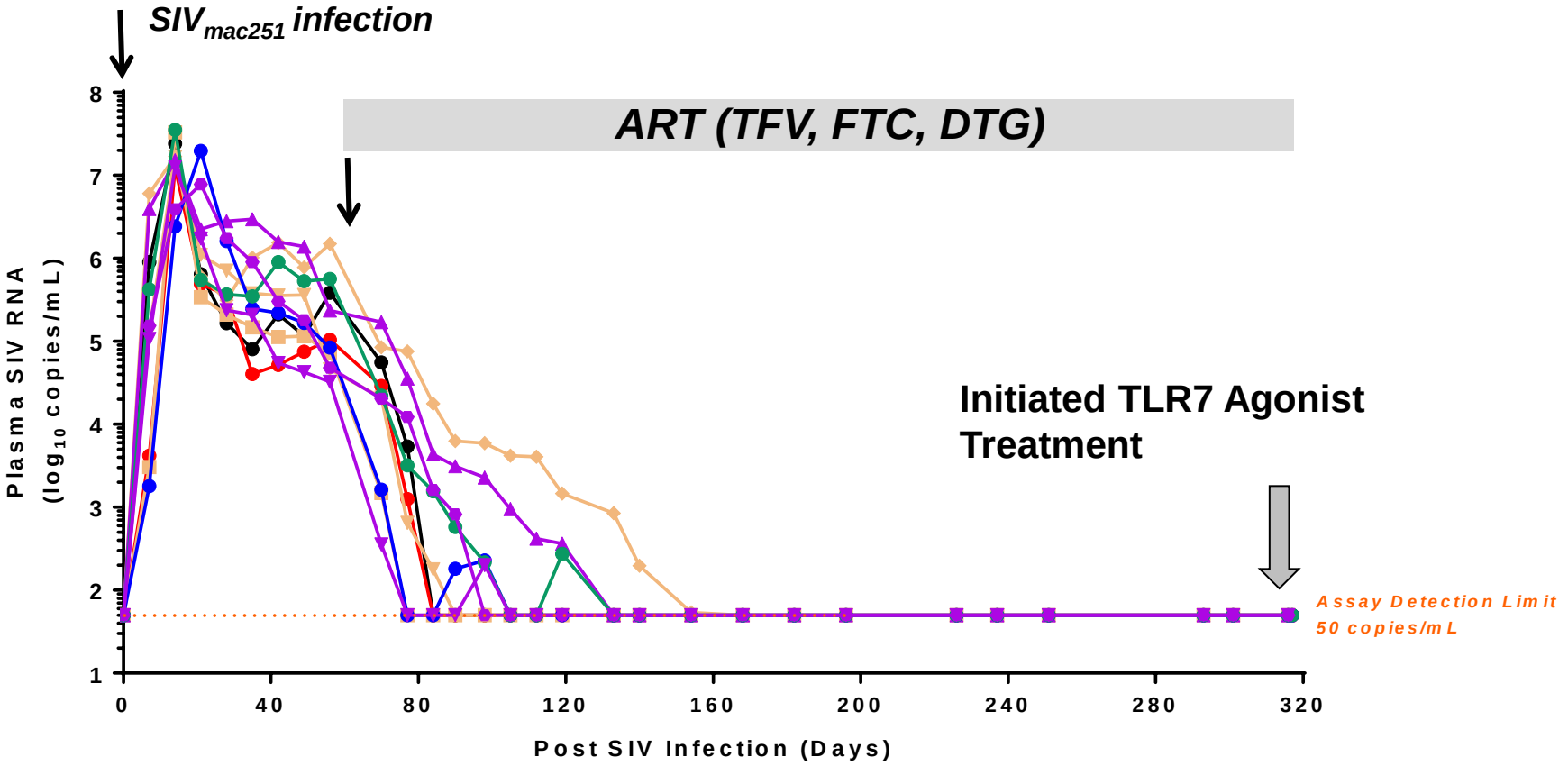
- **Dose ranging studies in healthy Cyno and Rhesus**
  - Establish MED (IFNα and ISGs)
  - Frequency of dosing (Weekly, EOW)

- **A Monkey cART regimen**
  - Formulation for once-daily subcutaneous administration of TFV, FTC, DTG

Testing TLR7 Agonist *in vivo (Pilot Study)* Rhesus Macaque Study Design

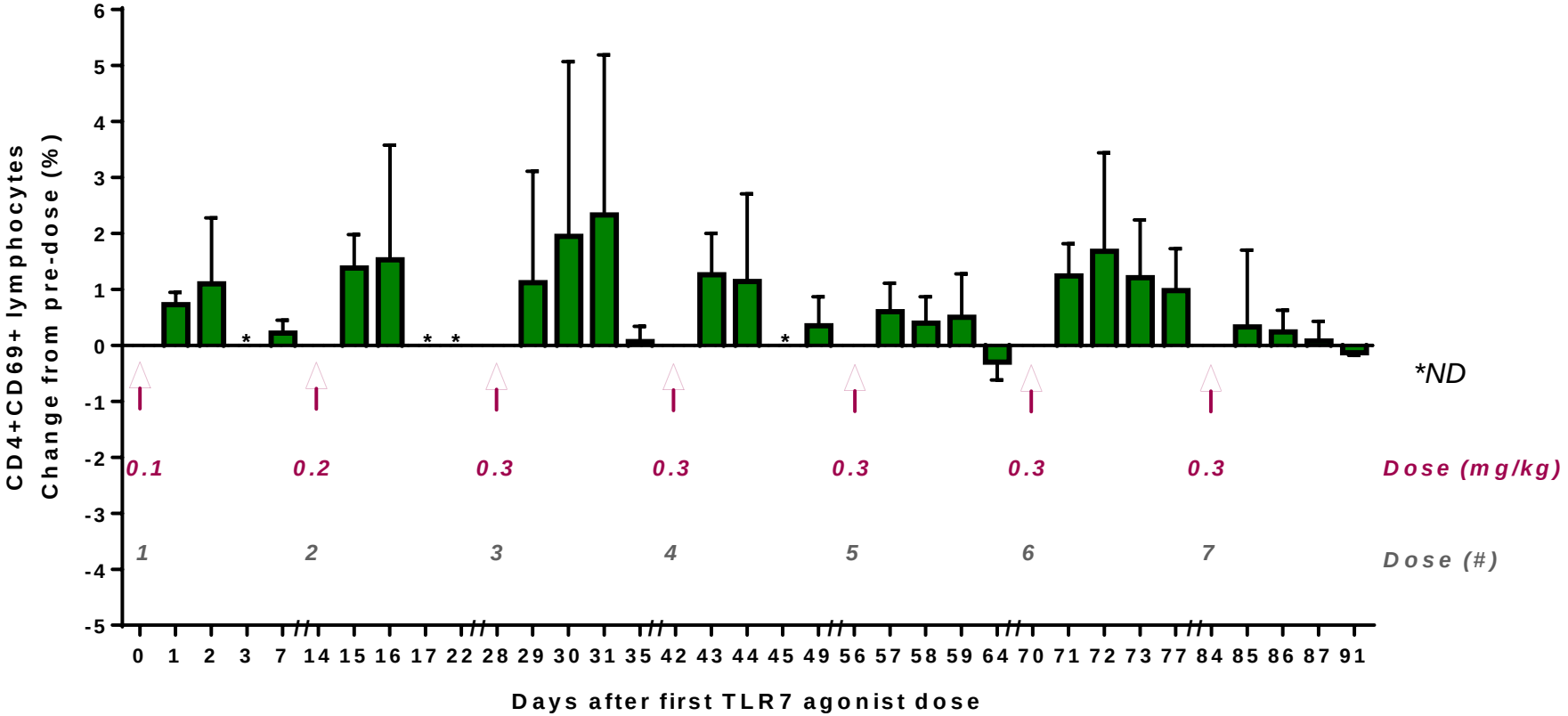
- **10 Indian rhesus macaques**
- **Infection: SIVmac251 Intra-rectal**
- **Subcutaneous cART (TFV, FTC, DTG) QD, day 65 post-infection**
- **Day 320 post-infection (8.5 months cART)**
  - **Dose escalation of GS-9620 analog (dosed orally) (n=4)**
  - **Every other week (7 doses)**
  - **Placebo (n=6)**
- **Primary end point:**
  - **Plasma viral RNA rebound kinetics after stopping ART**
- **Secondary endpoints:**
  - **Effects on plasma viremia, immune activation**

Effective cART in SIV-infected Rhesus Macaques

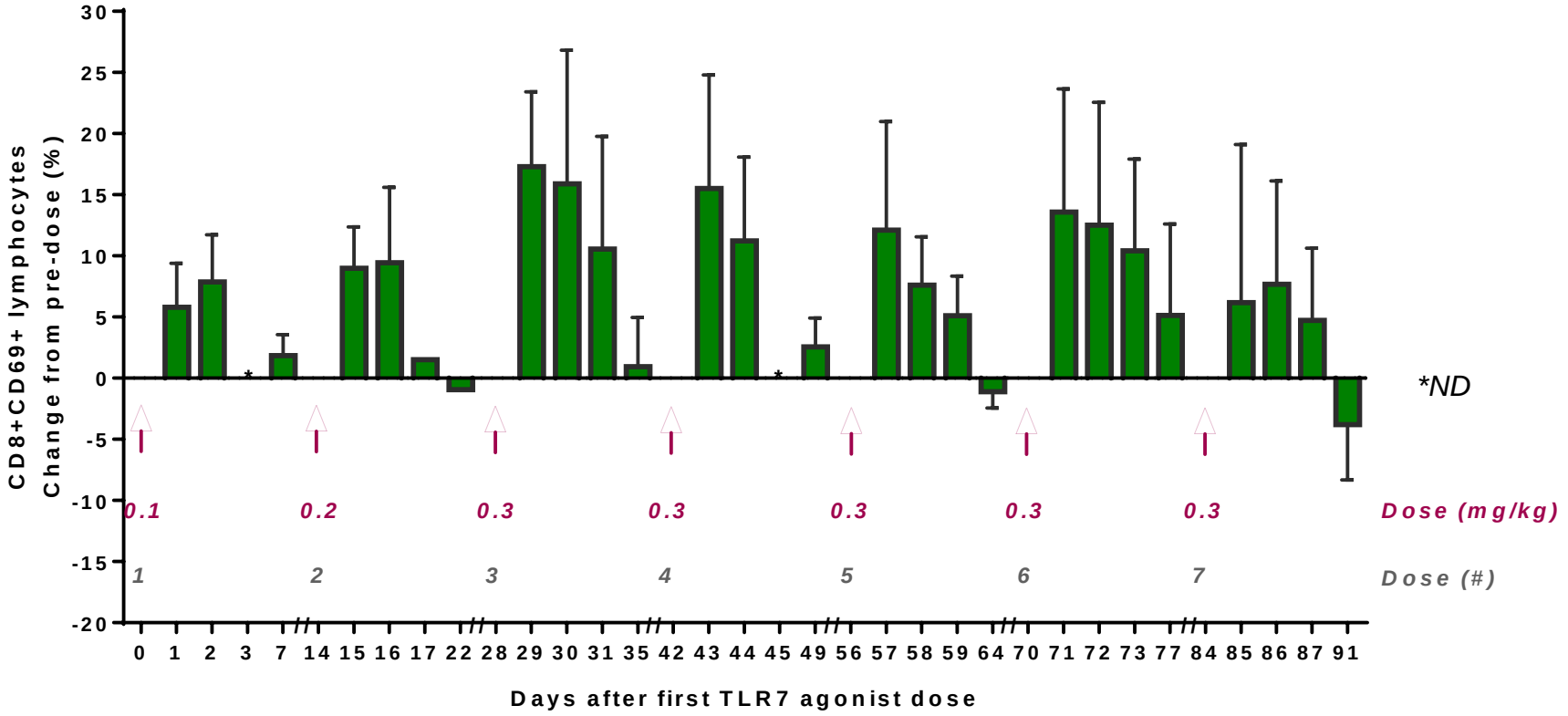


- **ART achieved complete suppression of plasma viremia (< 50 SIV RNA copies/mL)**

CD4+ T cell Activation by TLR7 Agonist In SIV+ Monkeys on cART

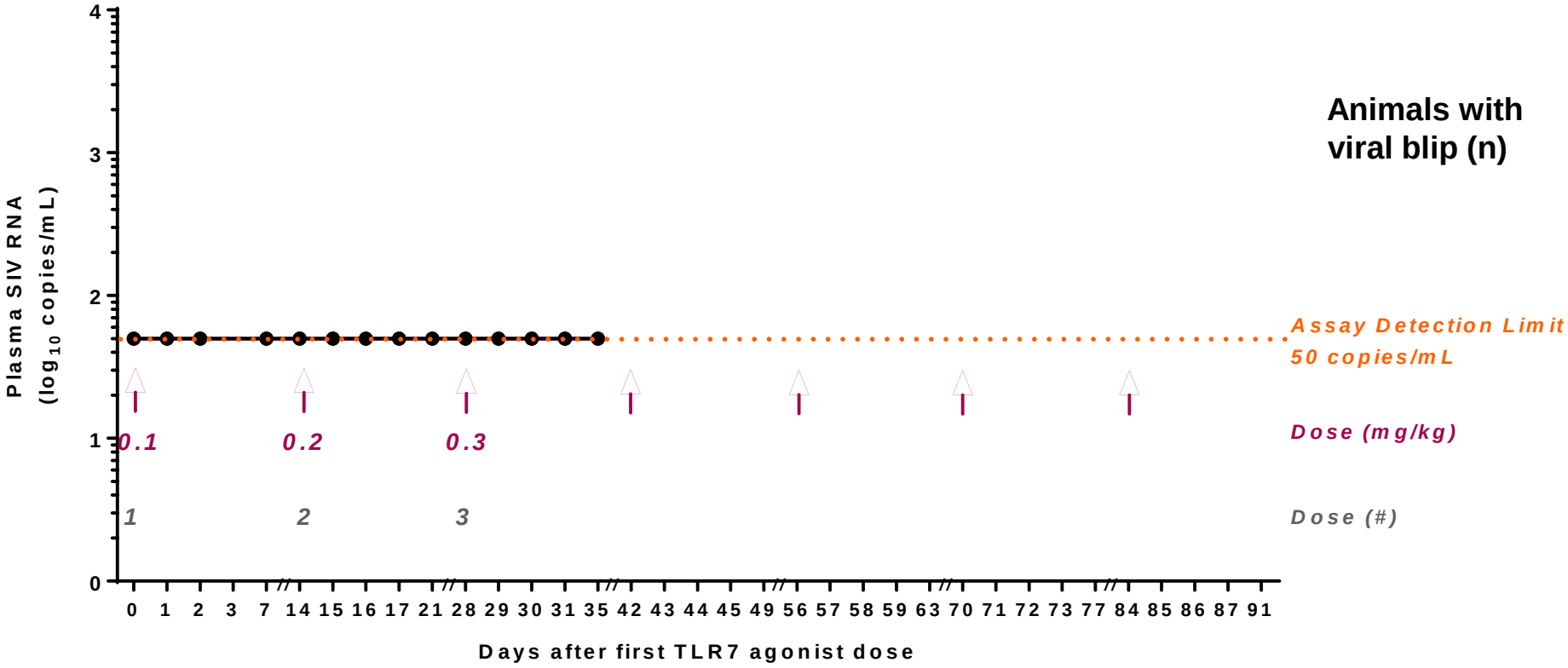


CD8+ T cell Activation by TLR7 Agonist In SIV+ Monkeys on cART



- Similar pattern of transient NK cell activation

Transient Plasma Viremia Induced by TLR7 Agonist Treatment of Monkeys on cART



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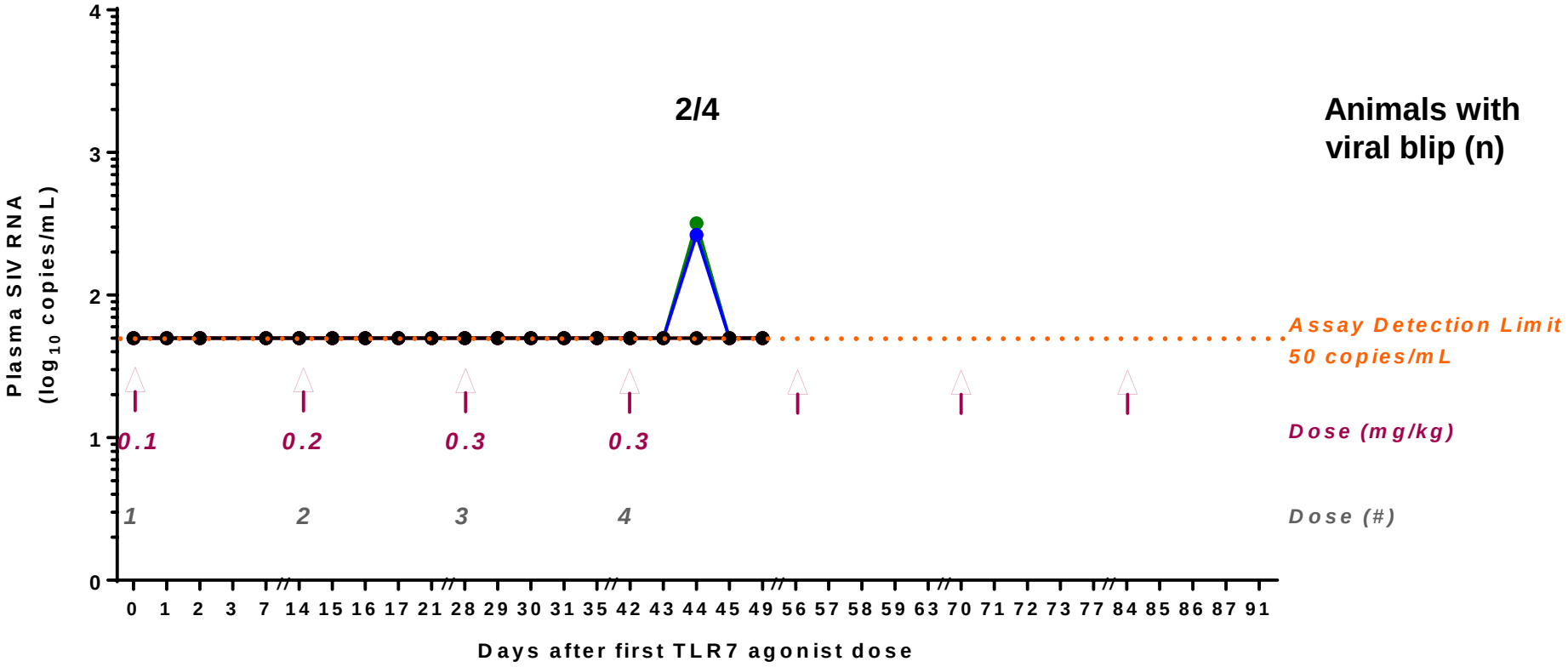

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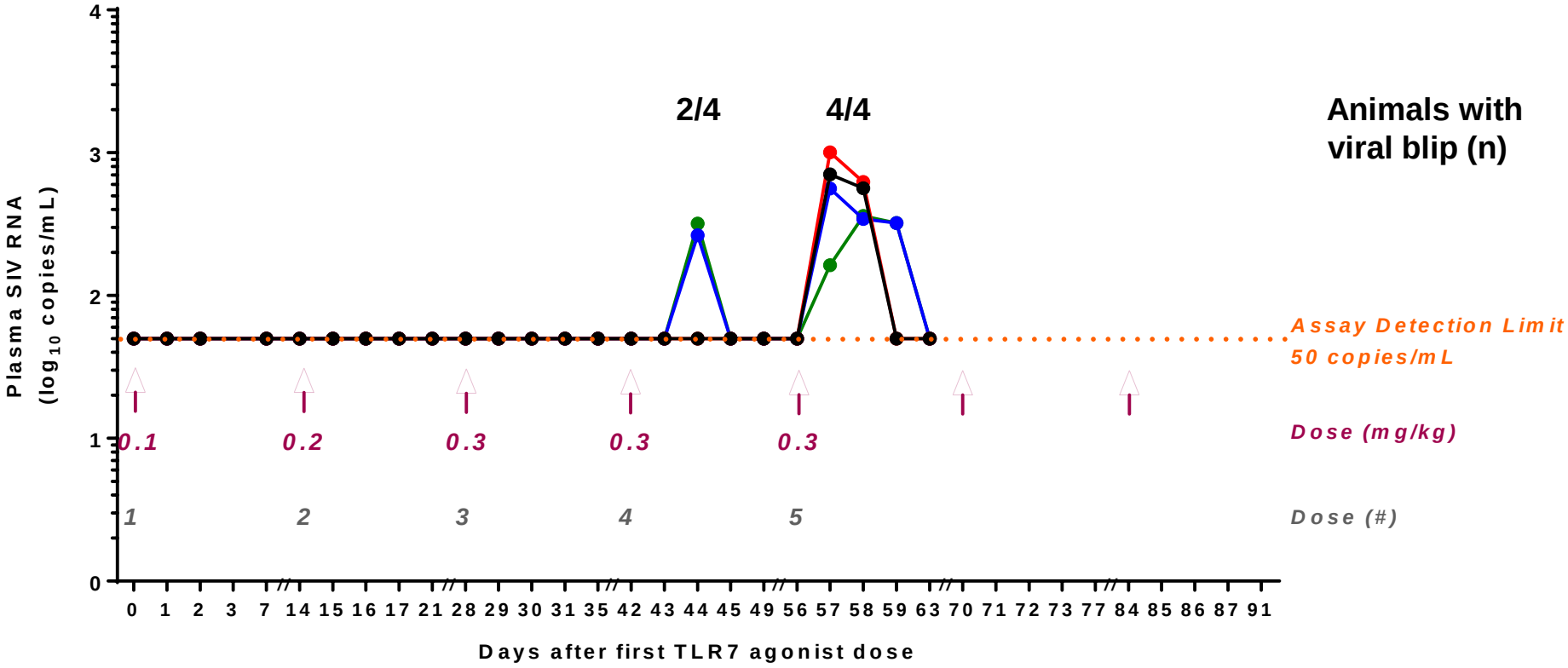

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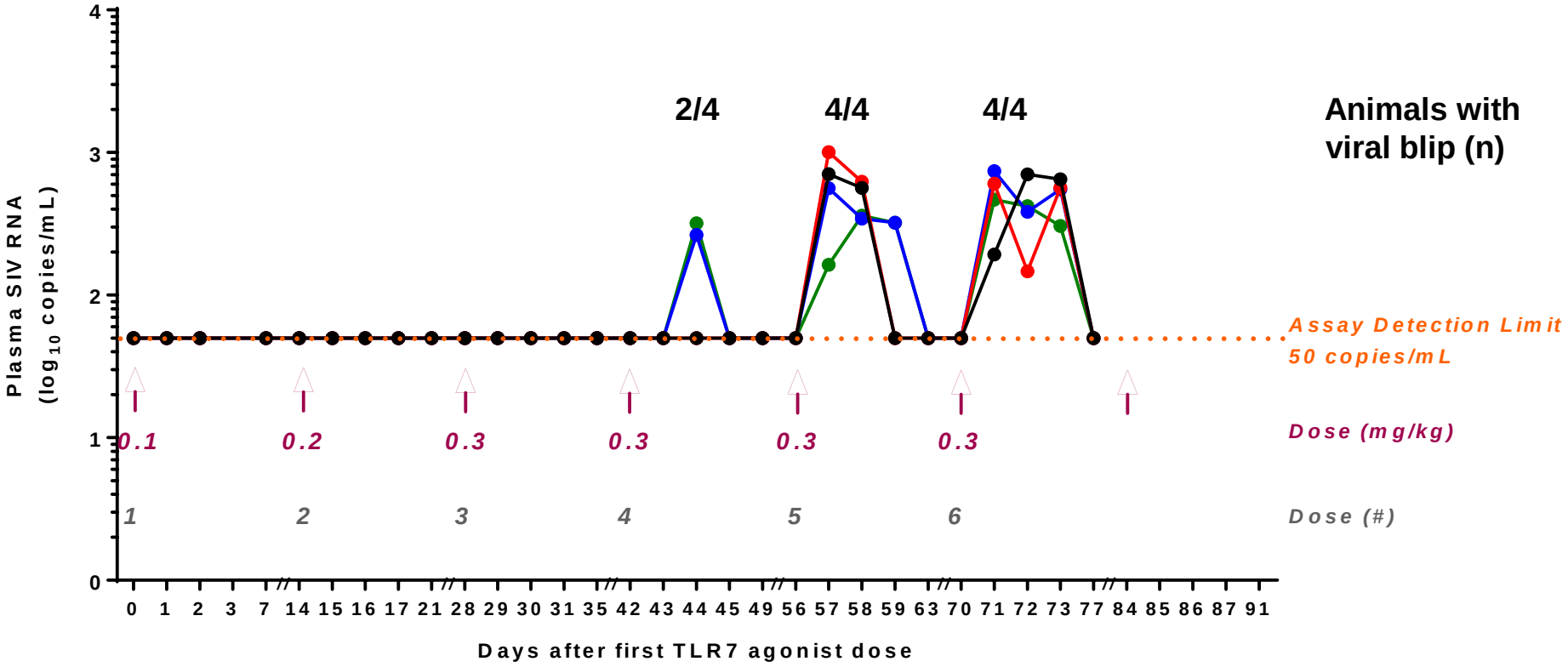
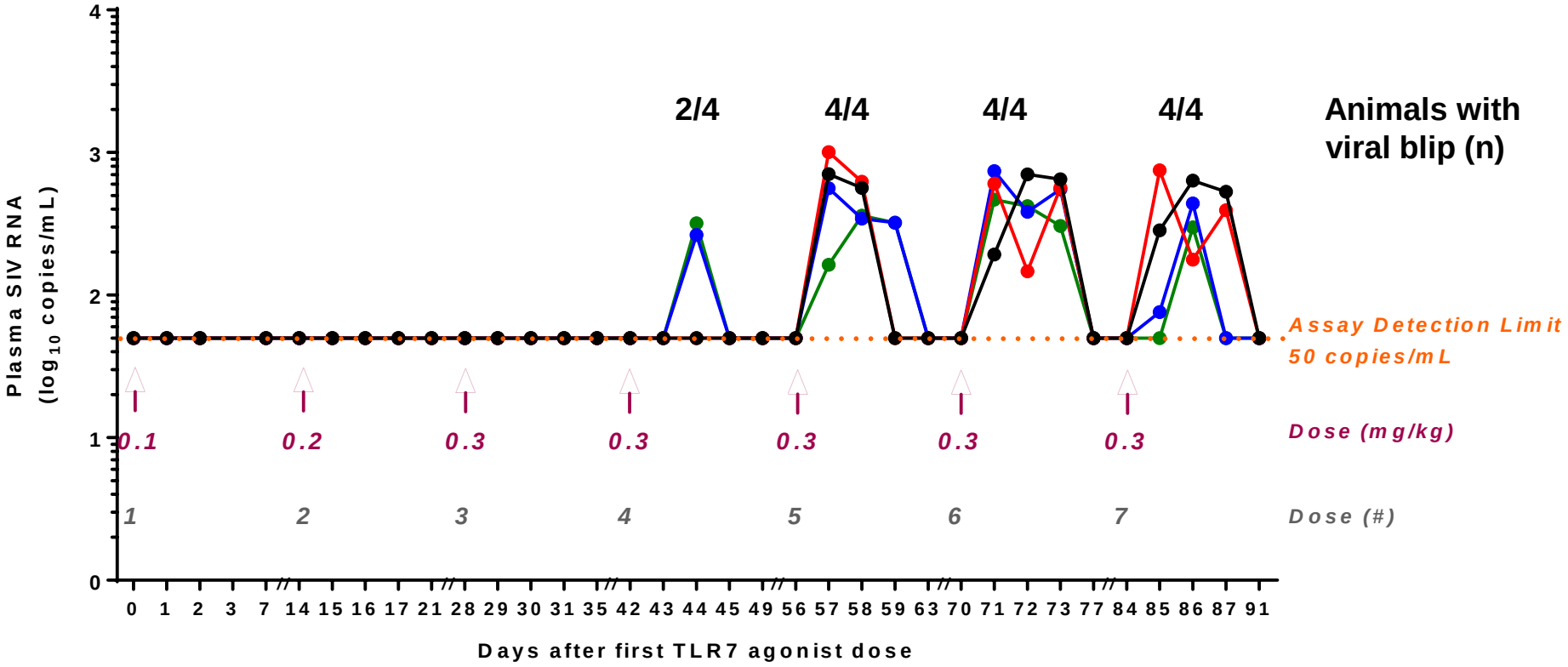
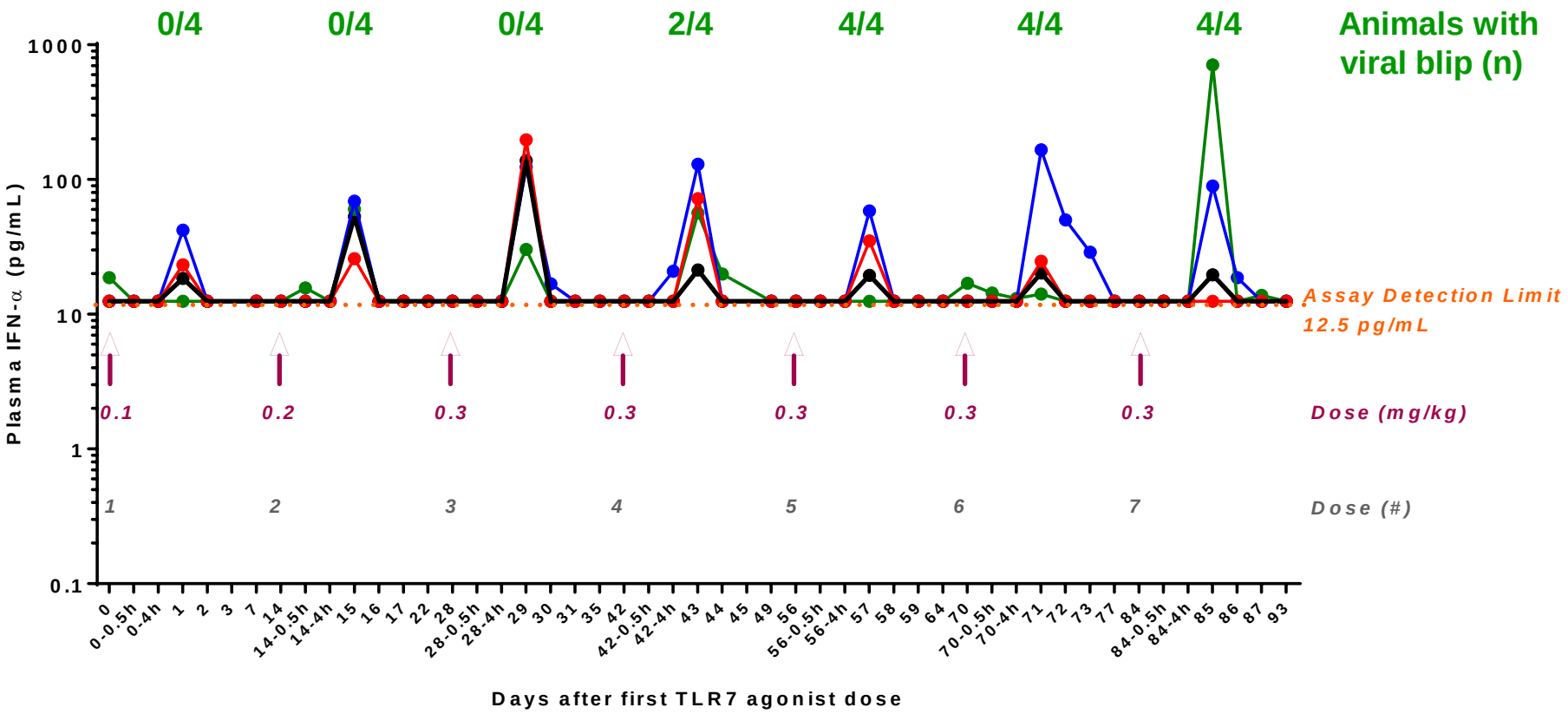


Transient Plasma Viremia Induced by TLR7 Agonist Treatment of Monkeys on cART



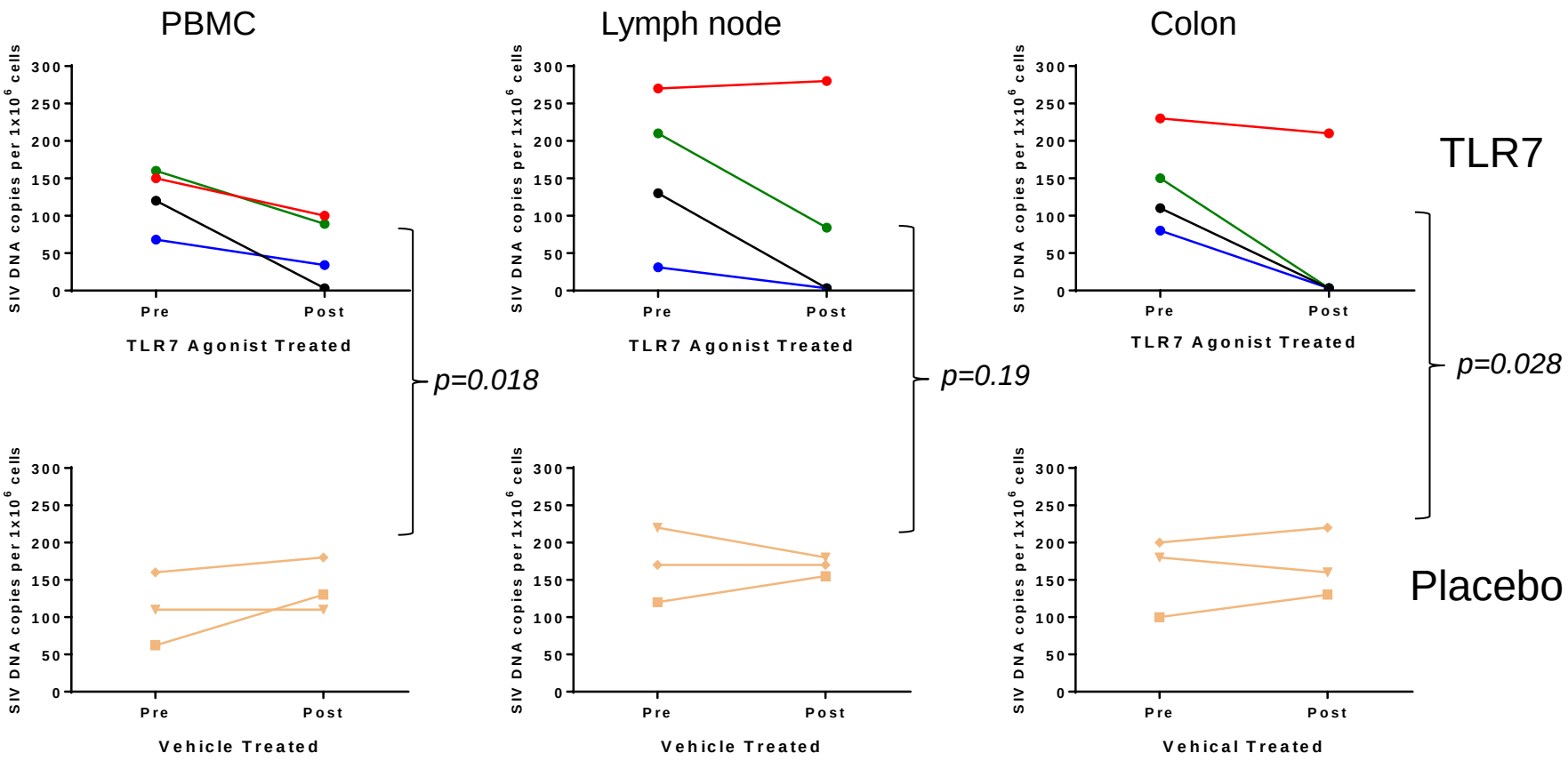
- No blips in placebo control animals (< 50 SIV RNA copies/mL)
- Identity between plasma “blips” and virus sequences from PBMCs, LN and colon
- Hypermutated sequences observed only in proviral DNA

Plasma IFNα Induced by TLR7 Agonist Treatment of Monkeys on cART



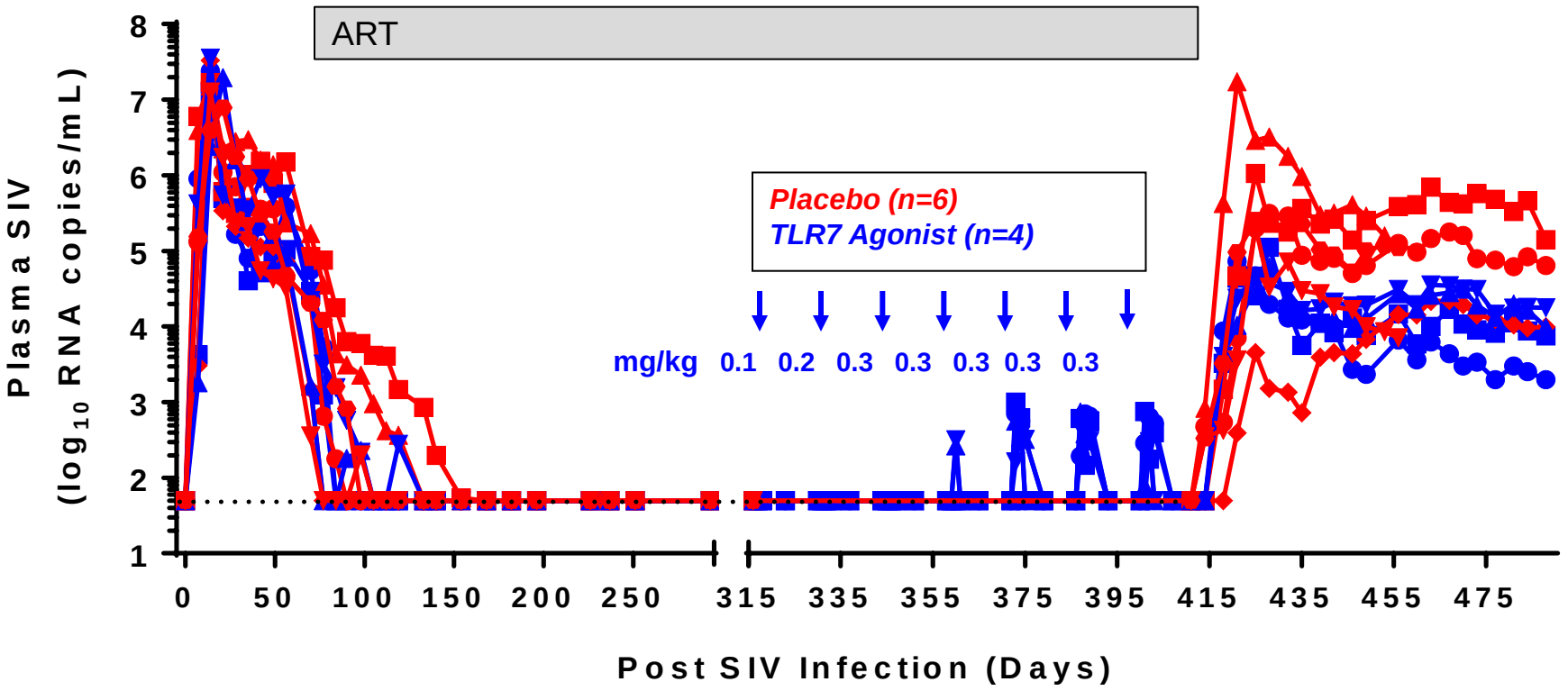
- TLR7 agonist doses 1-3 induced IFNα, but no plasma virus blips
- No correlation between IFNα and viral RNA induction in plasma

SIV DNA Levels Reduced in TLR7 Agonist Treated Monkeys on cART



- SIV DNA decrease in 3 of 4 animals treated with TLR7 agonist
- No significant SIV DNA change in placebo animals

Kinetics of Plasma Virus Rebound after Stopping ART



- No difference in plasma virus rebound kinetics after stopping cART in TLR7 agonist vs. placebo groups
- Lower plasma virus set point in TLR7 treated vs. placebo

TLR7 Agonists for HIV Summary

- **TLR7 agonist ex vivo:**
  - Activated HIV expression in PBMCs from HIV+ donors on cART
  - Induced ≥ 2x HIV expression in 13/18 (72%) donors (mean: 9.1x)
  - Activate CD8+ T-cells and NK cells from HIV+ donors on cART
  - Donor-dependent variation in HIV activation due to combined kick / kill?
- **TLR7 agonist in vivo:**
  - Induced transient plasma viremia in SIV-infected monkeys on ART
  - Induced transient activation of CD4 T cells, CD8 T cells, NK cells, and cytokines/chemokines
  - SIV DNA decreased in lymph node, colon and PBMCs
  - Reduced viral set point after stopping ART
- **Clinical study initiated with GS-9620 in HIV+ / cART persons**

Therapeutic Vaccines

CMV Vector-based Vaccine

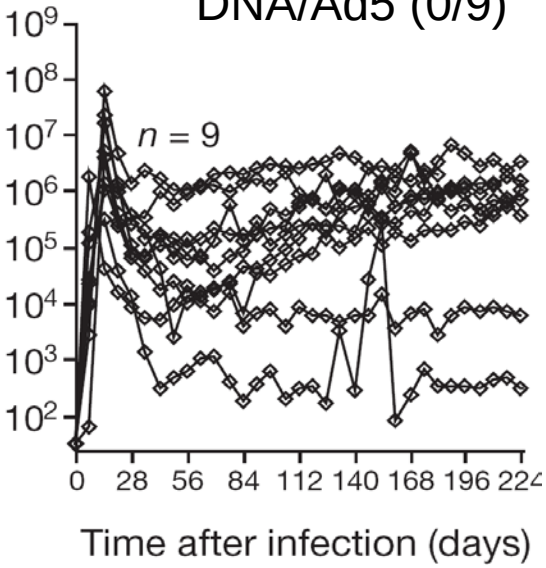
nature

26 MAY 2011 | VOL 473 | NATURE | 523

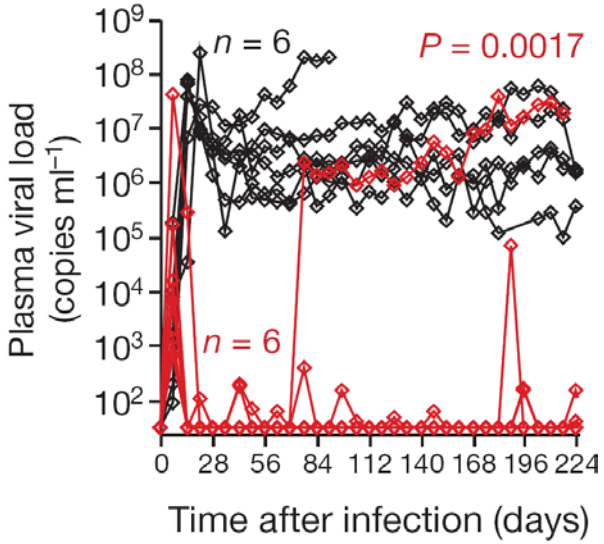
Profound early control of highly pathogenic SIV by an effector memory T-cell vaccine

Scott G. Hansen[1], Julia C. Ford[1], Matthew S. Lewis[1], Abigail B. Ventura[1], Colette M. Hughes[1], Lia Coyne-Johnson[1], Nathan Whizin[1], Kelli Oswald[2], Rebecca Shoemaker[2], Tonya Swanson[1], Alfred W. Legasse[1], Maria J. Chiuchiolo[3], Christopher L. Parks[3], Michael K. Axthelm[1], Jay A. Nelson[1], Michael A. Jarvis[1], Michael Piatak Jr[2], Jeffrey D. Lifson[2] & Louis J. Picker[1]

DNA/Ad5 (0/9)



CMV/CMV (6/12)



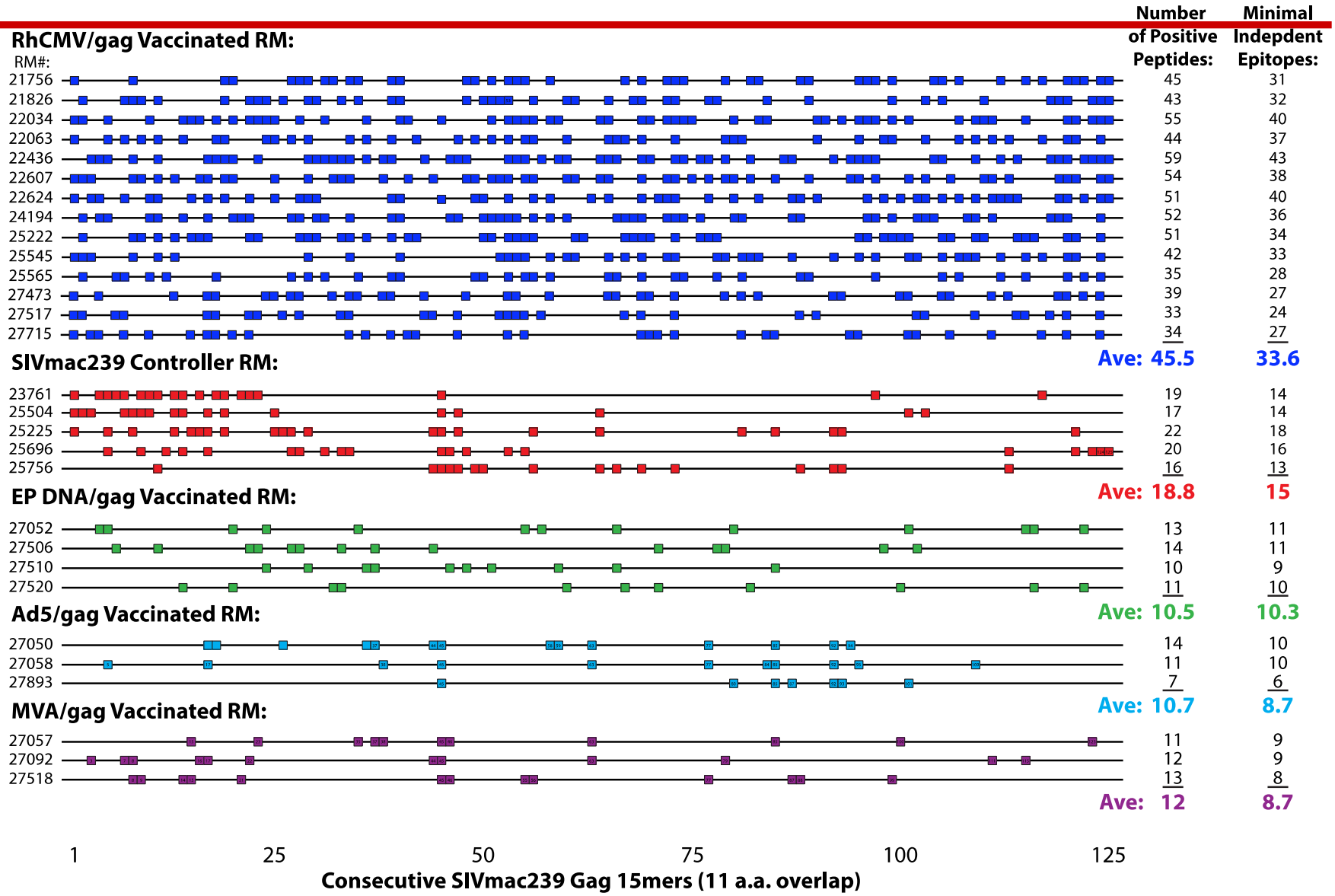
No recovery of infectious virus after 3 years

↓

Cure?

Broad, High Frequency, Durable Effector Memory CD8+ T-Cell Response

Wide breadth of CD8+ T-cell Responses Elicited by Immunization with RhCMV Vectors



Vaccine induced average of 34 distinct epitopes (~3x the breadth of conventional responses)

CMV-based vector Vaccine

26 MAY 2011 | VOL 473 | NATURE

Profound early control of highly pathogenic SIV by an effector memory T-cell vaccine

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- **50% protection as prophylactic vaccine in Rhesus Monkeys**
- **Leads to control of SIV infection but does not block SIV acquisition**
- **Effector memory response**

24 MAY 2013 VOL 340 SCIENCE

Cytomegalovirus Vectors Violate CD8+ T Cell Epitope Recognition Paradigms

Scott G. Hansen, Jonah B. Sacha, Colette M. Hughes, Julia C. Ford, Benjamin J. Burwitz, Isabel Scholz, Roxanne M. Gilbride, Matthew S. Lewis, Awbrey N. Gilliam, Abigail B. Ventura, Daniel Malouli, Guangwu Xu, Rebecca Richards, Nathan Whizin, Jason S. Reed, Katherine B. Hammond, Miranda Fischer, John M. Turner, Alfred W. Legasse, Michael K. Axthelm, Paul T. Edlefsen, Jay A. Nelson, Jeffrey D. Lifson, Klaus Früh, Louis J. Picker*

- **Broad, novel CD8+ T-cell responses**
- **Supertopes**
- **MHC Class II restricted CD8 responses**

NATURE | VOL 502 | 3 OCTOBER 2013

Immune clearance of highly pathogenic SIV infection

Scott G. Hansen[1]*, Michael Piatak Jr[2]*, Abigail B. Ventura[1], Colette M. Hughes[1], Roxanne M. Gilbride[1], Julia C. Ford[1], Kelli Oswald[2], Rebecca Shoemaker[2], Yuan Li[2], Matthew S. Lewis[1], Awbrey N. Gilliam[1], Guangwu Xu[1], Nathan Whizin[1], Benjamin J. Burwitz[1], Shannon L. Planer[1], John M. Turner[1], Alfred W. Legasse[1], Michael K. Axthelm[1], Jay A. Nelson[1], Klaus Früh[1], Jonah B. Sacha[1], Jacob D. Estes[2], Brandon F. Keele[2], Paul T. Edlefsen[3], Jeffrey D. Lifson[2] & Louis J. Picker[1]

- **Control of SIV leads to eradication**

Test vaccine therapeutically in SIV+ / ART suppressed rhesus monkeys

OREGON HEALTH & SCIENCE UNIVERSITY

BILL & MELINDA GATES foundation

Frederick National Laboratory for Cancer Research

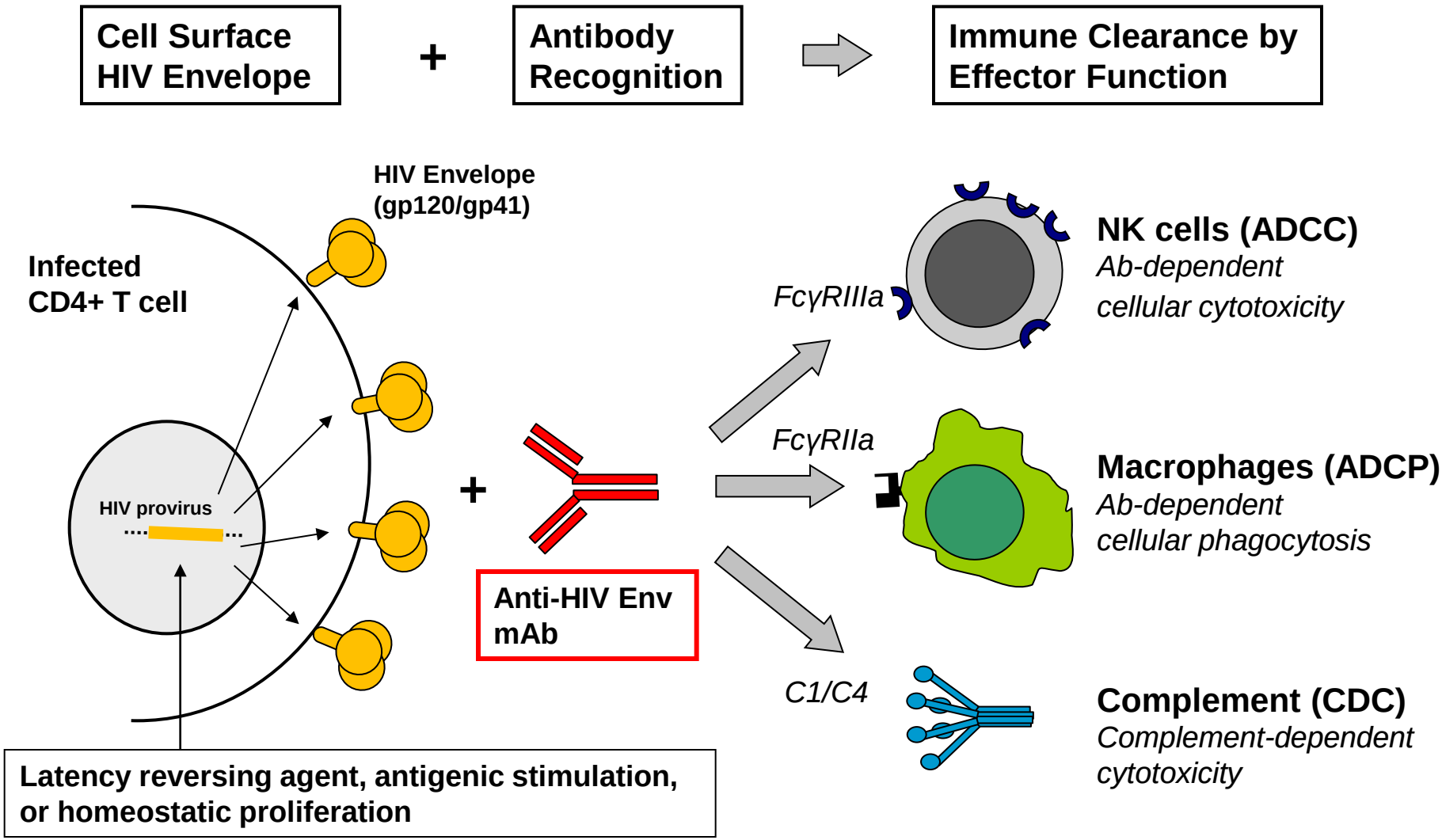
leidos
Leidos Biomedical Research, Inc.

Delaney AIDS Research Enterprise DARE to find a cure

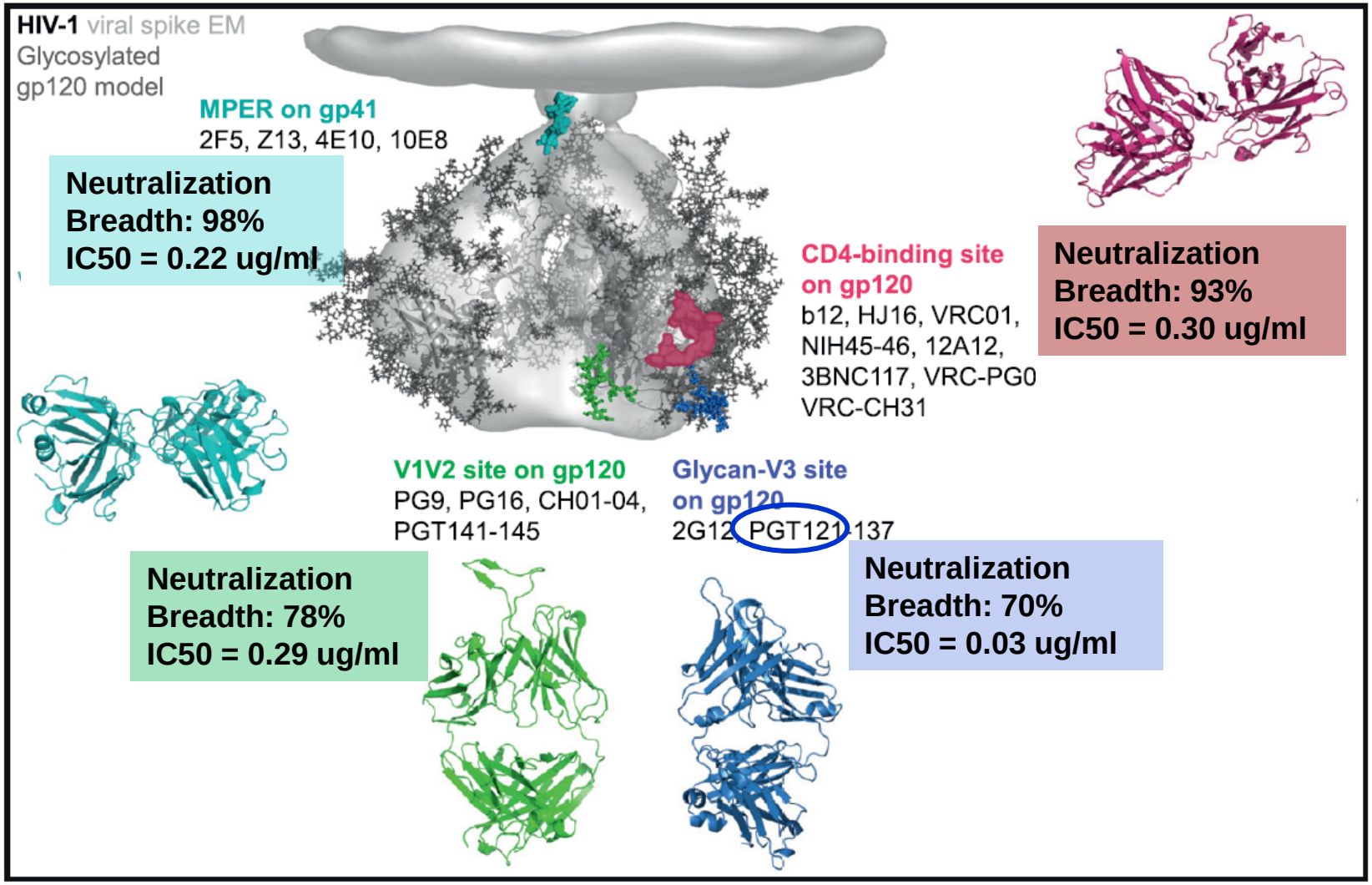
GILEAD

Monoclonal Antibodies Against HIV Envelope Proteins

Can Antibody-mediated Effector Functions Clear HIV Reservoirs (Active and Latent) that Persist During ART?

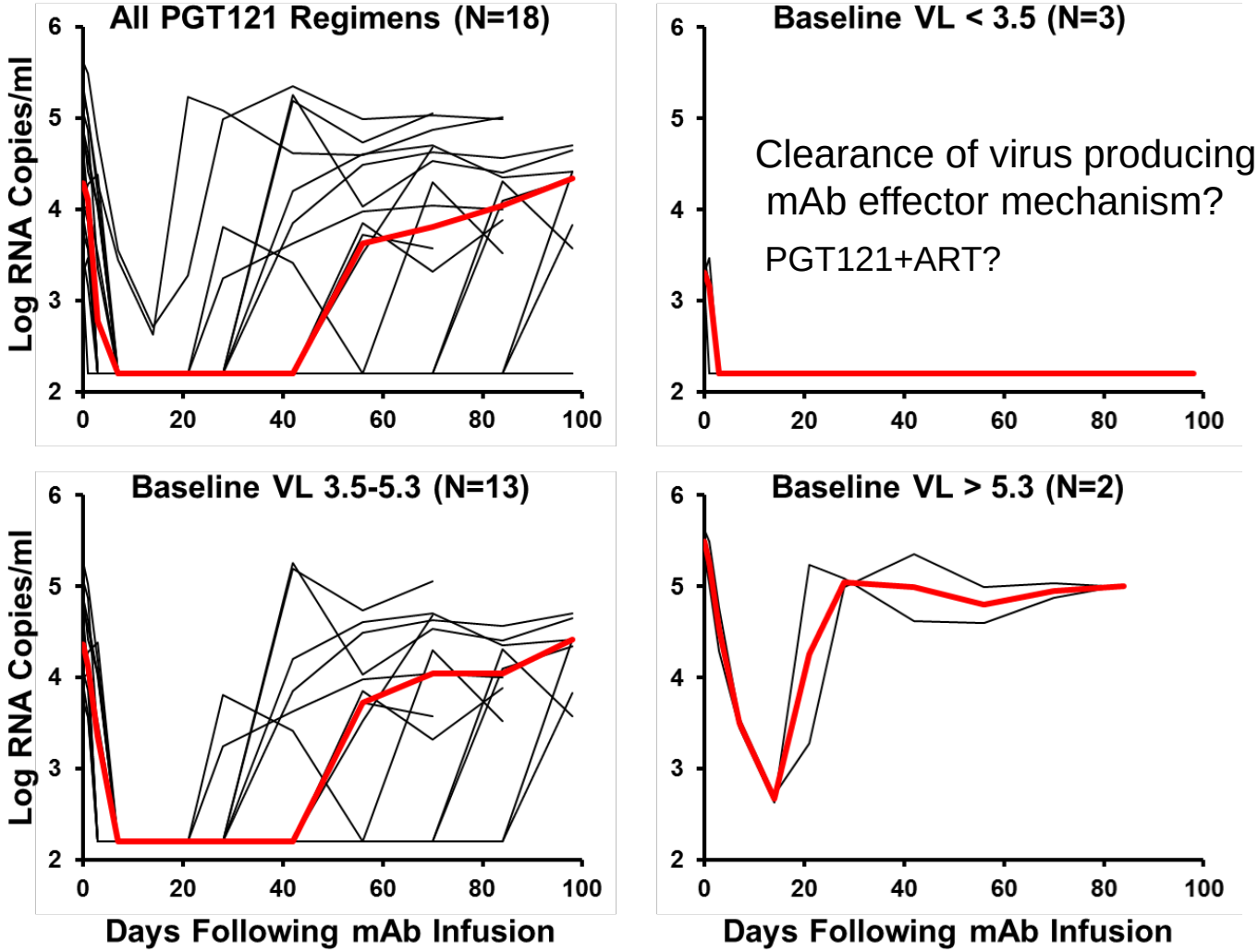


New Generation of Potent and Broadly HIV Neutralizing Human Monoclonal Antibodies

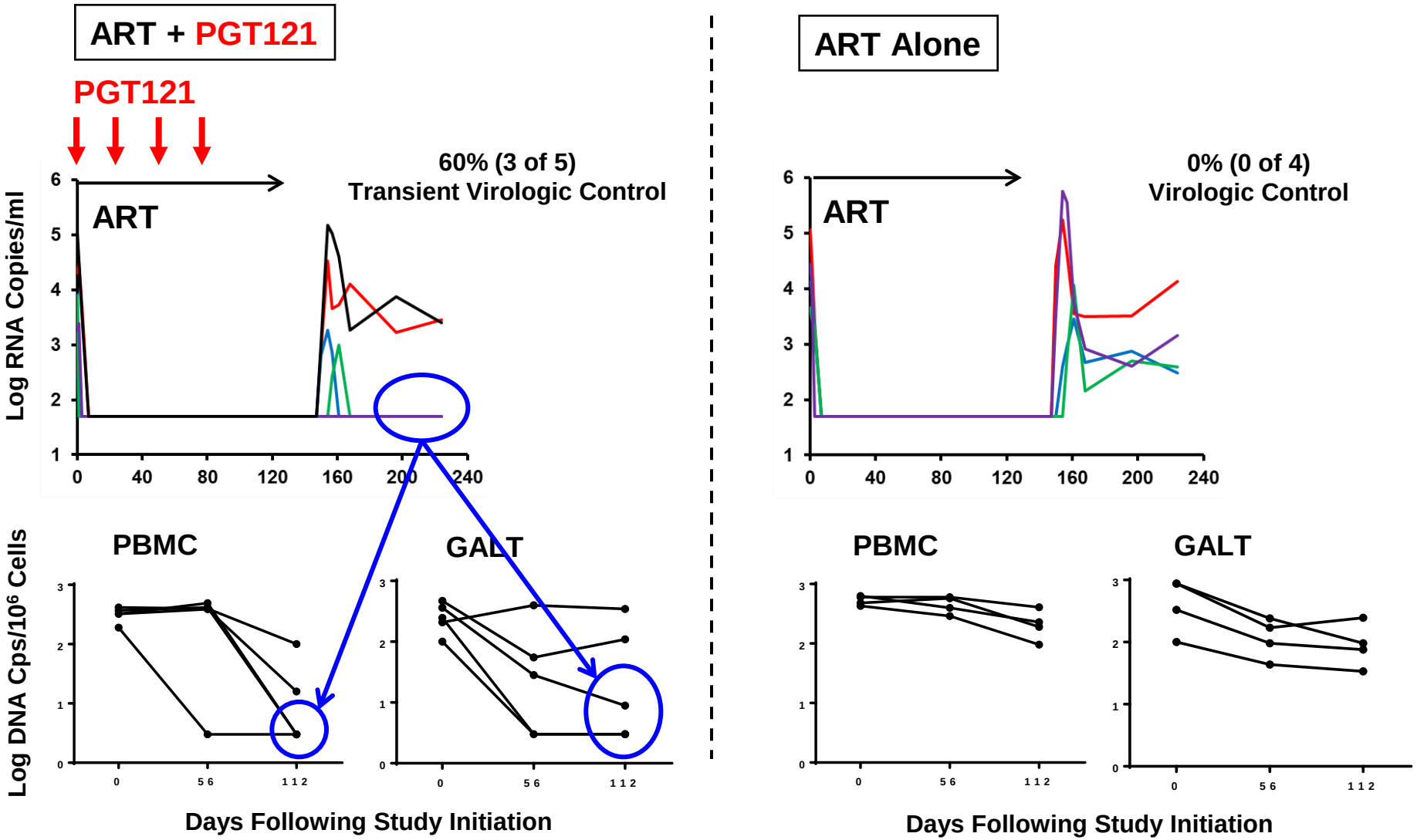


Immunity *37*, September 21, 2012 ©2012

Summary of Plasma Virus Suppression by PGT121 or PGT121-Containing mAb Cocktails (Barouch *et al.* Nature Oct. 30, 2013)



Virologic Control and Tissue vDNA Reduction in SHIV-Infected NHPs Treated with cART and PGT121



Barouch, Strategies for HIV Cure (2014)

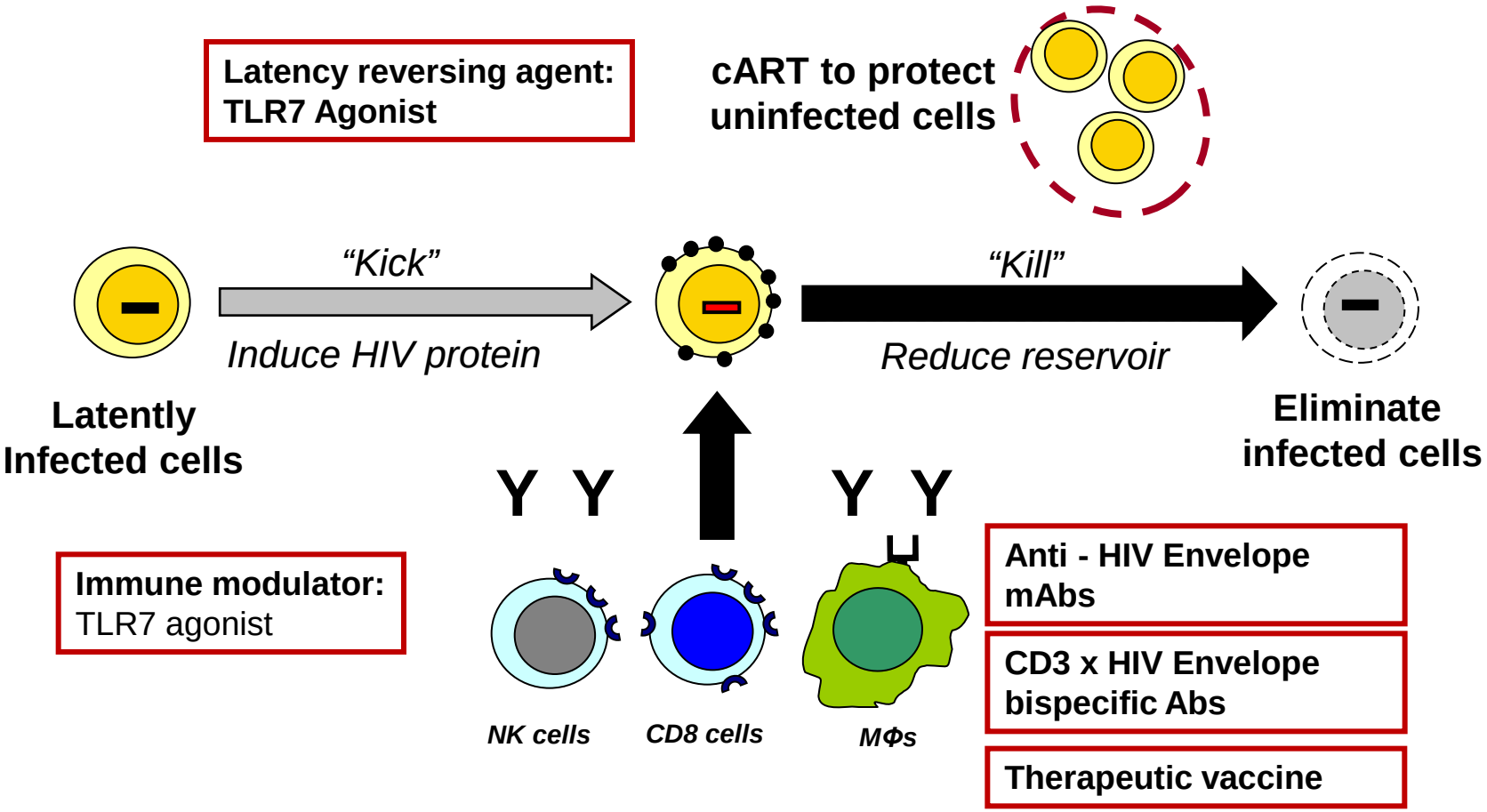
HIV bNabs (Path Forward)

- **Gilead has exclusive license (Theraclone Sciences) to develop anti-gp120/gp41 mAbs, including PGT121**

- **Launched Internal lead optimization program**
  - Which effector function(s) is best for clearing viral reservoirs?
  - Engineer antibodies with enhanced effector function(s)
  - Select antibody for clinical testing

- **Collaborating with Dan Barouch (BIDMC) / Gates Foundation on PGT121 GMP manufacturing and clinical testing**

Potential Next Generation Combination Therapies for the Treatment of HIV Infection



Acknowledgements

Gilead

- Bei Li
- Jillian Hattersley
- Angela Tsai
- Alivelu Irrinki
- Jasmine Kaur
- Jeff Murry
- Derek Sloan
- Tomas Cihlar
- John Corbin
- Tiffany Barnes
- Joe Hesselgesser

Quest Clinical

- Jay Lalezari
- Michele King
- Donors

Univ. of Pittsburgh

- John Mellors
- Deb McMahon
- Elizabeth Fyne

ACTG and Celgene

Beth Israel Deaconess Medical Center

- Dan Barouch
- James Whitney

Scripps

- Dennis Burton

Theraclone

- Kristine Swiderek
- Po-Ying Chan-Hui