The potential role of PD-1/PD-L1 blockade in HIV Remission and Cure Strategies

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Definitions and Quantifications of HIV cure

Extremely difficult to achieve

Viral Eradication → **Elimination of all** virus from the body

More feasible?

Virologic Remission →

- Host control of viral replication without continued treatment
- Immune function restored and stabilized
- Reduction of HIV-induced inflammation
- Reduced risk of transmission to others

Ultimate goal
→ Life-long or completely drug-free remission

… how do we get there?

Katlama C *et al. Lancet* 2013; 381(9883):2109–2117.

HIV remission likely will require combination of agents targeting different barriers to eradication

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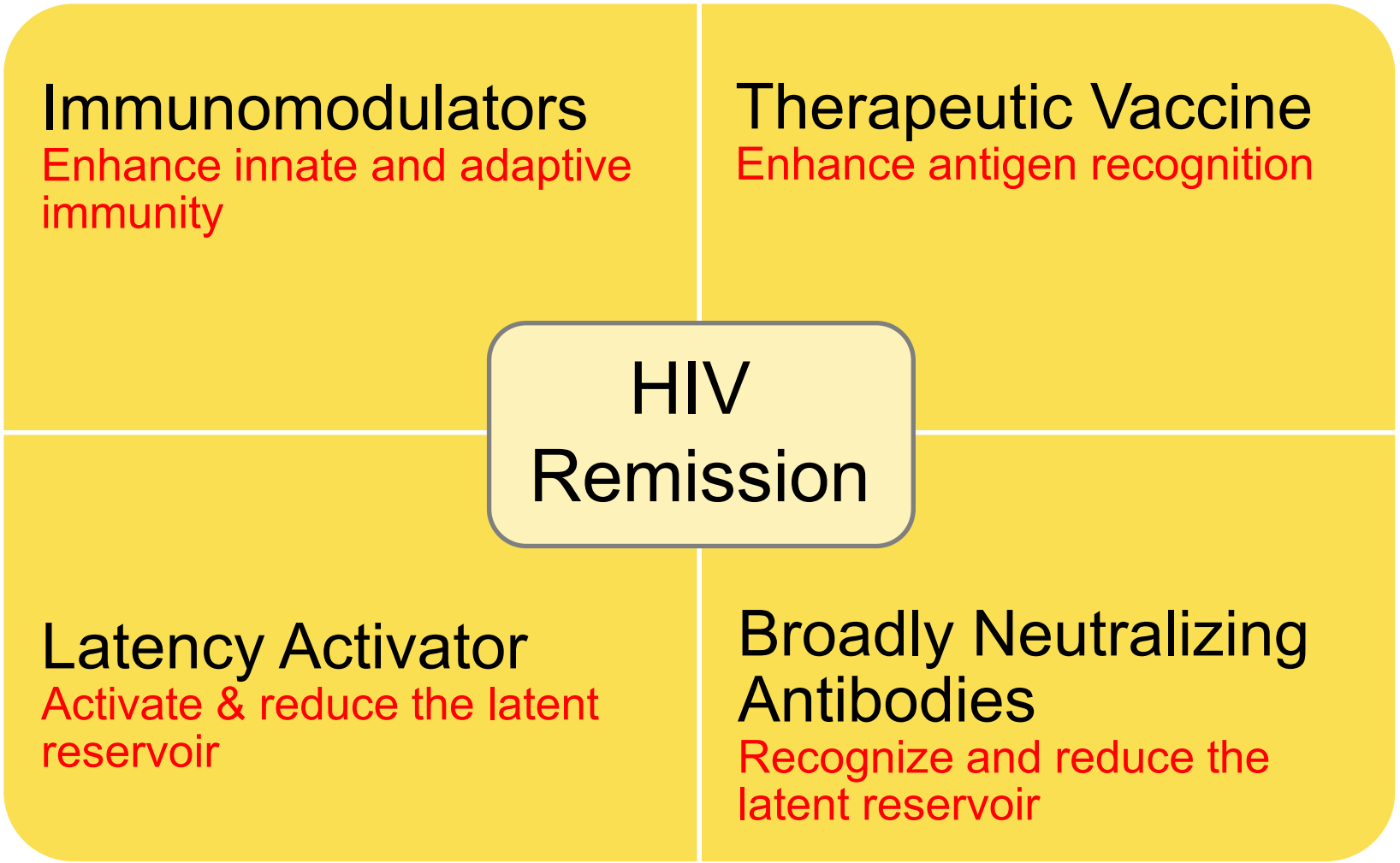
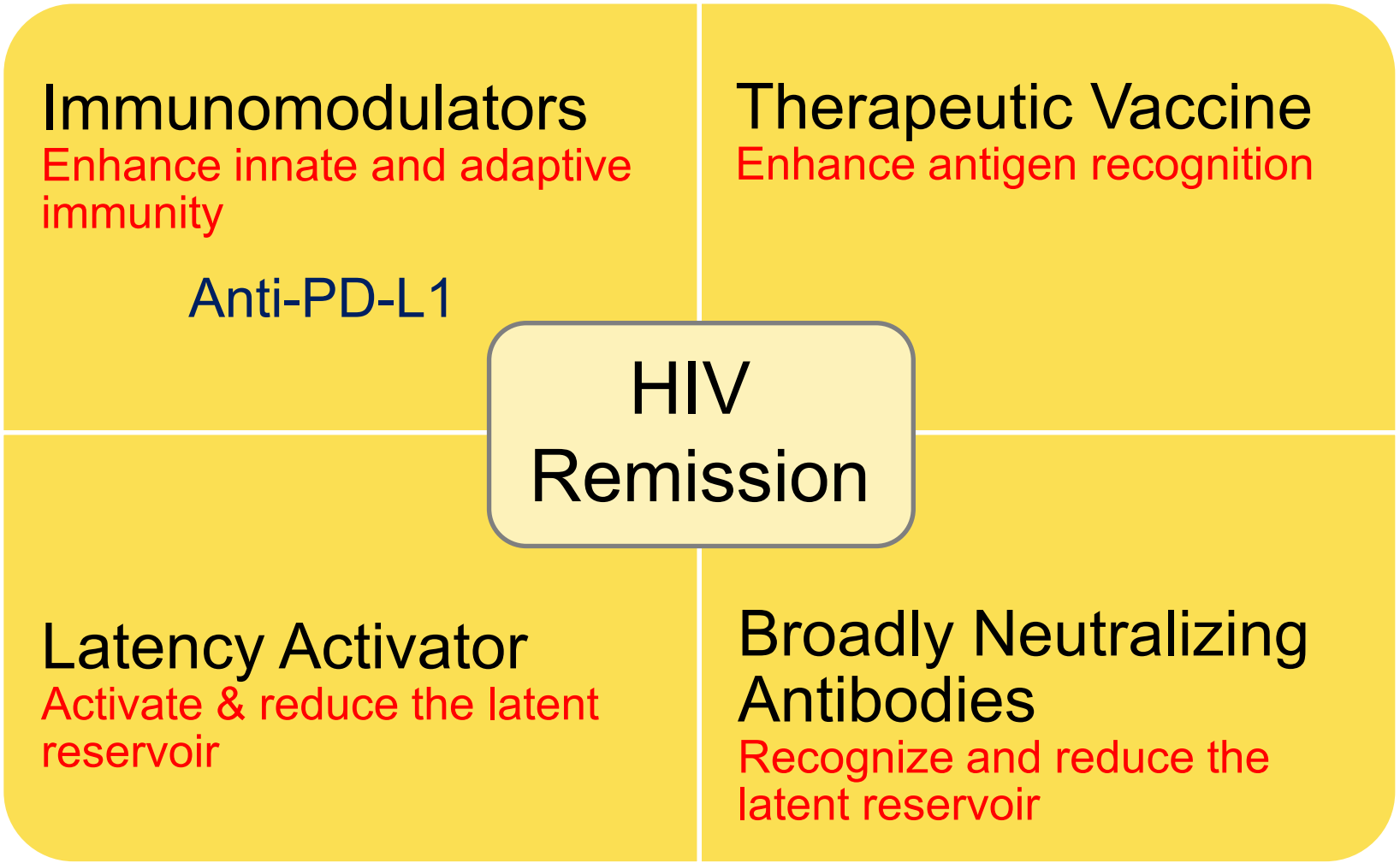
Which combinations … ?

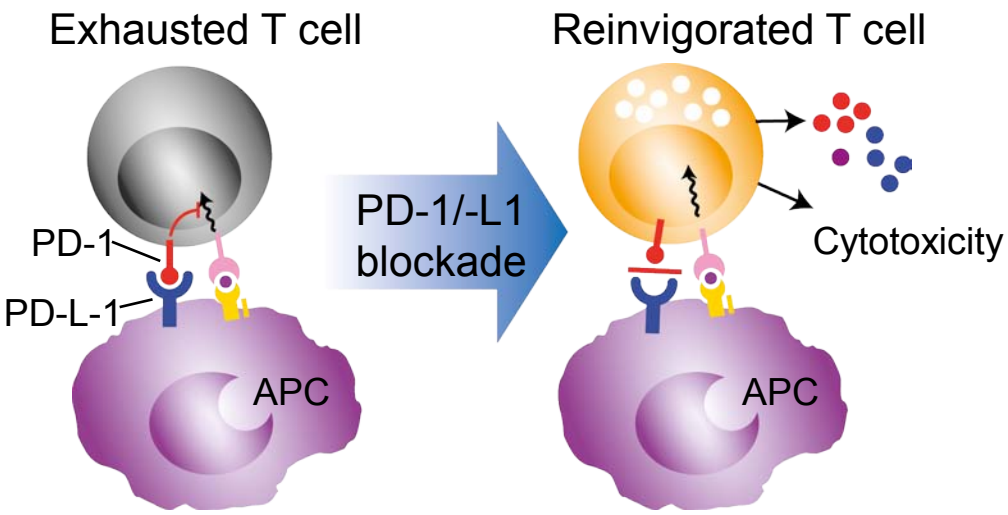


Which combinations … ?



PD-1/PD-L1 pathway in T cell exhaustion

- **Virus-specific T-cells are critical to control of chronic viral infections[1,2,3,4,5]**
- **PD-1 is a key inhibitory receptor affecting T-cell response[6]**
  - Elevated on virus-specific T-cells in chronic HIV[3,7], HBV[8] and HCV[9] infection
    - Both CD4+ and CD8+ subsets
      - Cells display exhausted phenotype *ex vivo / in vitro*
    - Decreases with epitope escape mutation[7,10] or control of infection[3,4,7]

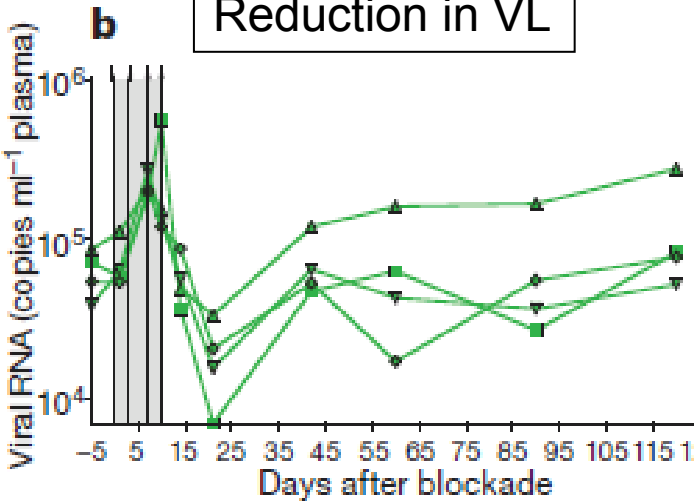


- **PD-1/PD-L1 blockade restores function to exhausted T cells**
  - Significant effects on T-cell function and viral load observed upon PD-1/PD-L1 blockade both *in vitro*[3,4,11,12] **and *in vivo*[5,6,13]**

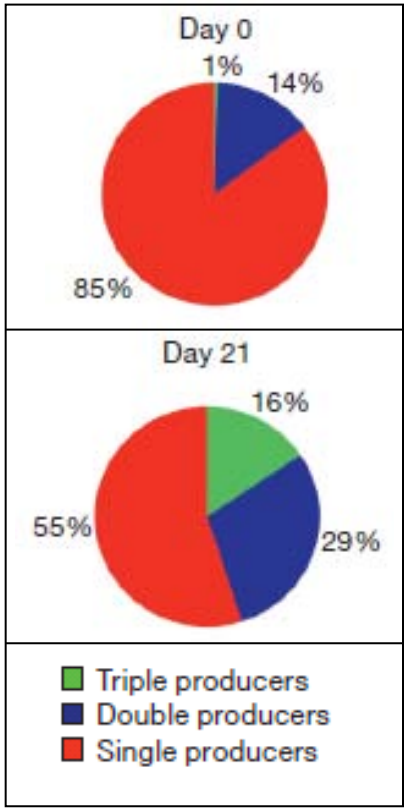
1. Day CL. et.al. J Virol. 2002; 2. Thimme R. et.al. J Virol. 2003; 3. Trautmann L. et al Nat.Med. 2006; Day CL. et.al. Nature. 2006; Petrovas C. et al., JEM 2006; 4. Evans A. et.al. Hepatol. 2008; 5. Velu V. et al. Nature. 2009; 6. Barber D.L. et al. Nature. 2006; 7. Streeck H. PLOS Med. 2008; 8. Boni C. et.al. J Virol. 2007; 9. Golden-Mason L. et.al. J Virol. 2007; 10. Rutebemberwa A. et.al. J Immunol. 2008; 11. Urbani S. et.al. J Hepatol. 2008; 12. Fisicaro J. et al. Gastro. 2010; 13. Palmer B. et al J. Imm. 2012.

PD-1 blockade in unsuppressed SIV-infected macaques

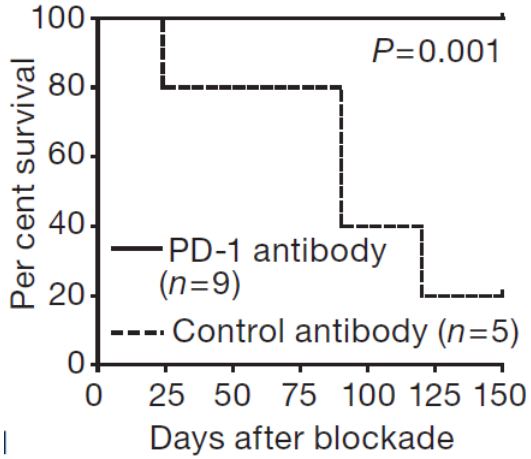
Reduction in VL



T Cell Function



Survival



Velu et al, Nature 2009

Treatment with αPD-1:

- Transiently affected viremia
- Restored T and B cell numbers & functions
- Prolonged survival

PD-1 pathway blockade during suppressive cART?

- Most relevant situation for HIV-infected patients

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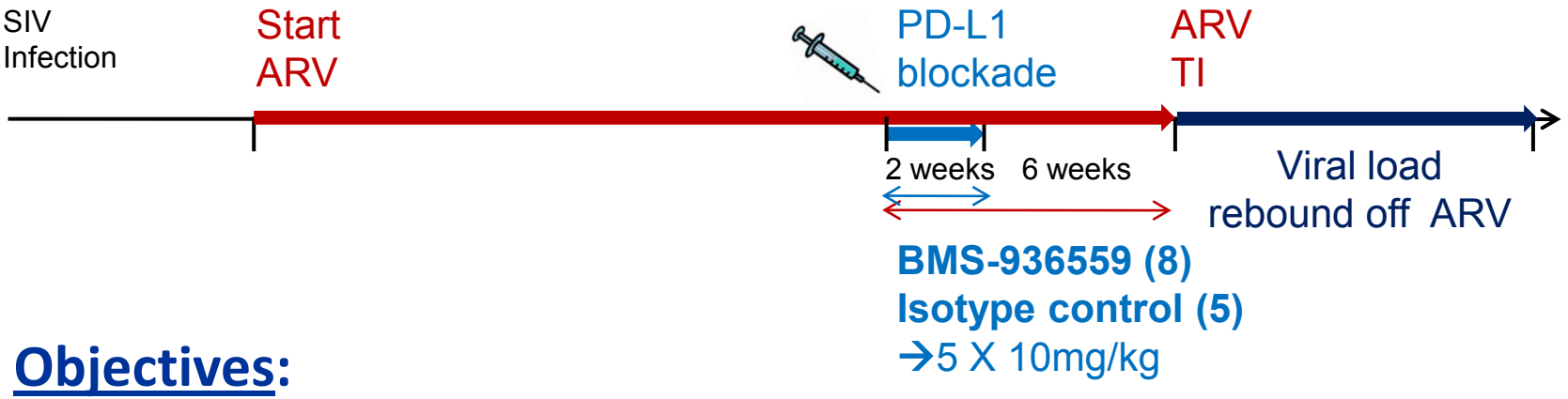
PD-L1 blockade in ARV suppressed SIVmac251-infected Rhesus Macaques

In collaboration with James Whitney (BIDMC, Boston)

Hypothesis:

- **Treatment of ARV-suppressed SIV infected macaques with αPD-L1 should:**
  - restore SIV-specific T cell function. Subsequently, this may:
    - reduce the latent SIV reservoir
    - lead to host control of virus following interruption of ARV

Study design:



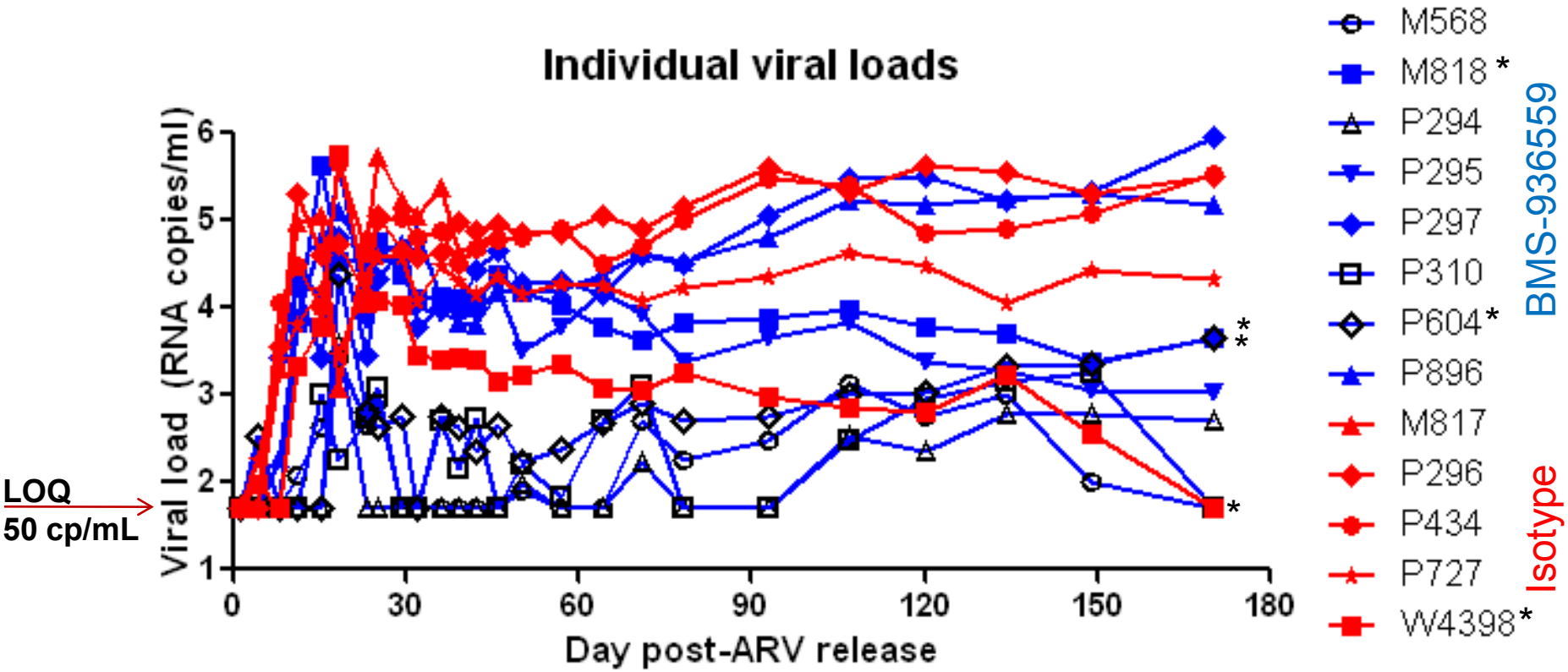
Objectives:

- **Determine whether multiple doses of BMS-936559 affect:**

1. Cell-associated viral DNA (latent reservoir) in tissues and periphery,
2. Virus recrudescence after cessation of ARV treatment.

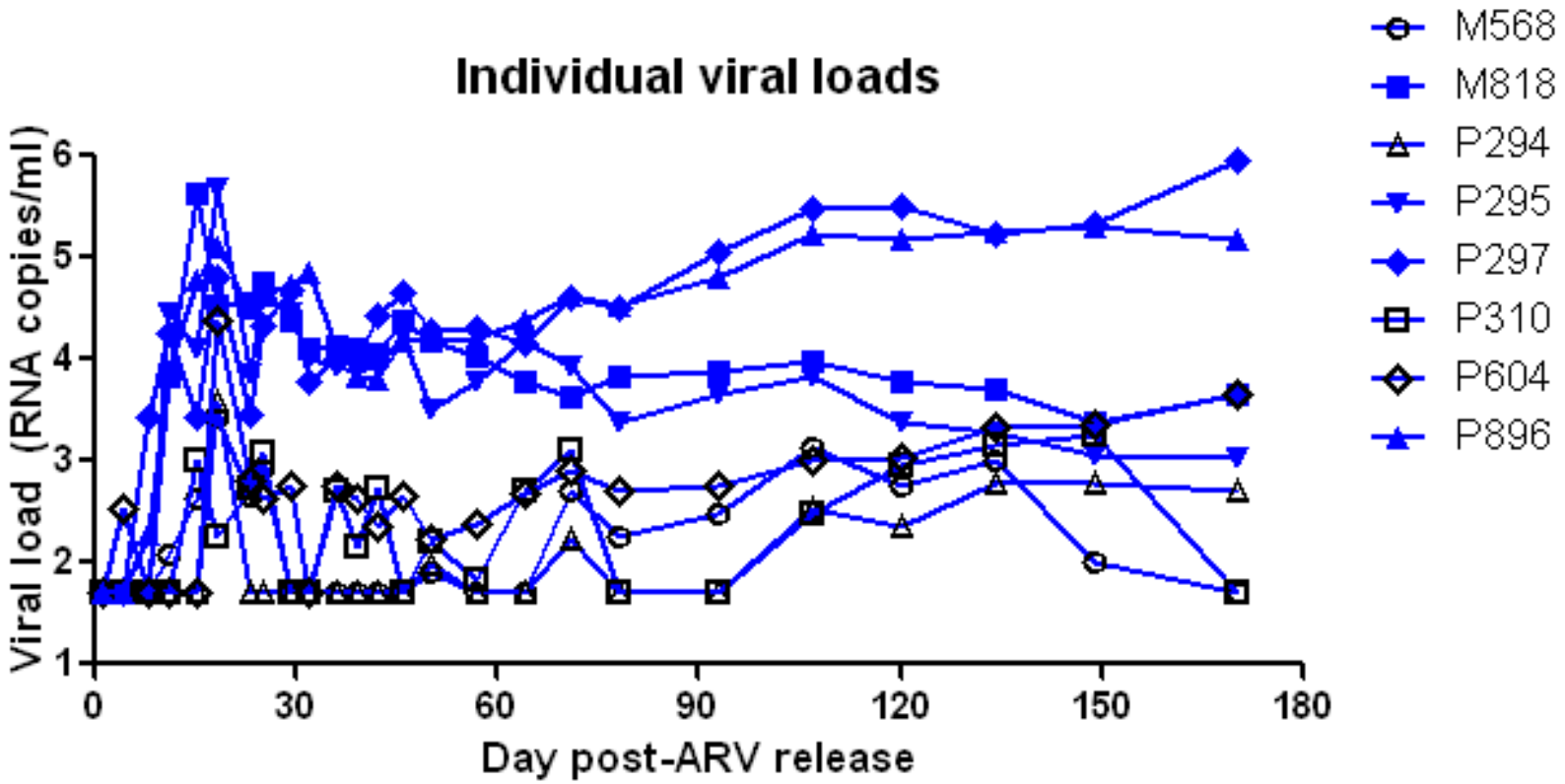
Individual post-TI VL rebound kinetics:

Comparison of BMS-936559- and Isotype-treatment groups



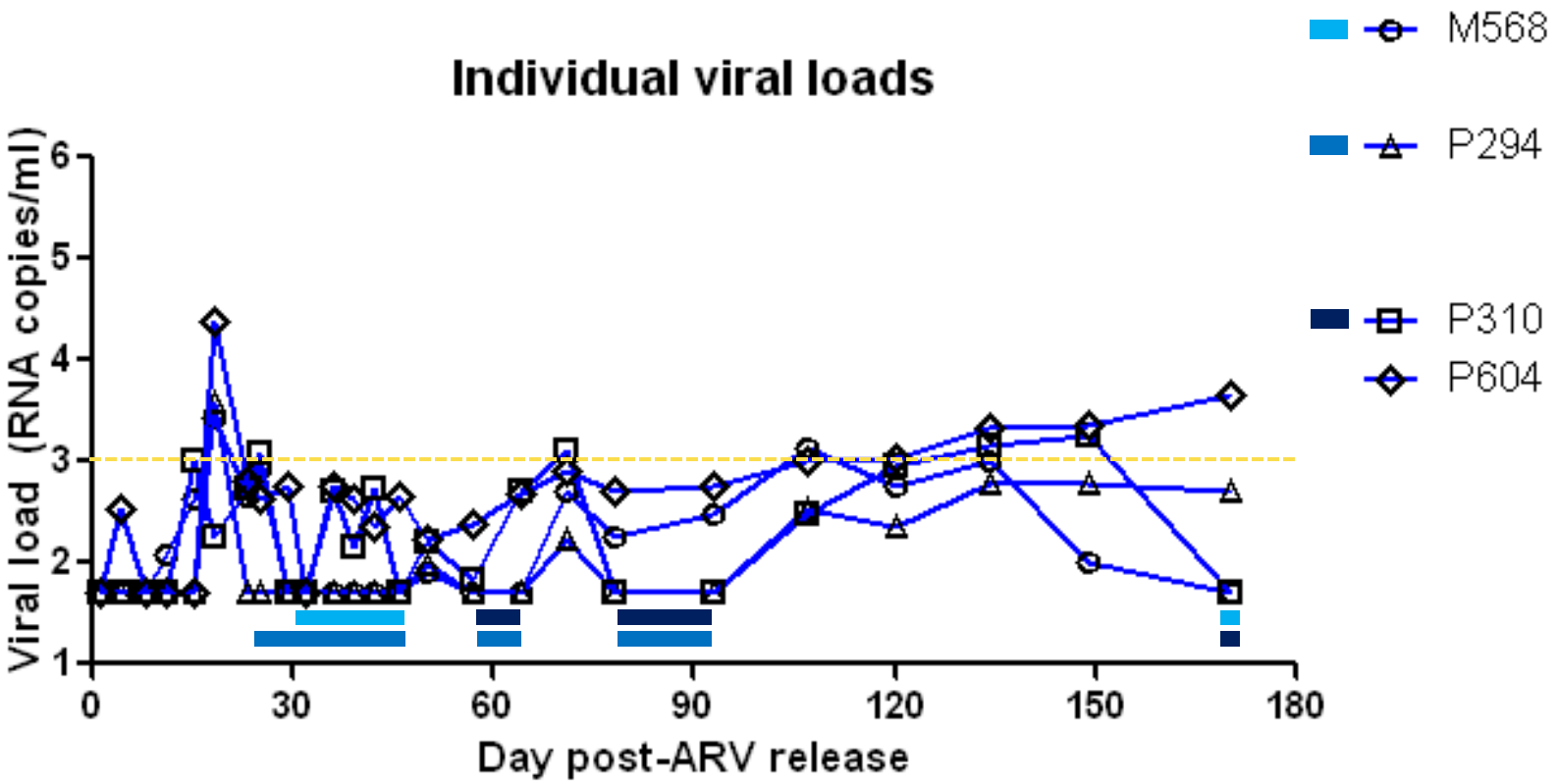
- All animals experienced rebound in viral load post-TI
- Most viral loads stabilized at an apparent a new set-point

Individual post-TI VL rebound kinetics:
BMS-936559 Treatment Group



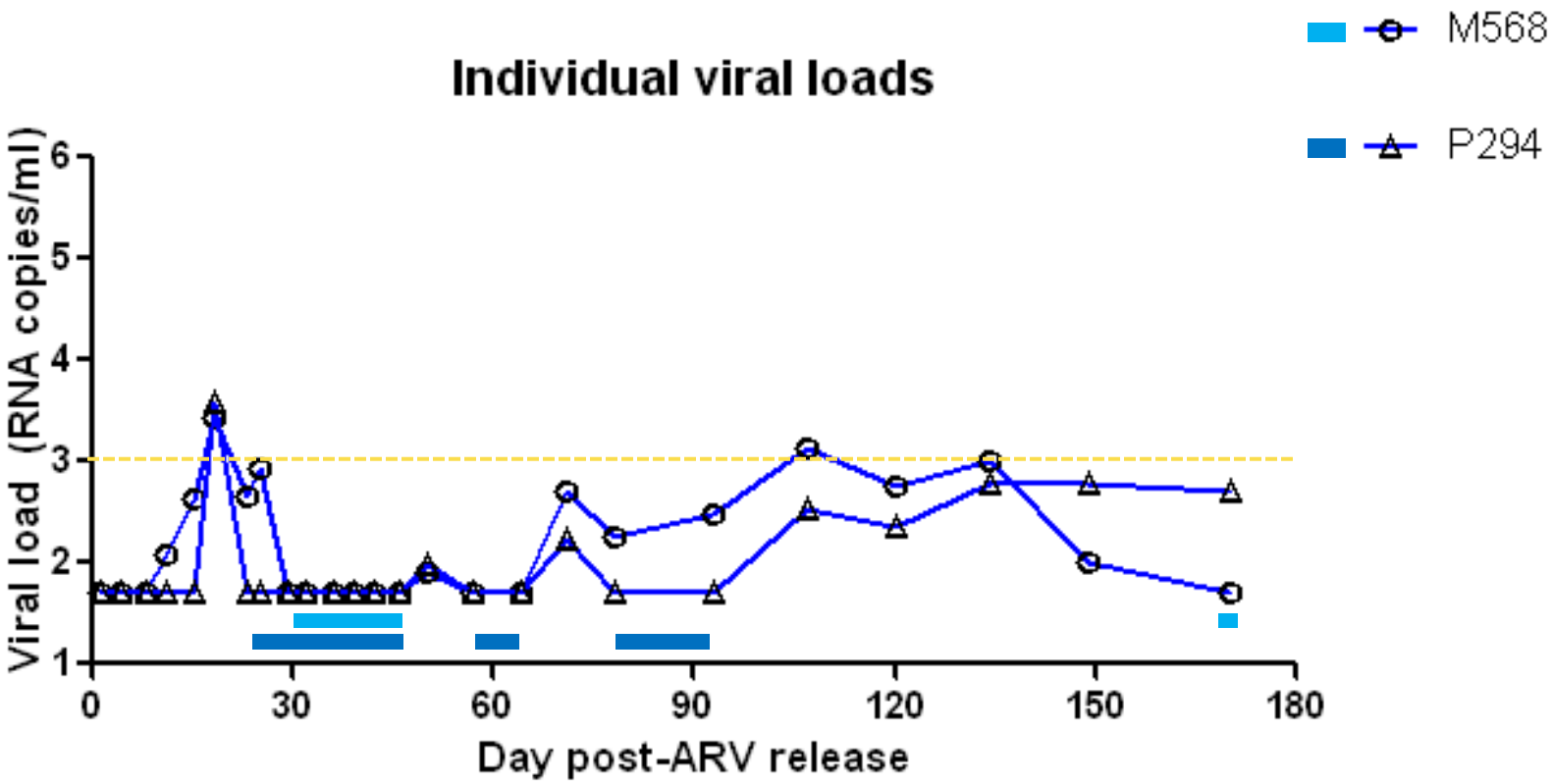
- BMS-936559 treatment group could be separated into two distinct groups: BMS-936559-responders and -non-responders

Individual post-TI VL rebound kinetics:
BMS-936559 Treatment-response group



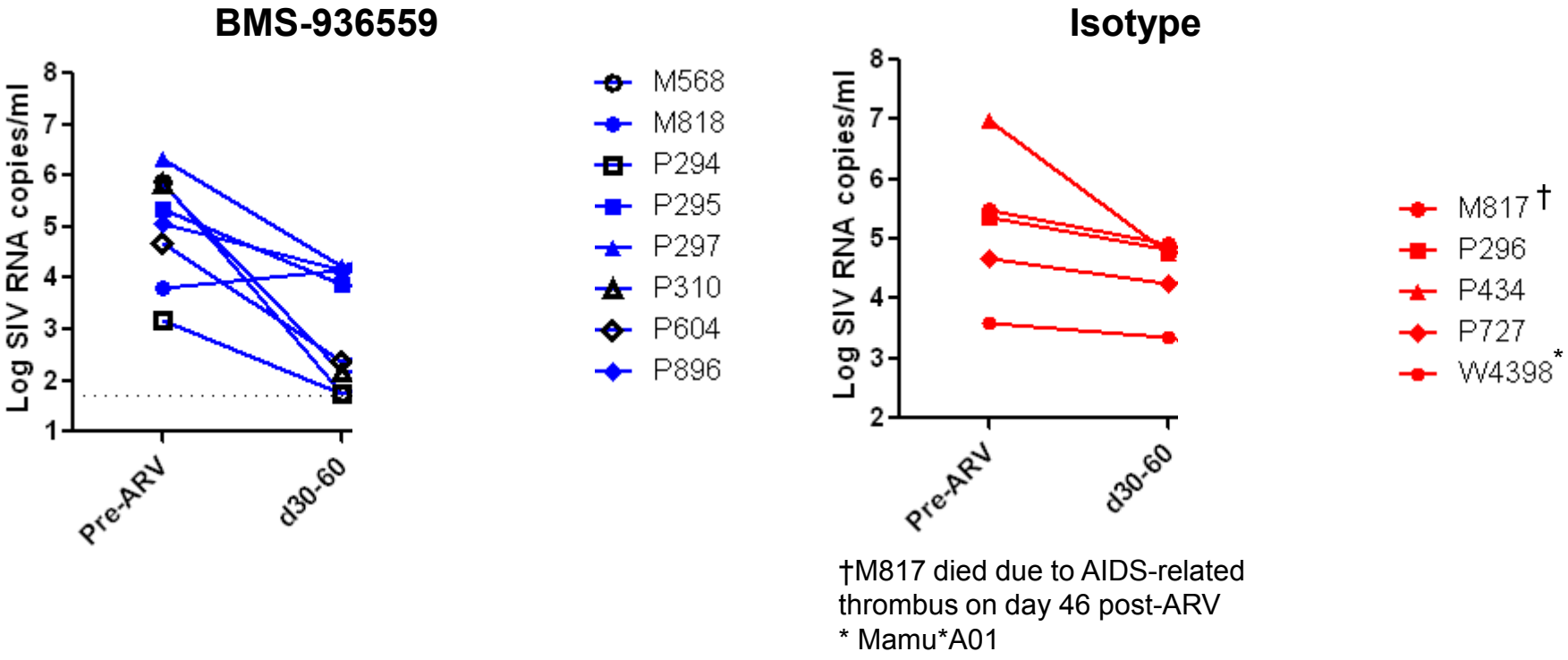
- BMS-936559-responders: 4 out of 8 BMS-936559-treated animals had lower viral loads
- 3 had episodic periods of undetectable VL

Individual data on kinetics of post-TI VL rebound:
BMS-936559 Treatment-response group (2)



- 2 of 4 treatment responders had undetectable VL for 3-4 weeks
- These treatment responders remained below 1000 RNA cp/mL until the end of the study (day 170 post-TI)

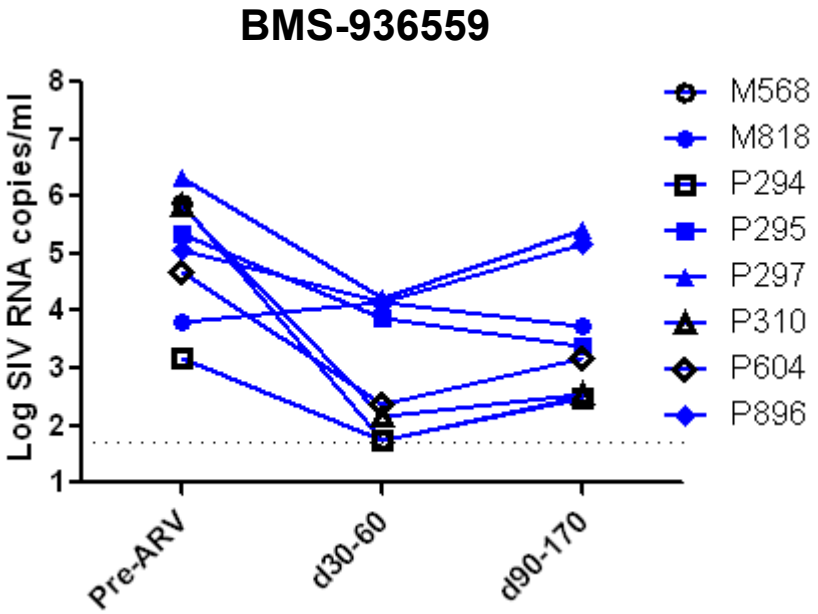
Comparison of pre-ART and post-TI VL

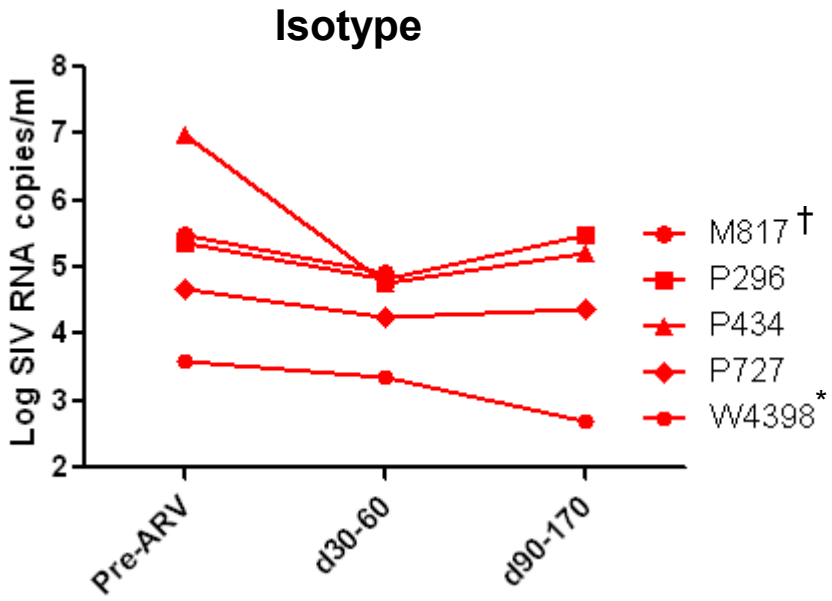


†M817 died due to AIDS-related thrombus on day 46 post-ARV
* Mamu*A01

- Most animals in the BMS-936559-treatment group had significantly lower post-TI VL compared to pre-ART VL set point

Comparison of pre-ART and post-TI VL





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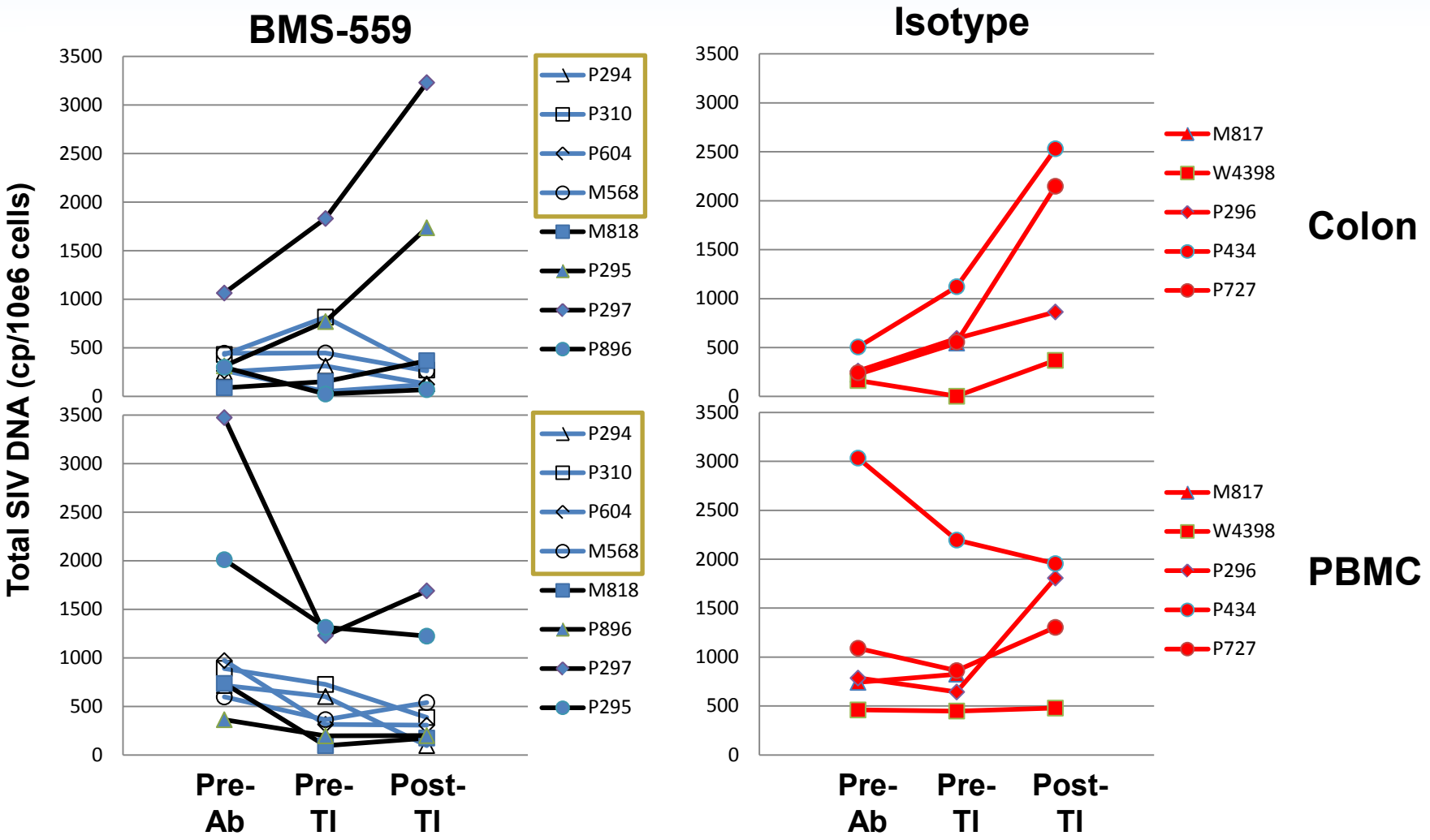
Trend in Total SIV DNA



- SIV DNA in isotype group increased post-TI, but not in the BMS-936559 treatment responders

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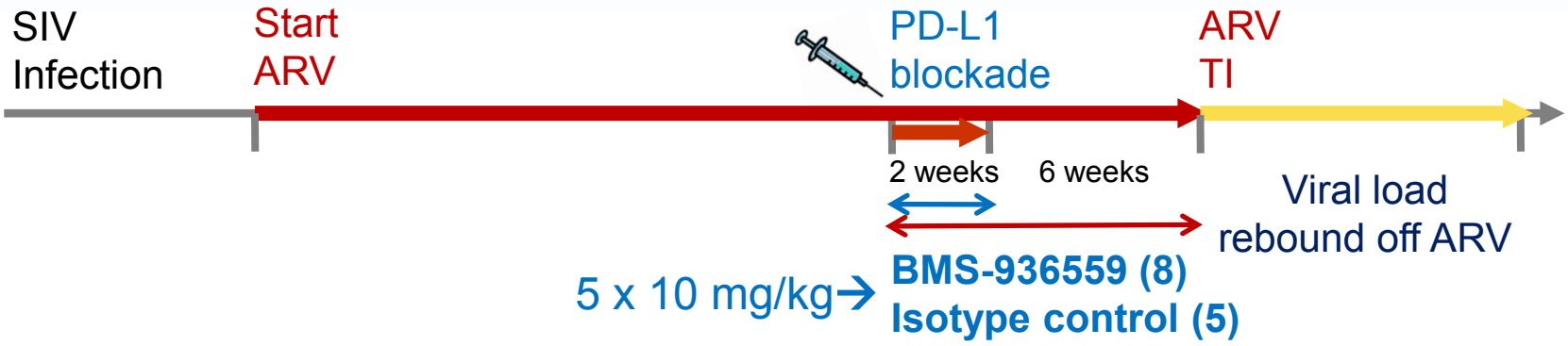
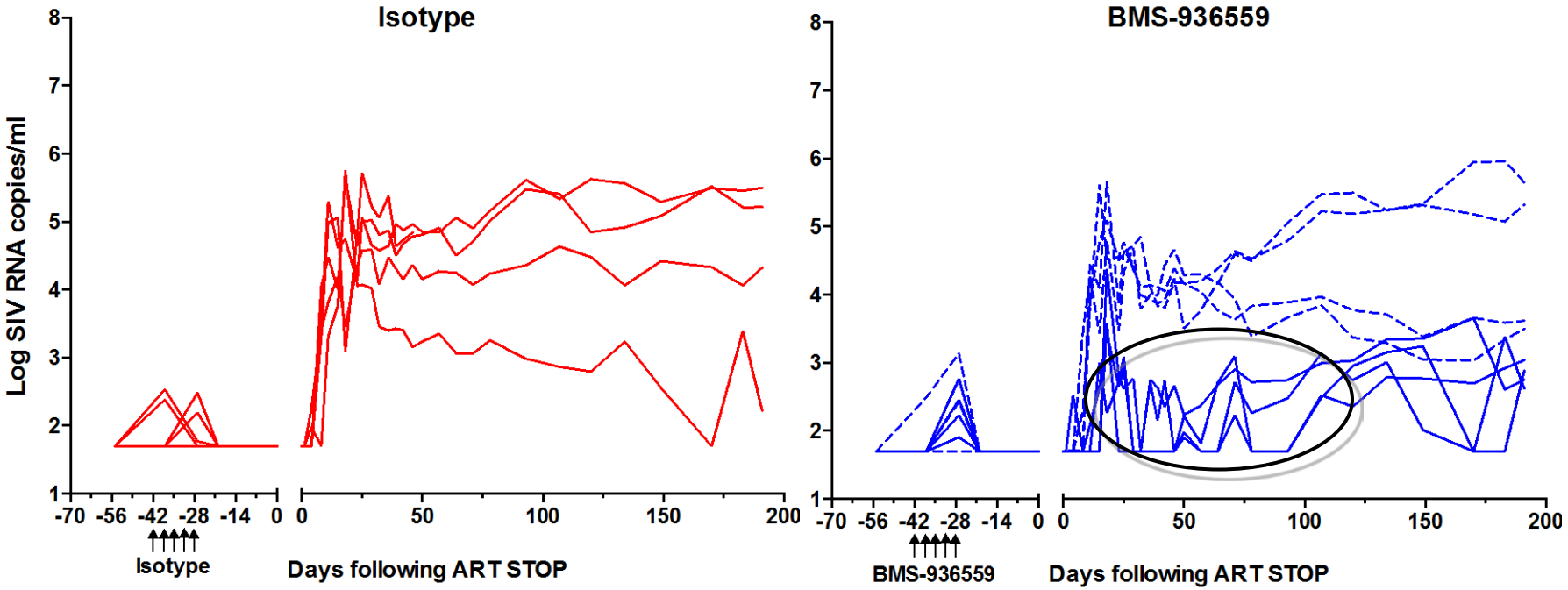
Effect of Anti-PD-L1 in SIV-infected Monkeys





How can anti-PD-L1 post-ATI responses be expanded and sustained?

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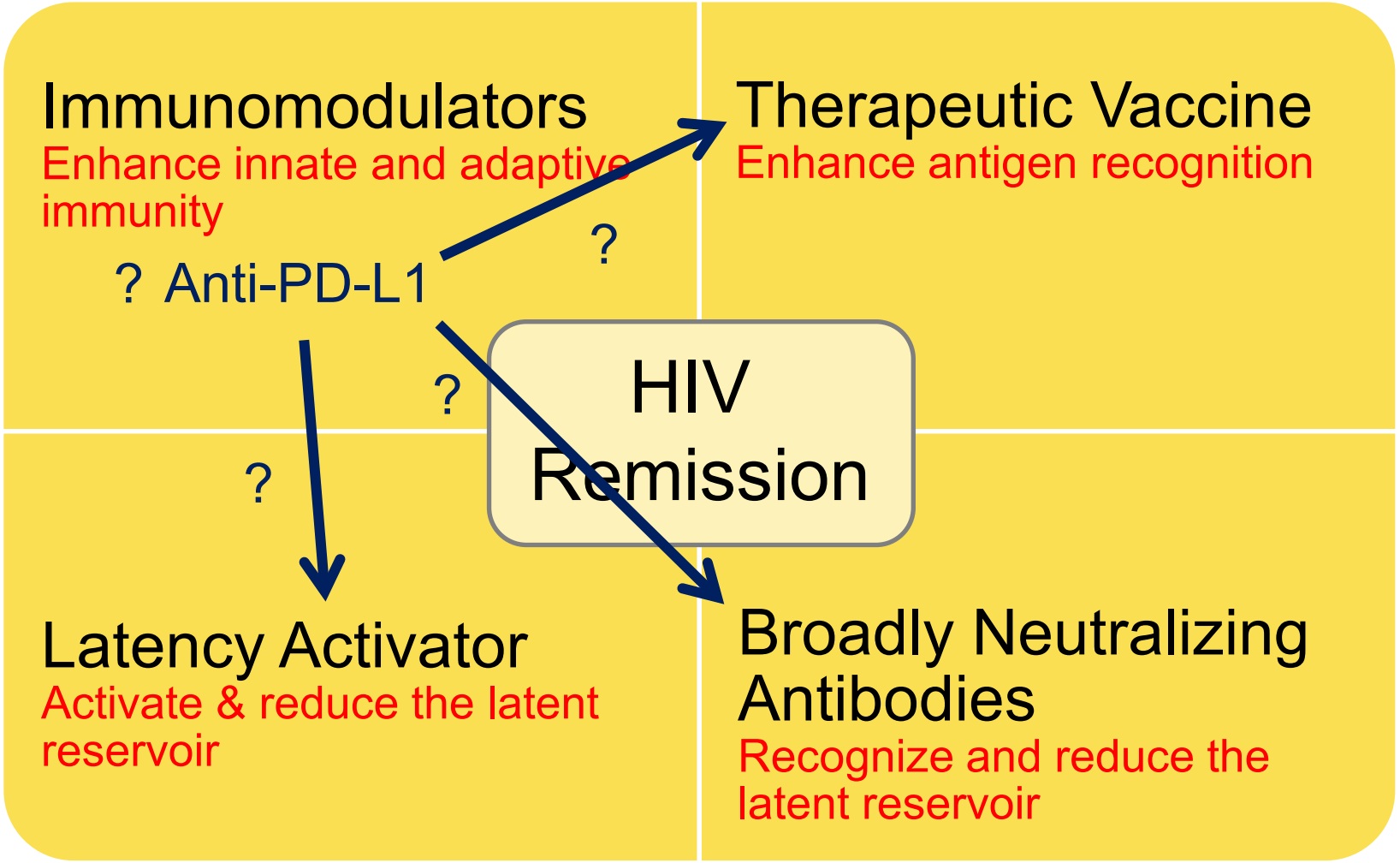
Combinations of modalities likely will be required to Achieve Remission…



…which ones?

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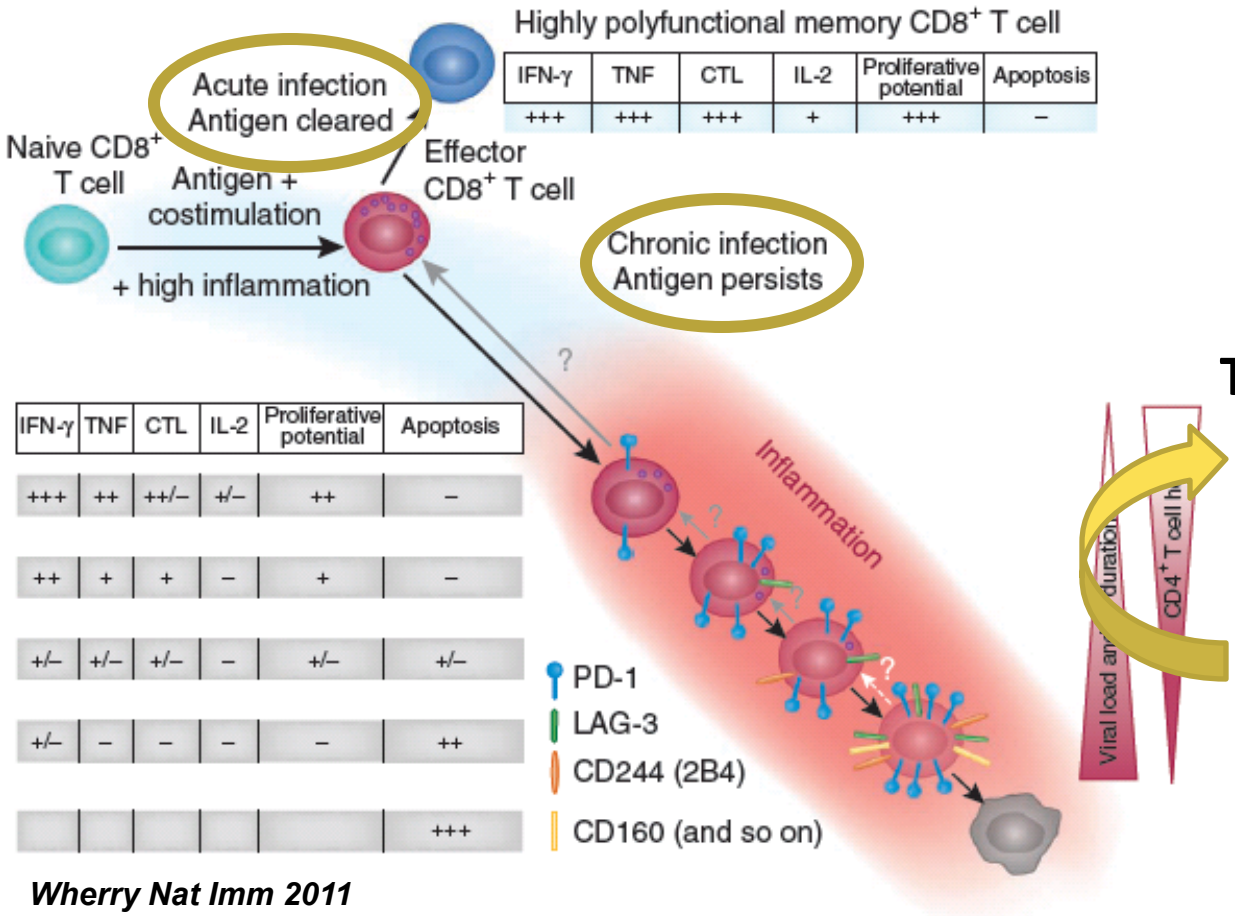
Fully Addressing T Cell Exhaustion



Wherry Nat Imm 2011

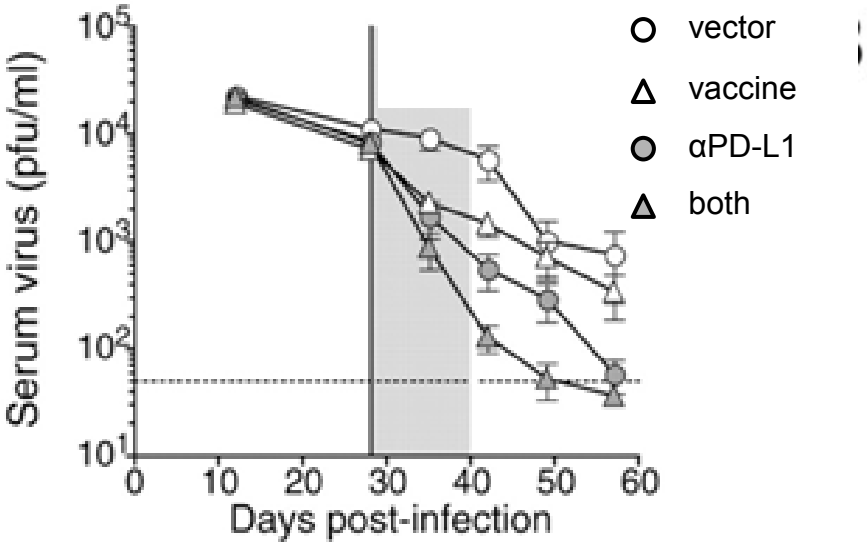
T cell Exhaustion:

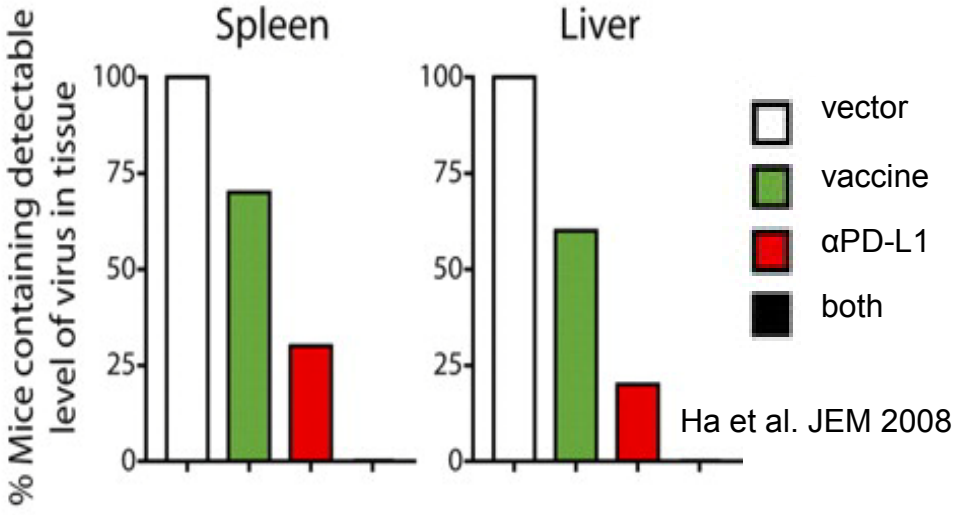
- Progressive loss of function
- Accompanied by expression of multiple inhibitory receptors

Are multiple Checkpoint blockades required to fully restore T cell function?

Evidence that combination of αPD-L1 & Therapeutic Vaccination can clear chronic viral infections

LCMV mouse model of chronic viral infection





Ha et al. JEM 2008

Combination therapy provided:

- Better virologic control both in periphery and tissues
- Correlated with improved LCMV-specific T cell number/function
- Produced a response in a greater number of animals

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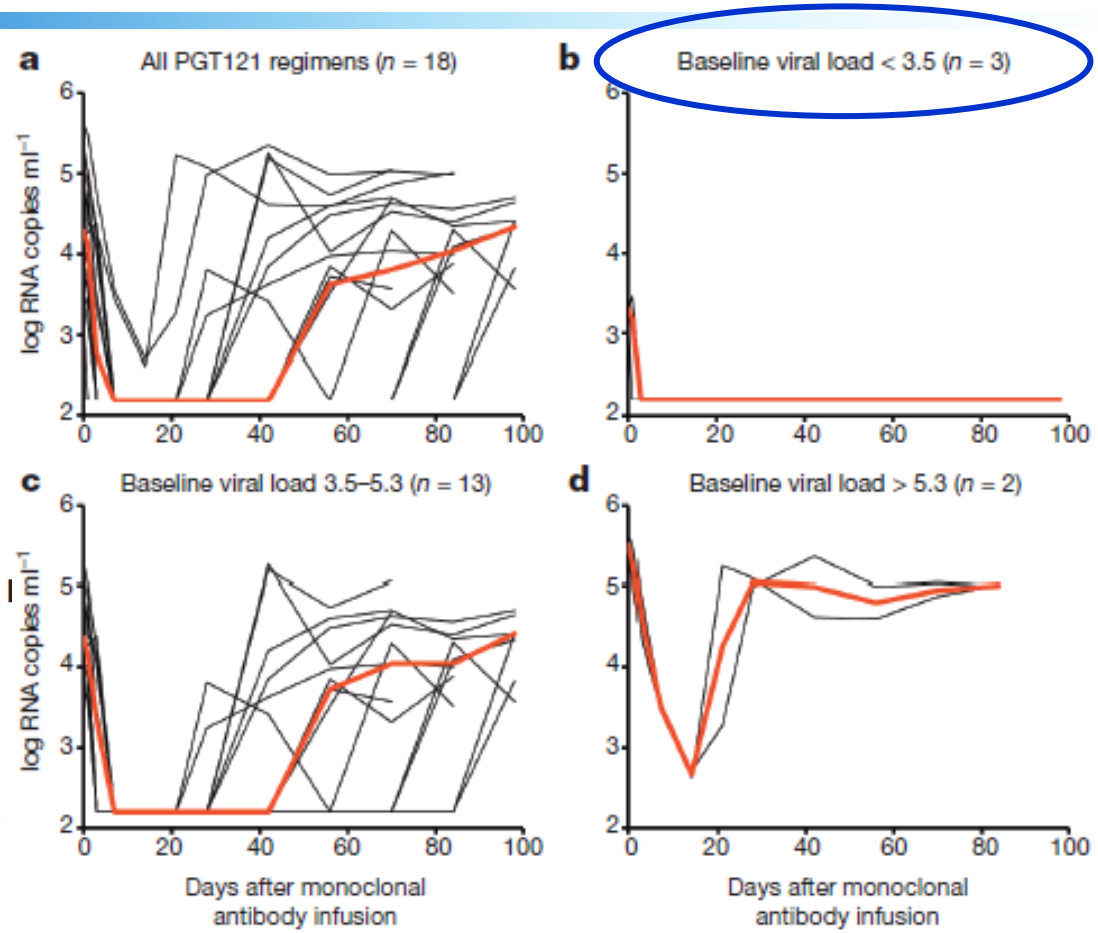
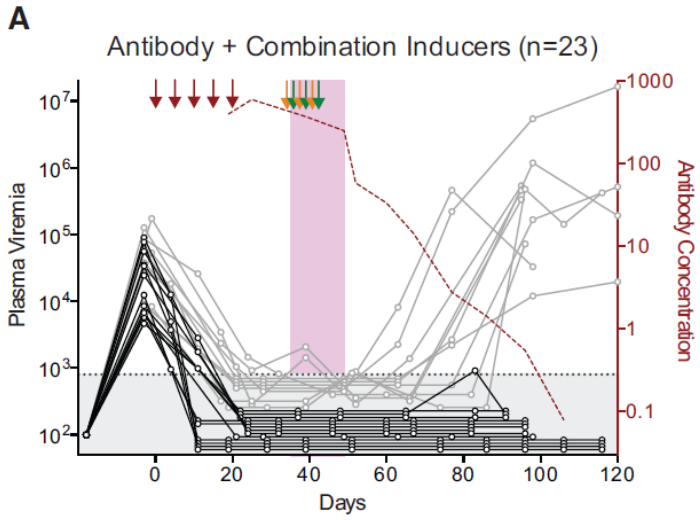
Can additional agents add to the arsenal?

BnAb therapeutic effect in viremic SHIV-infected monkeys

- Particularly effective in those animals with low baseline VL



Barouch et al., Nature 2013



Stromberg et. Al., Cell 2014

Combination of BnAb with latency activators produced sustained effect in HIV/Hu Mouse model

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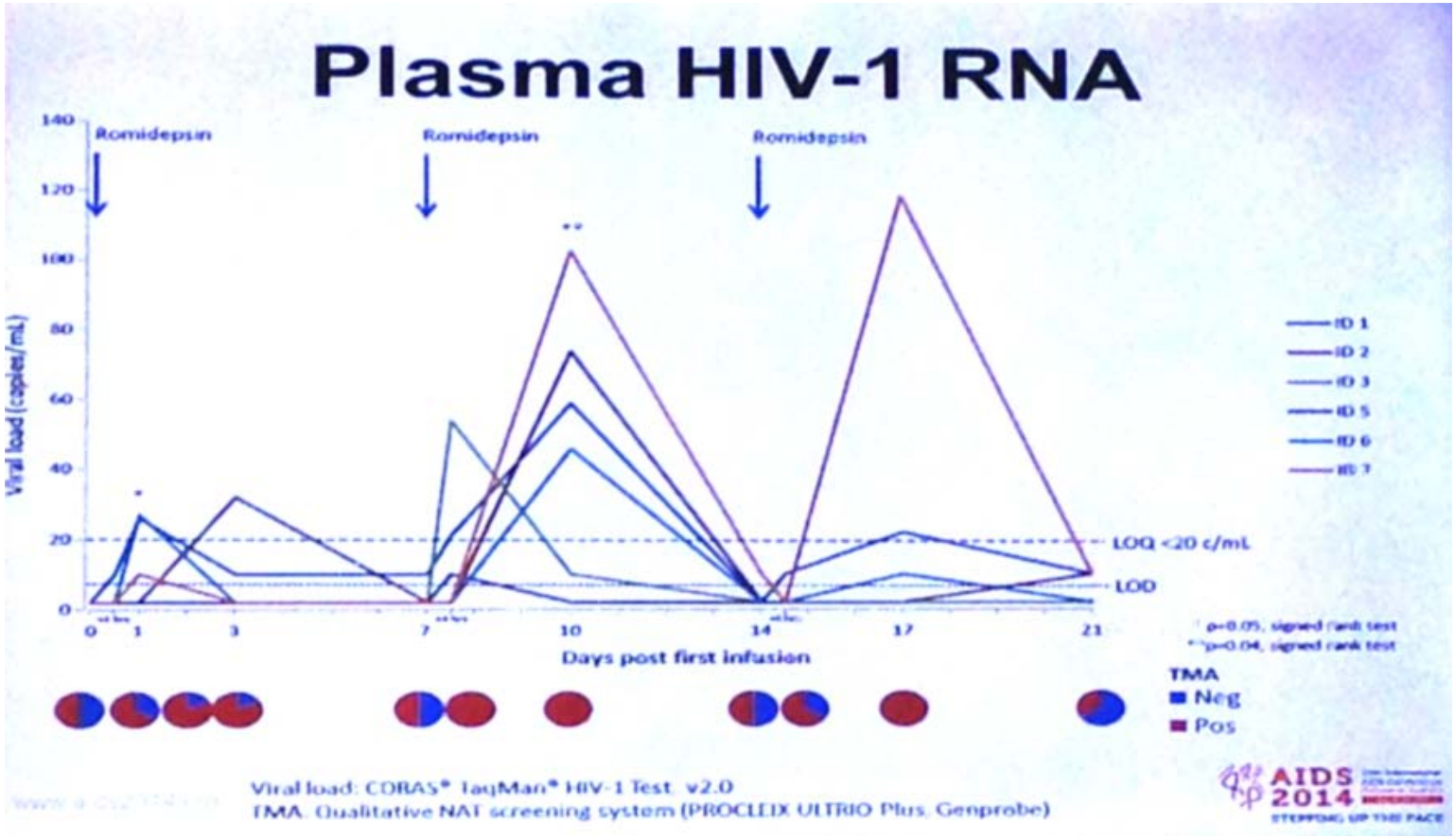
Effect of a strong Latency Re-activating Agent on VL



Sogaard et al Melbourne, July 20. 2014

→ Screening and characterizing new compounds as LRAs

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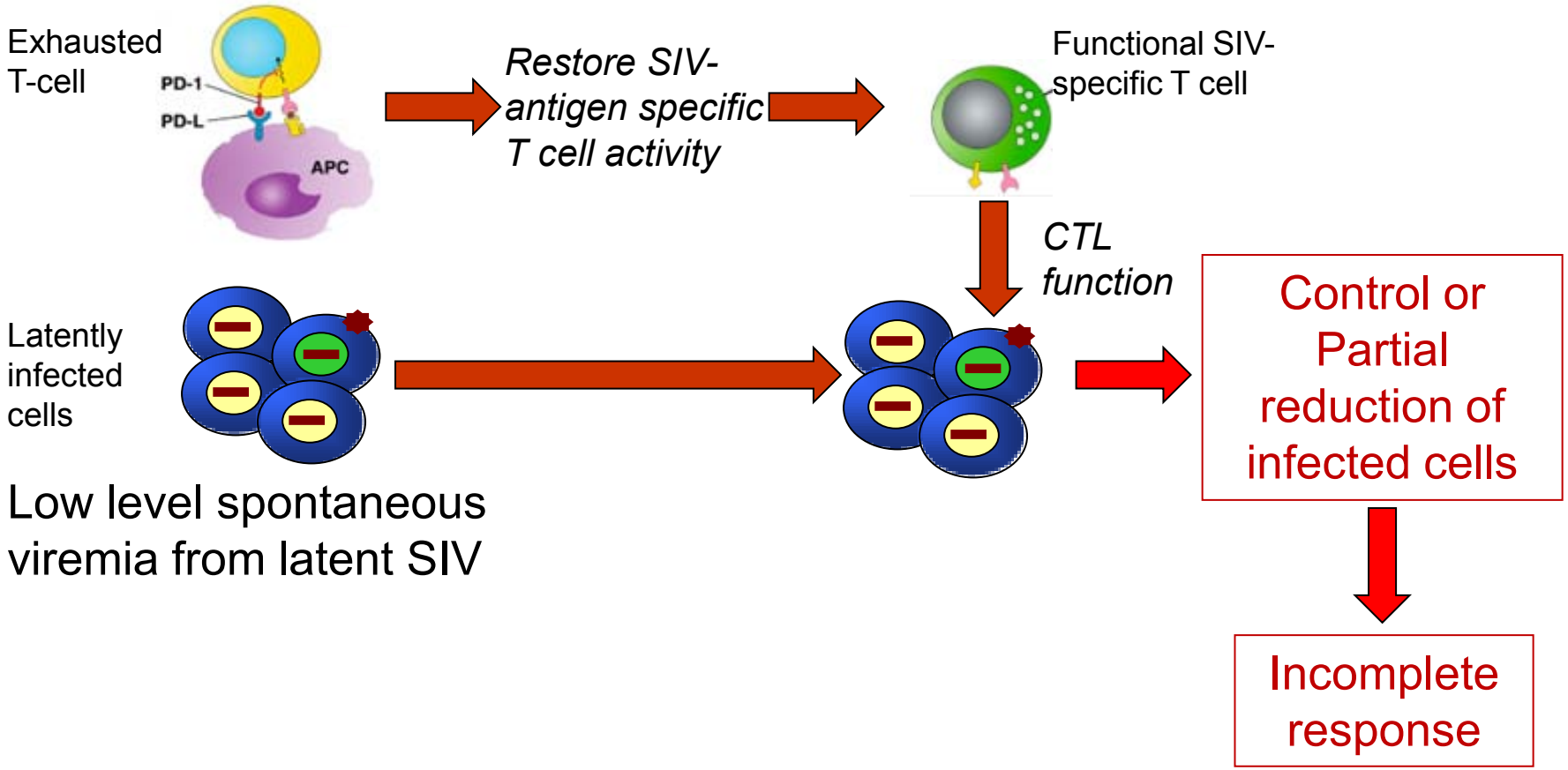
Model for effect of anti-PD-L1 in SIV study

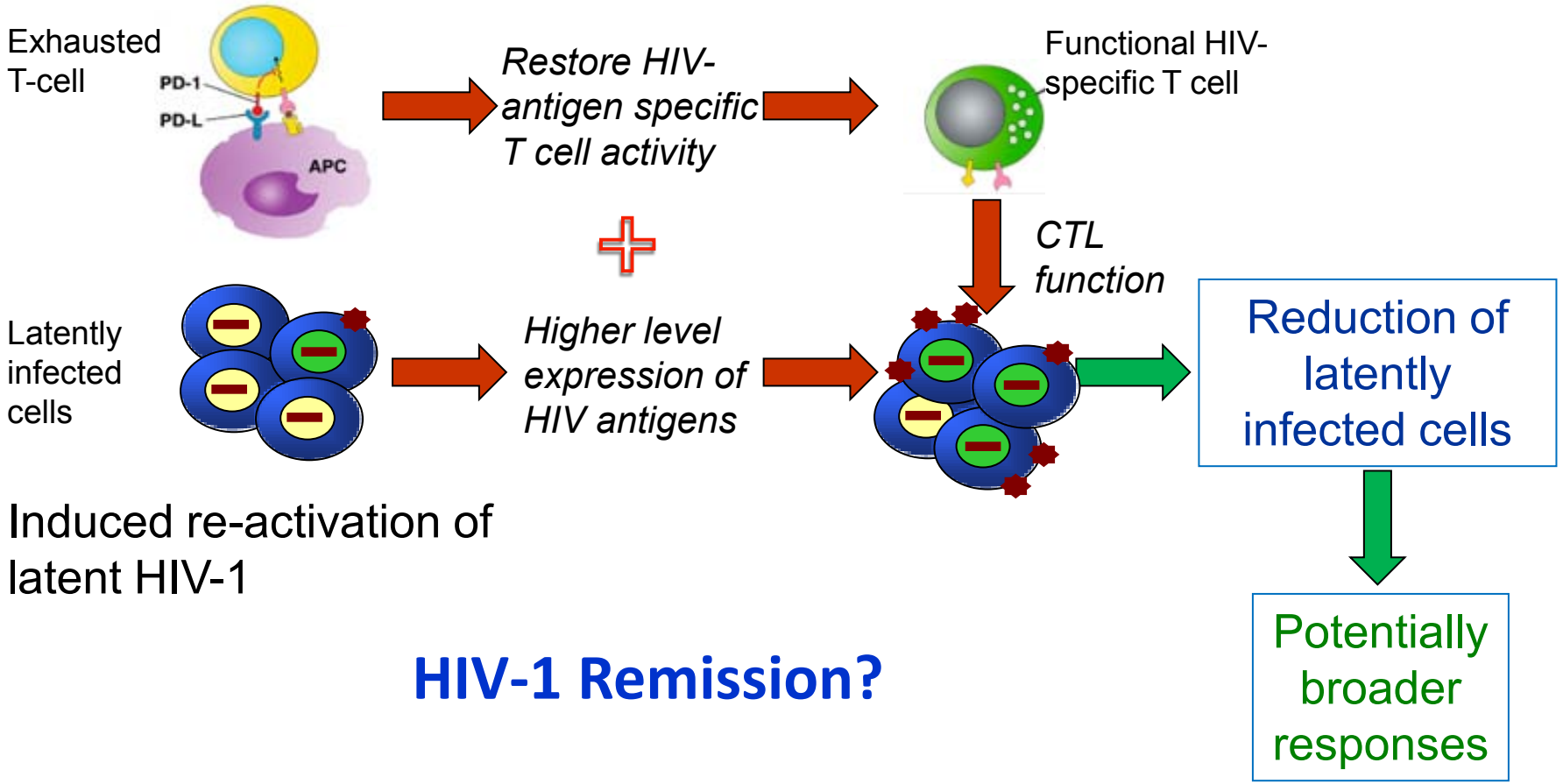
Treatment with αPD-L1



Low level spontaneous viremia from latent SIV

BMS Strategy for HIV-1 Functional Cure:
Dual Approach

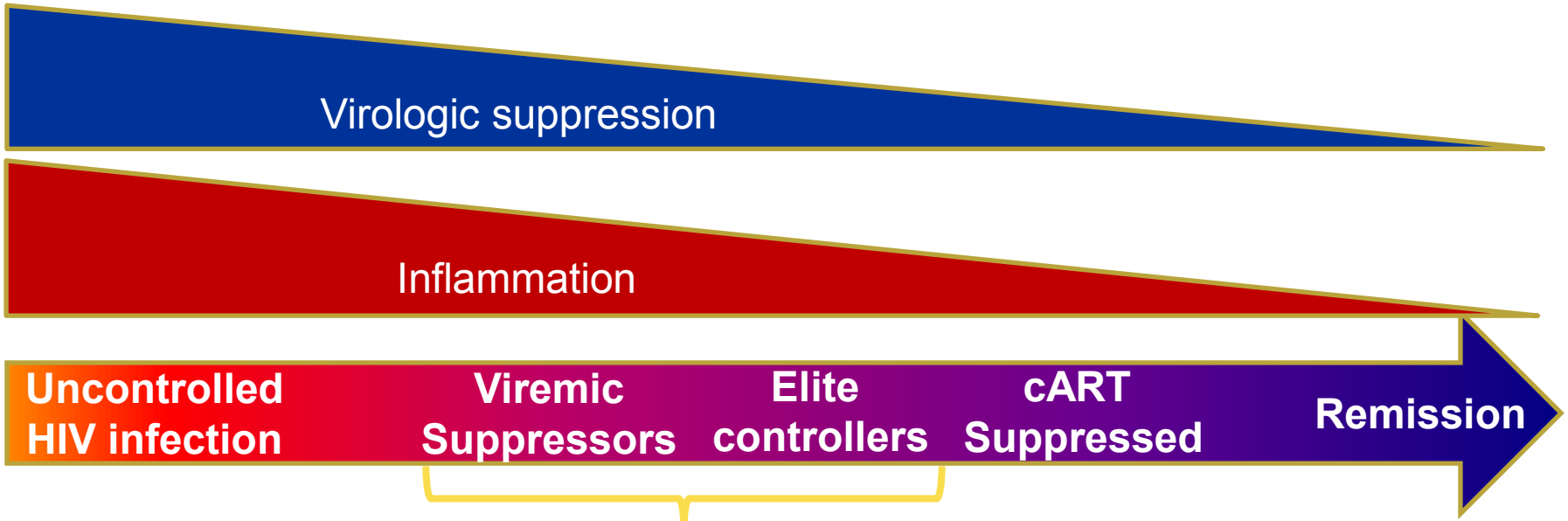
Treatment with αPD-L1



Induced re-activation of latent HIV-1

HIV-1 Remission?

Spectrum of virologic control and inflammatory states



- Complete HIV remission must surpass EC-state:
  - better virologic suppression
  - lower inflammatory state

- **Can these states be approximated therapeutically as intermediate steps toward complete remission?**
- **Is there medical benefit to "Controller-like states" to make such intermediate goals worthwhile?**

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If Complete HIV remission is our goal…

…it likely will require:

- Combinations of modalities
- Intermediate goals to find the right combinations along the way to complete remission

Is there an intermediate state that would provide value to patients?

- *What could that intermediate state look like?*
  - *Low level yet detectable viremic state?*
  - *Shorter periods of drug-free suppression?*
  - *Requiring re-dosing of agents?*
  - *How to reduce inflammation?*

Acknowledgements

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