Update sulle possibilità di immunoterapia di HIV

Immunoterapia di HIV come approccio di cura funzionale?

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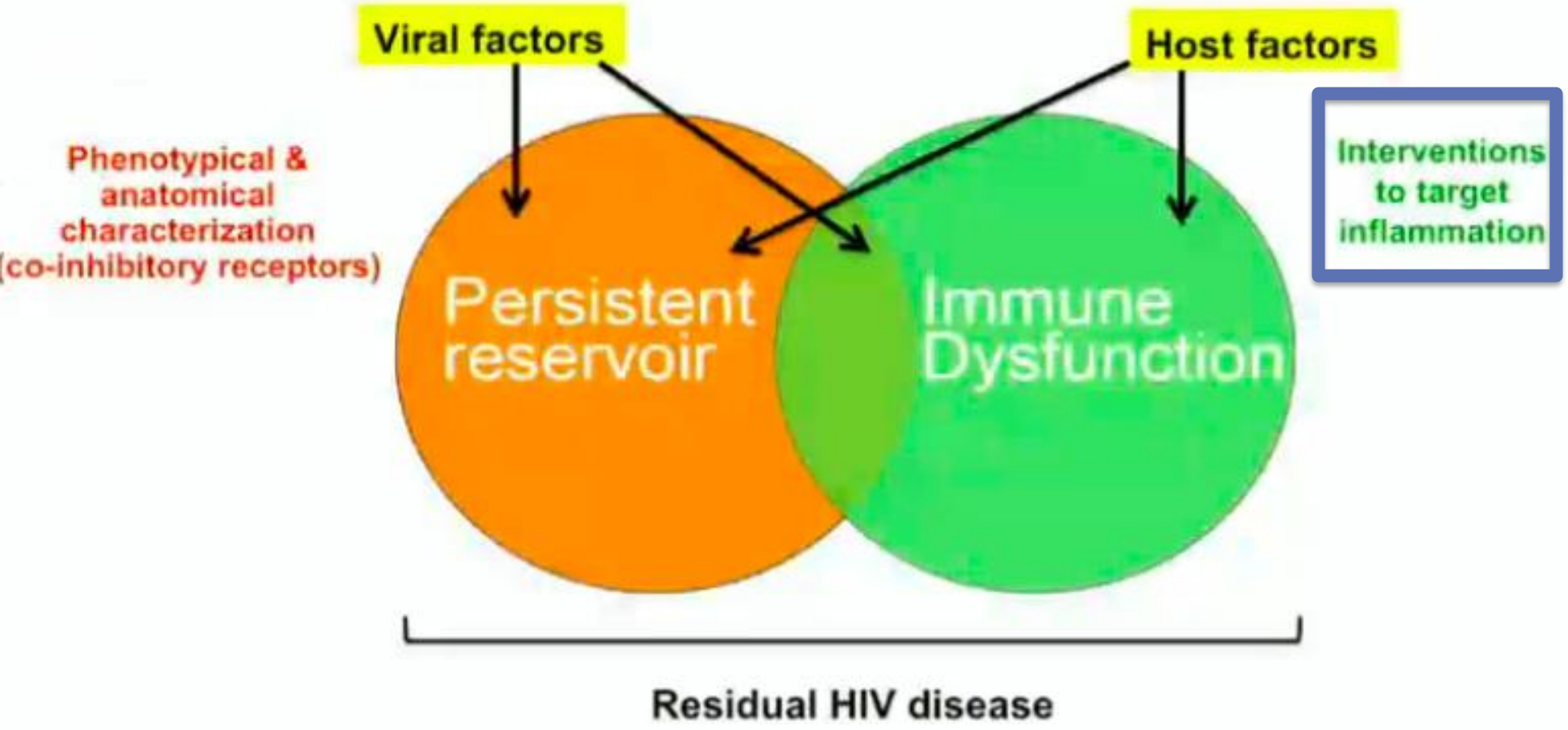
Functional cure – the question(s)

Can we generate HIV-specific immune responses capable of fully contain viral replication even in tissue (sanctuaries) once cART is stopped?

Why is a cure needed?

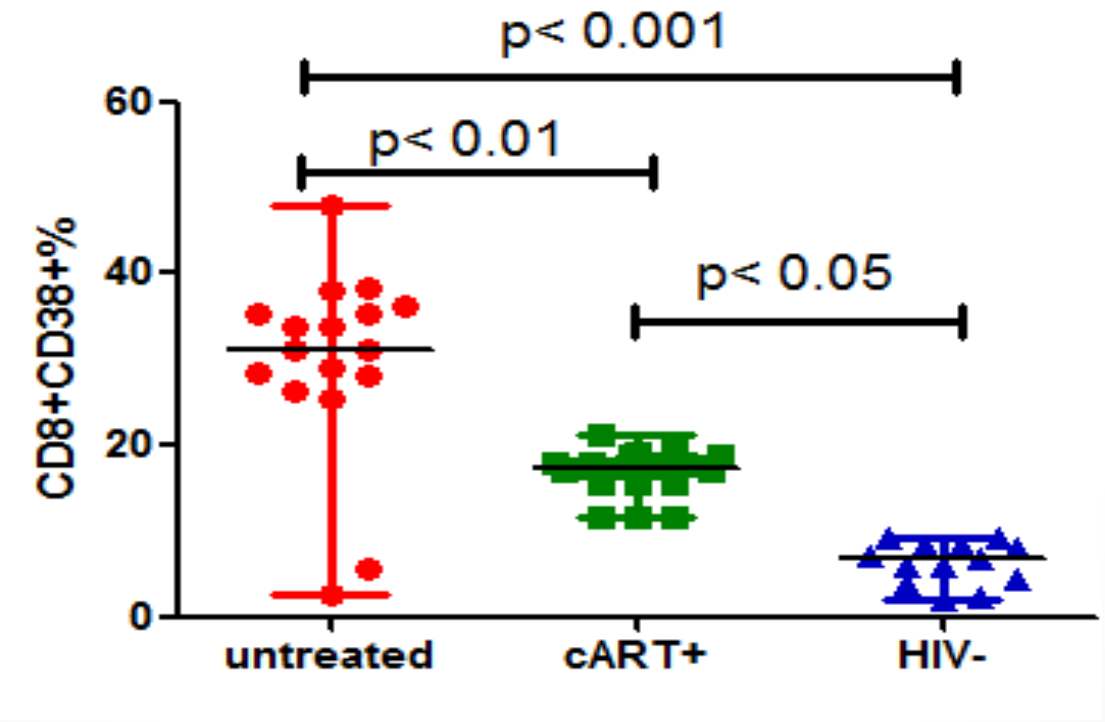
- HAART does not fully restore health
  - Residual disease (due to inflammation and suboptimal immune restoration) and direct drug toxicity are important contributing factors
- Life-long adherence is often difficult
- A scalable and effective cure could prevent transmission and end the epidemic

Residual disease in ART-treated HIV-infection



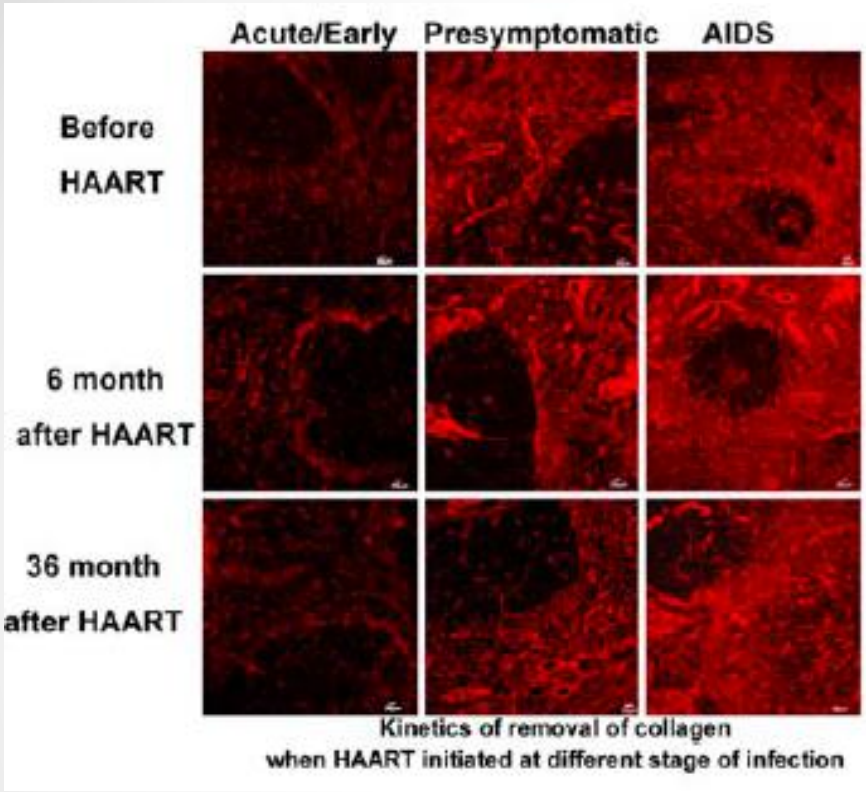
- Curing HIV infection is a virological AND immunological problem
- It is possible that eliminating the "last copy" of HIV in the body will not "cure" the immune dysfunction (inflammation, loss of mucosal integrity, immune senescence, fibrosis, etc.)

Inflammation/immune activation persists on cART



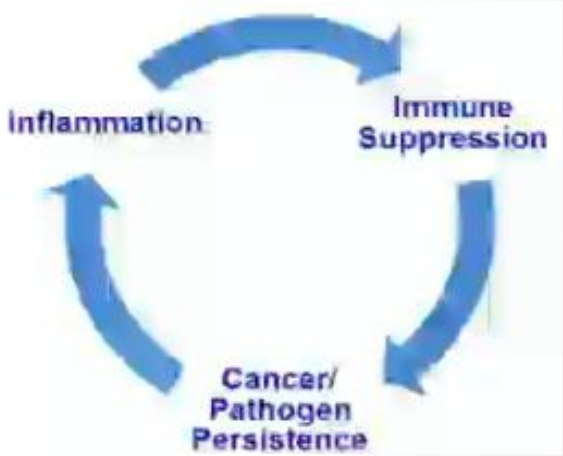
Cannizzo et al. JID 2015; 211(9):1511; see also: Hunt PW, et al. JID 2003

Inflammation causes immune dysfunction



Kinetics of removal of collagen when HAART initiated at different stage of infection

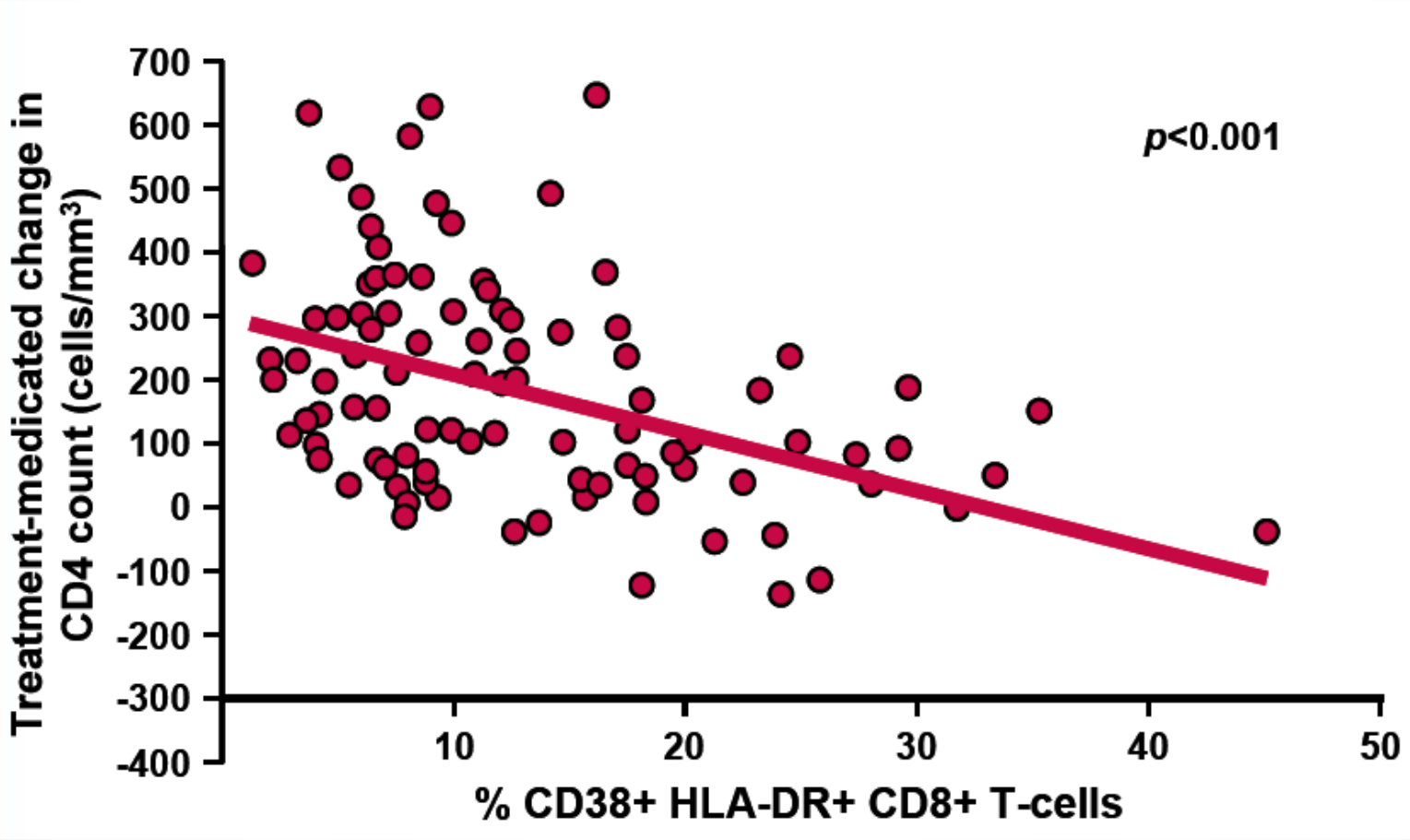
Hyper-inflamed cytokine *milieu* → Treg response → TGF-β → collagen deposition → Fibrosis → Reduced IL-7 → Reduced T cell regeneration → inflammation



Zeng et al. PlosPathogens 2012

Interventions that reduce inflammation/immune suppression may also be beneficial in containing viral persistence

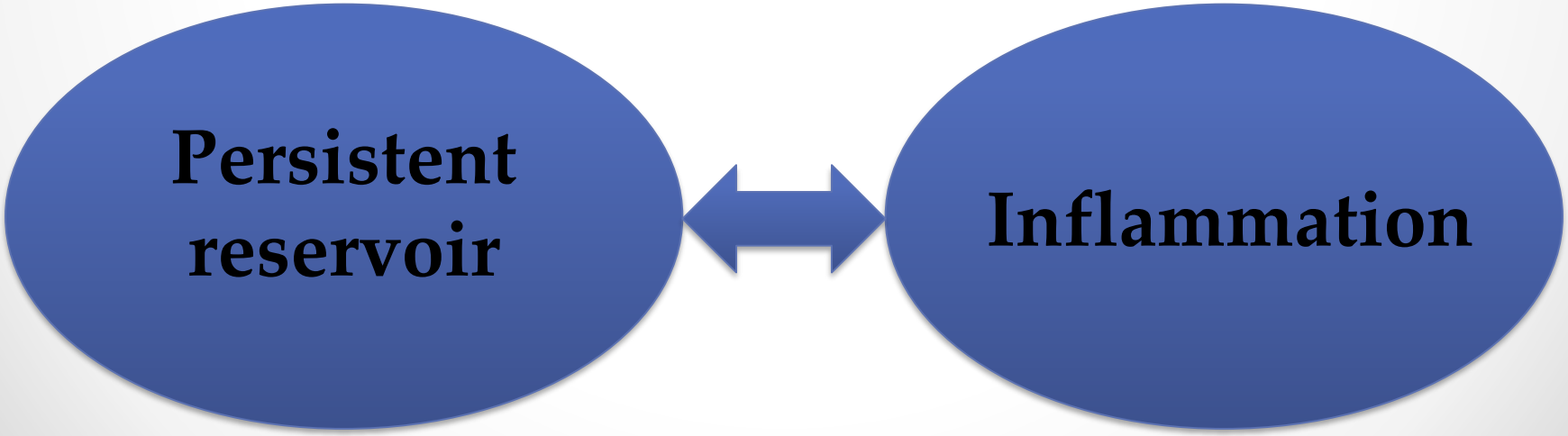
Immune activation during cART hampers CD4 recovery



Hunt PW, et al. JID 2003

Functional cure: what contribution of immune-based therapy?

Hypothesis #1: reduce immune activation/inflammation

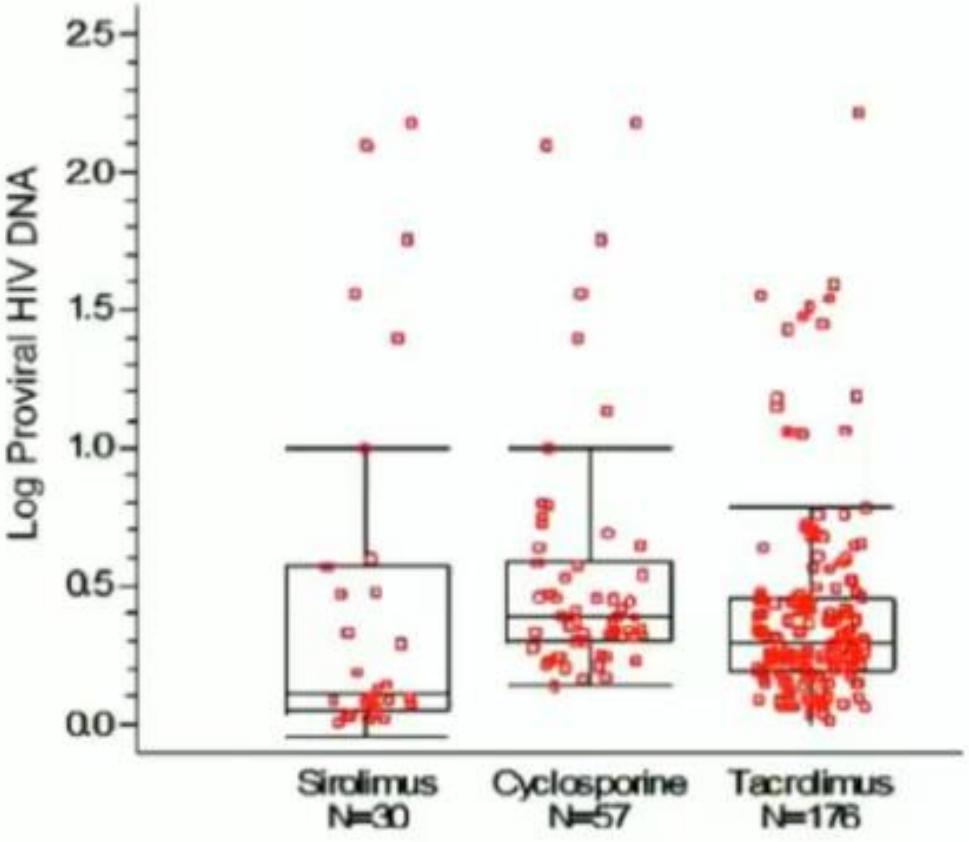


American Journal of Transplantation

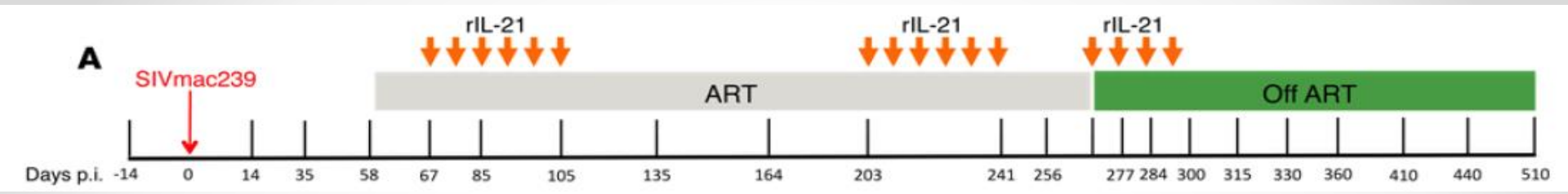
Reduction of HIV Persistence Following Transplantation in HIV-Infected Kidney Transplant Recipients

P. G. Stock[1], B. Barin[2], H. Hatano[3], R. L. Rogers[1], M. E. Roland[3], T.-H. Lee[4], M. Busch[4], and S. G. Deeks[3,*] for Solid Organ Transplantation in HIV Study Investigators

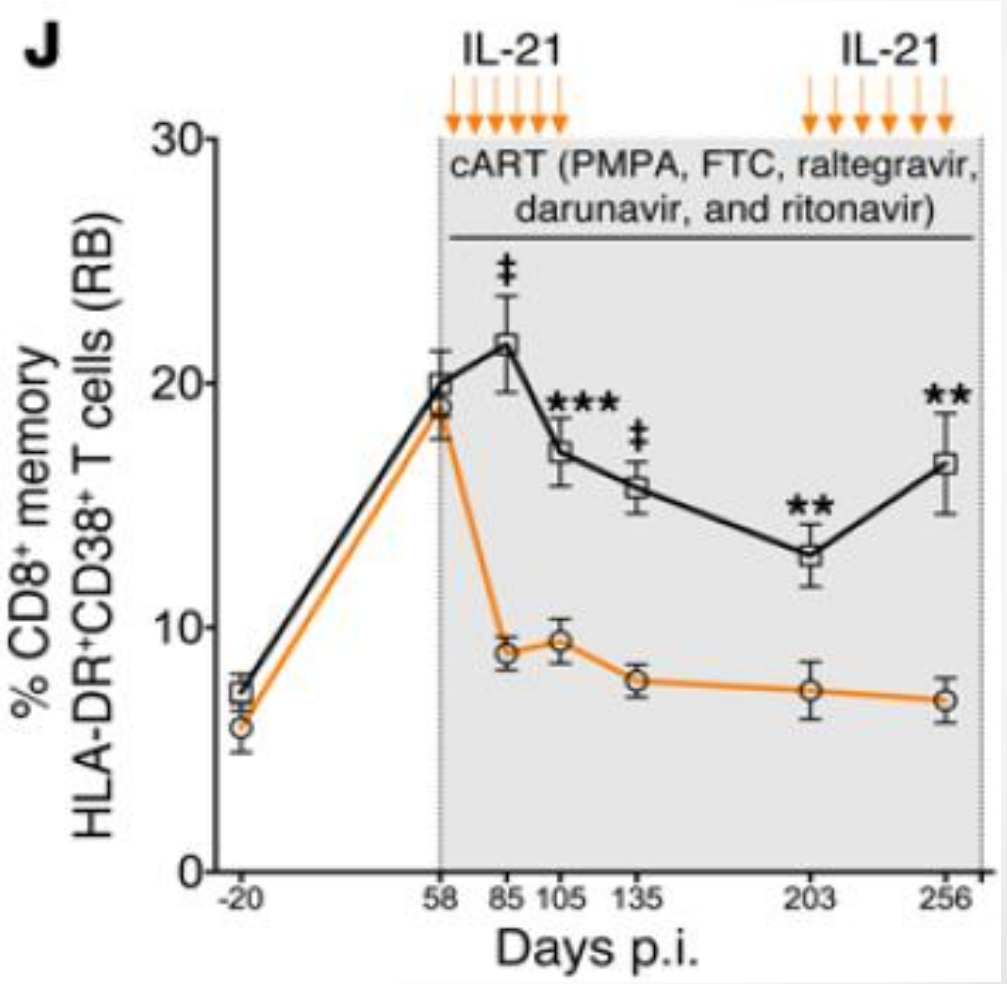
2014



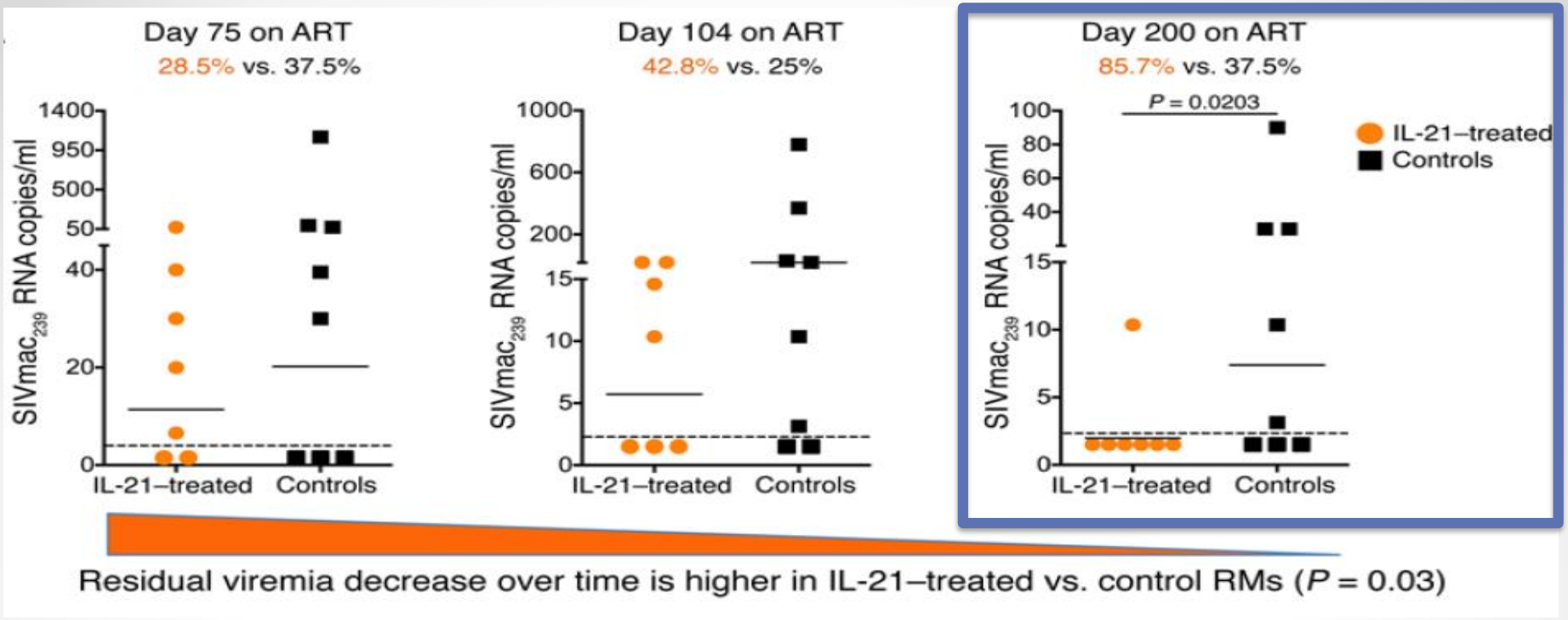
Sirolimus (rapamycin)—which reduces CCR5 expression, T cell activation and T cell proliferation—is associated with low "reservoir" size post-renal transplant

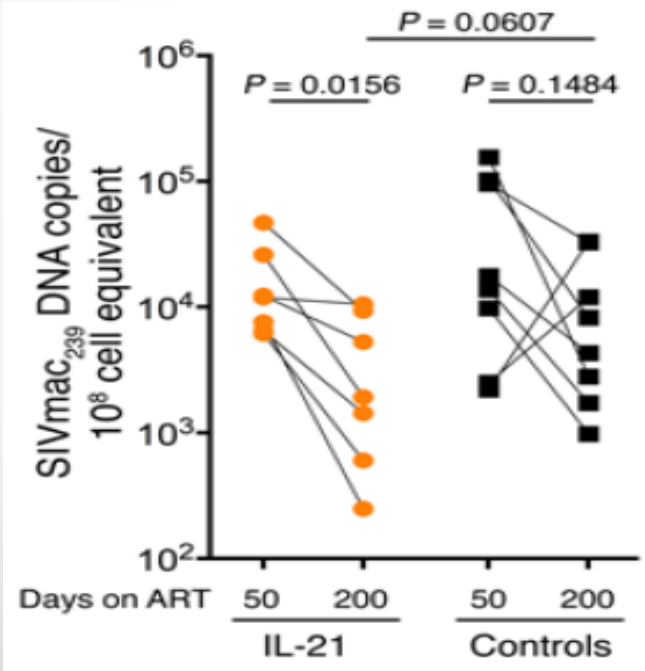


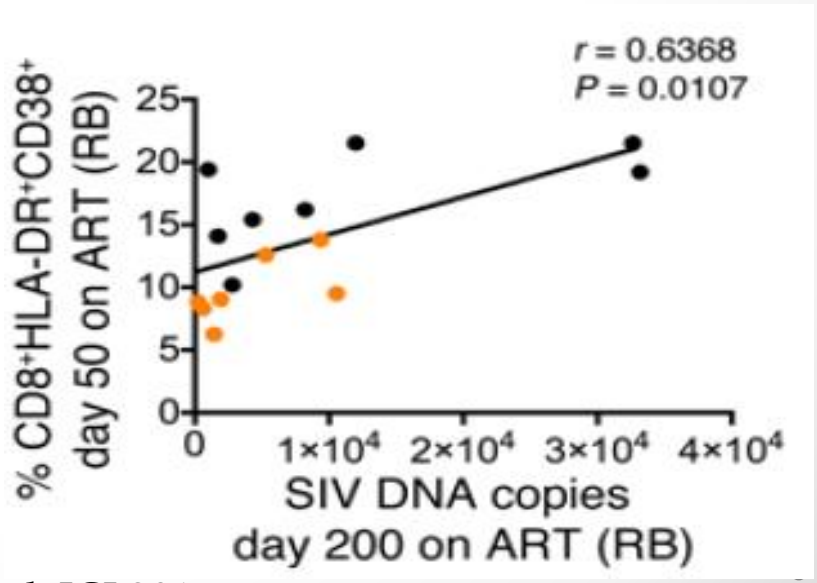
IL-21 immunotherapy



Micci et al. JCI 2015

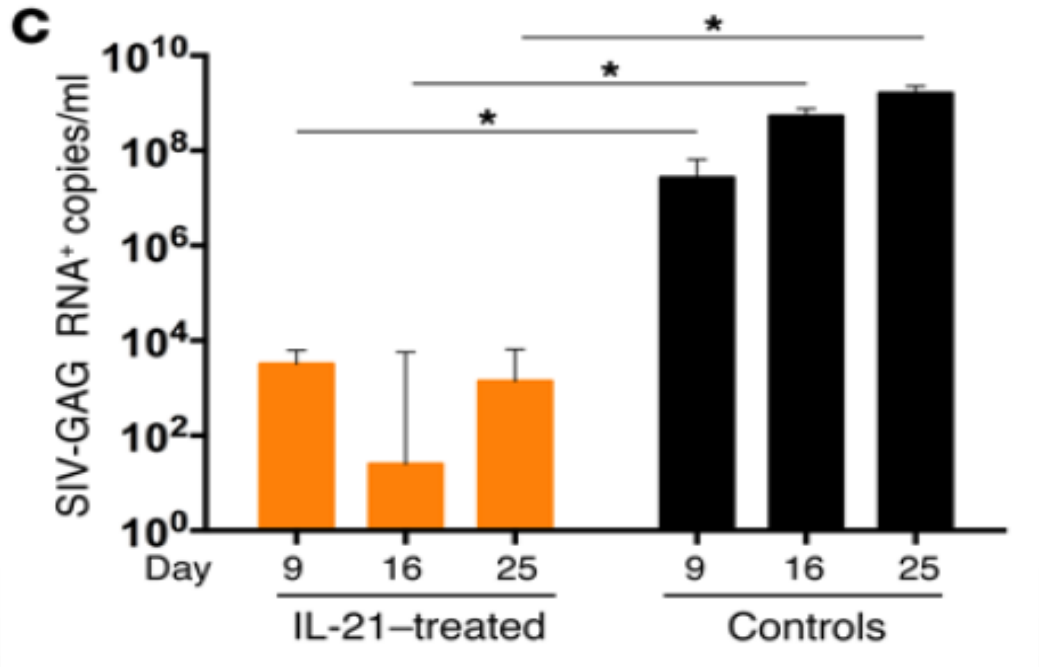






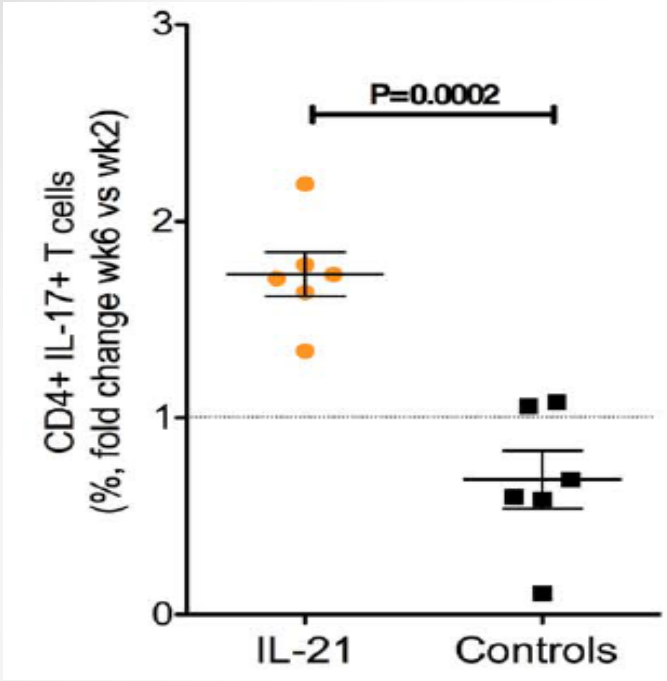
Micci et al. JCI 2015

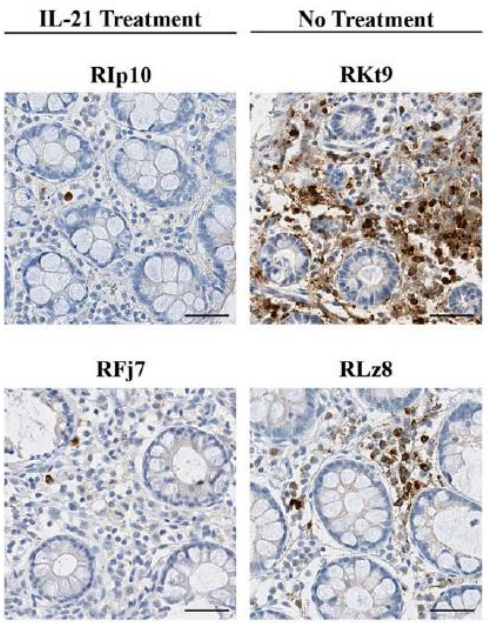
Reduction in replication-competent virus by IL-21

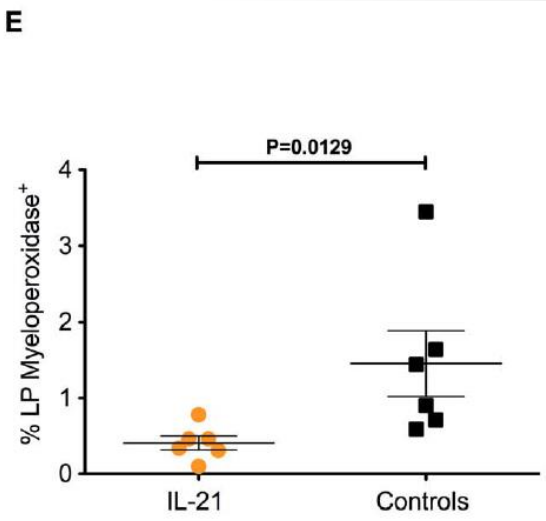


Micci et al. JCI 2015

IL-21 immunotherapy



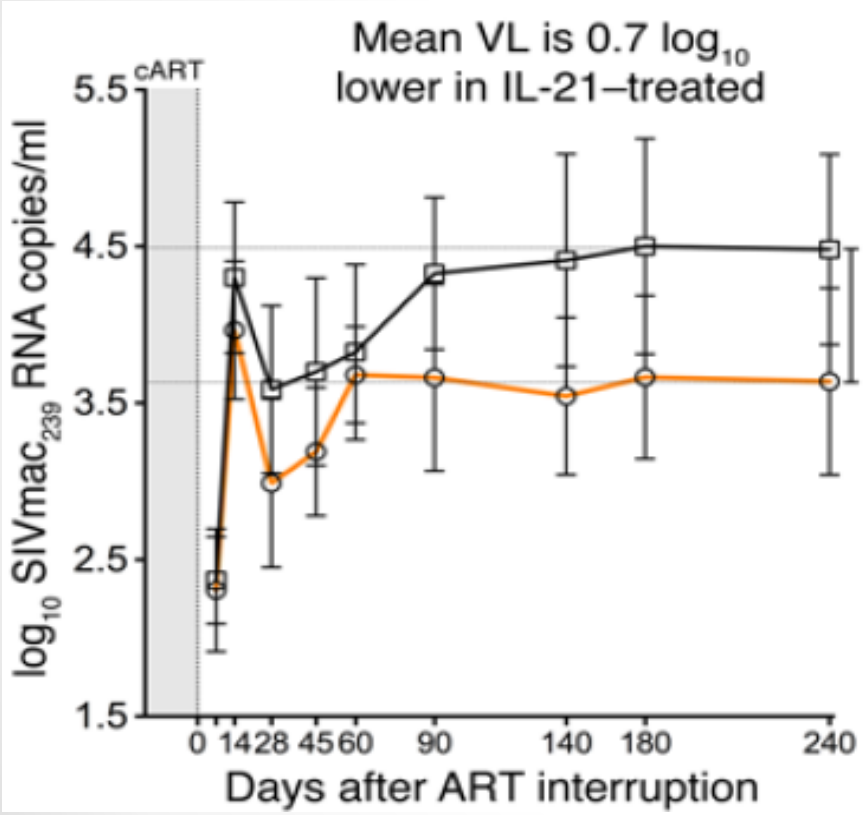


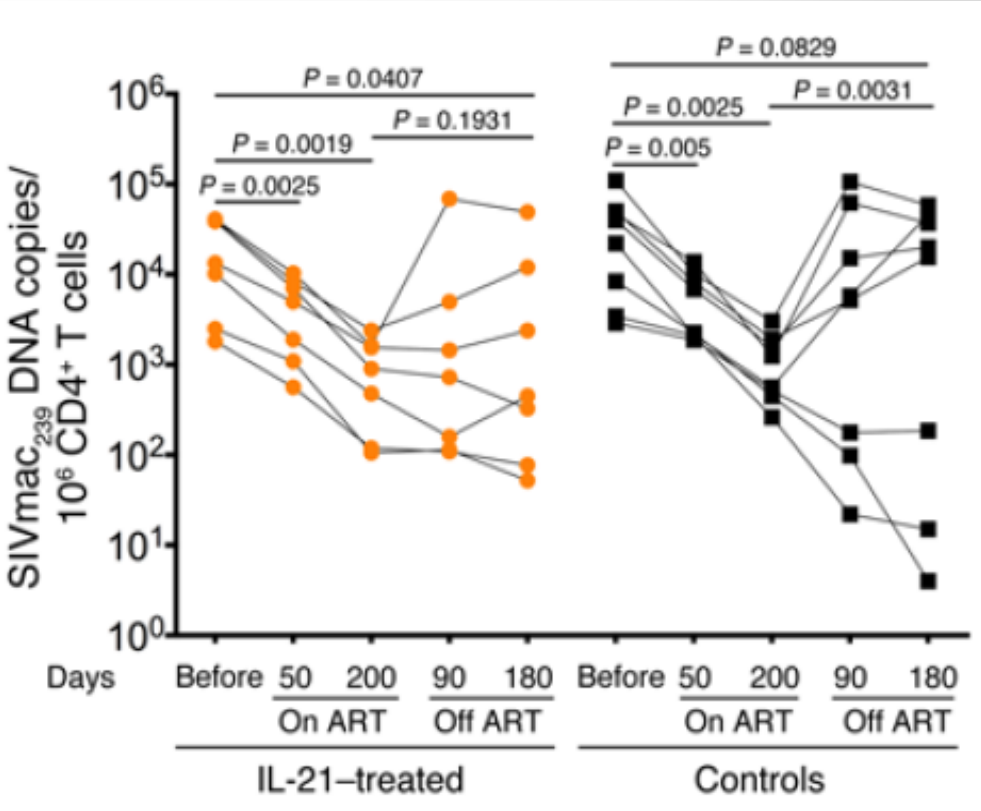


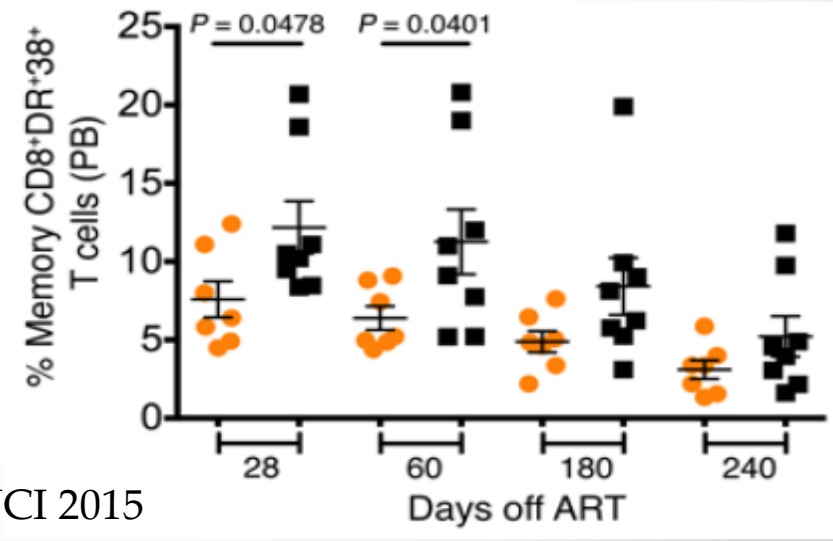
Pallikkuth et al. Plos Path 2013

IL-21 in the course of cART limits inflammation and HIV persistence

However,

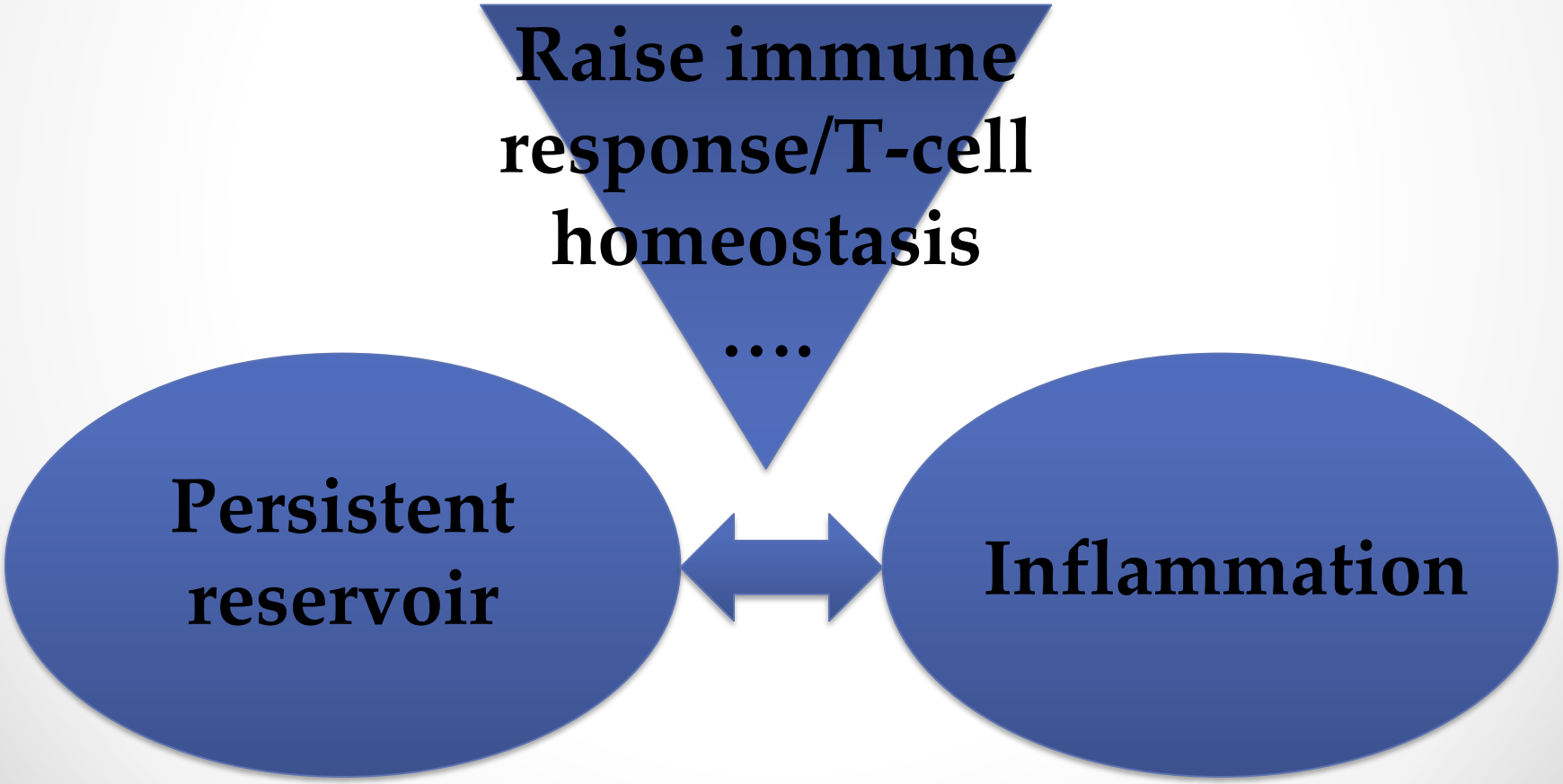






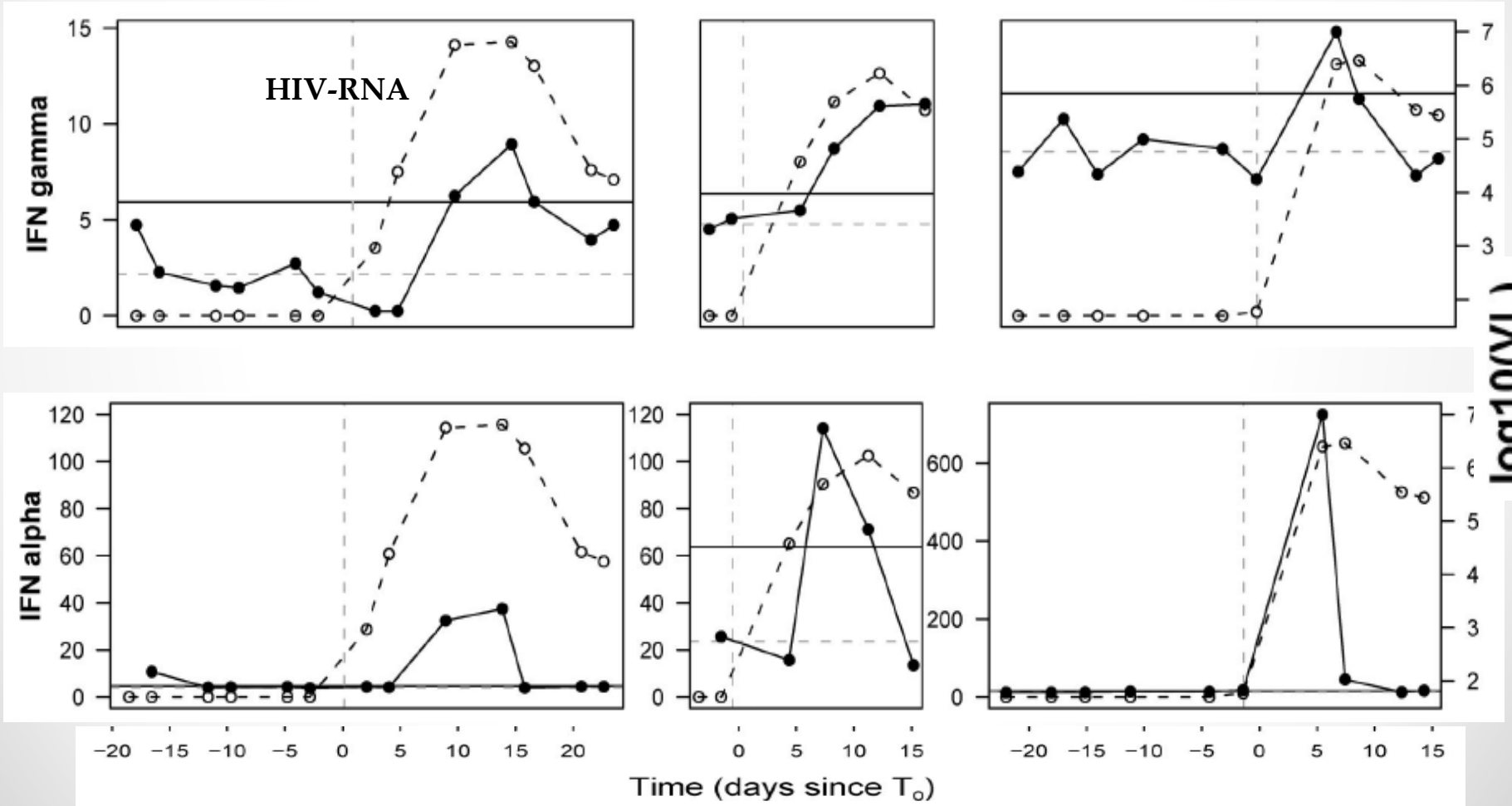
Micci et al. JCI 2015

Hypothesis #2: combination strategies



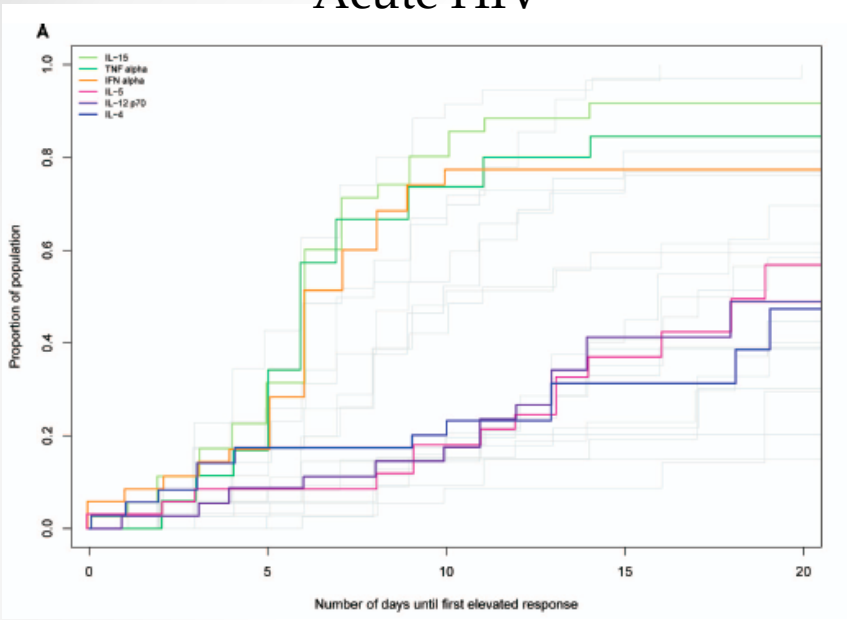
Raised circulating interferons in acute HIV

35 acute HIV (sequential plasma samples)

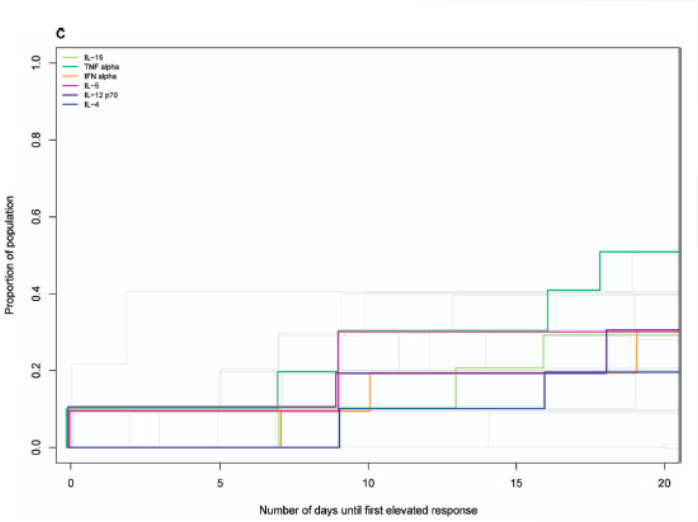


Stacey et al. J Virol 2009

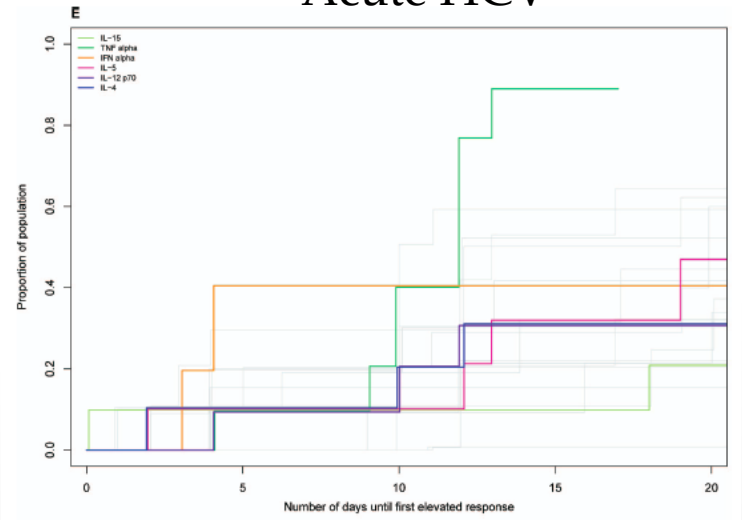
Acute HIV



Acute HBV

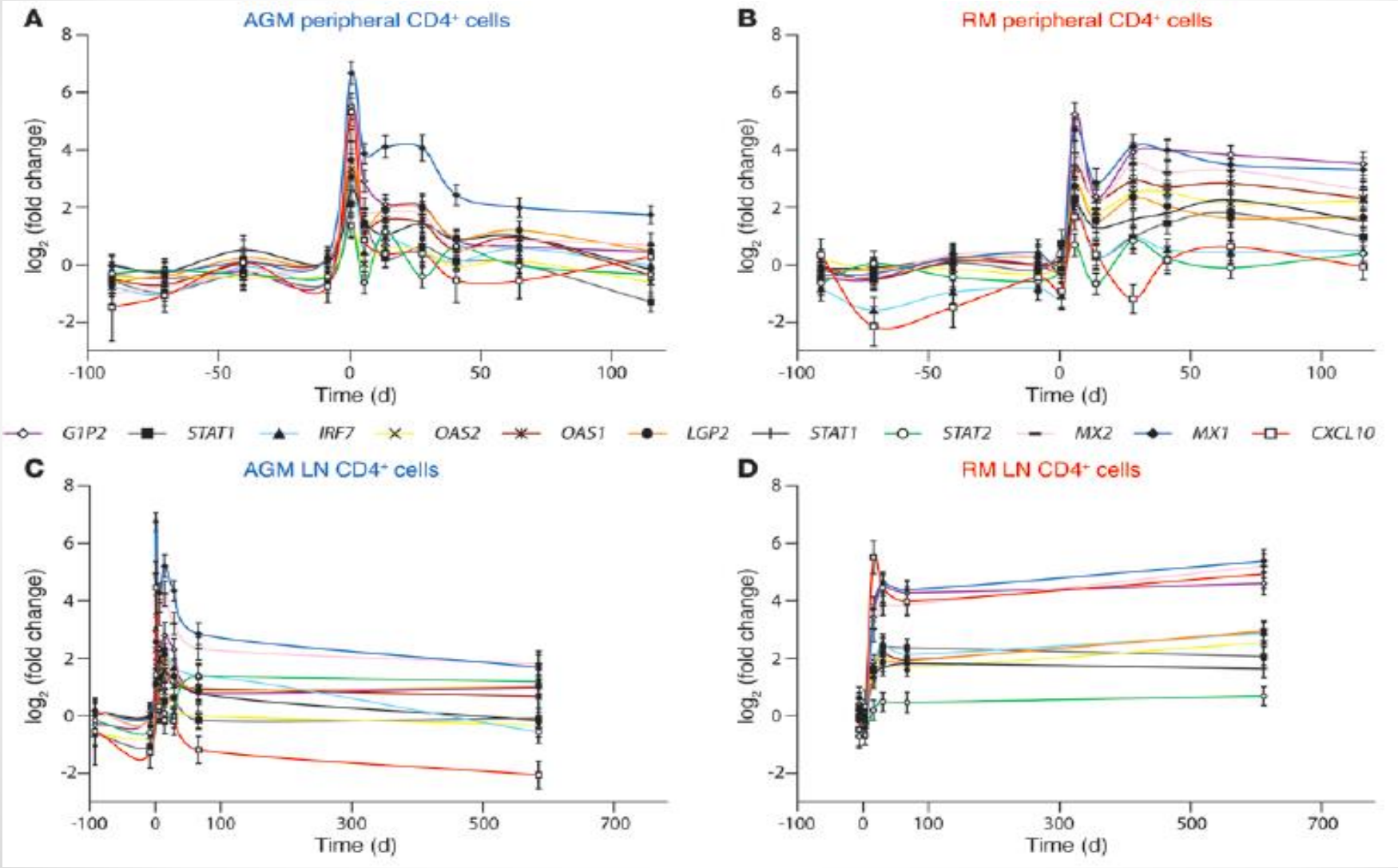


Acute HCV



Stacey et al. J Virol 2009

Raised ISG during chronic infection



Jacquelin J Clin Invest 2009

HIV

The mixed blessing of interferon

HIV-infected monkey:
Sandler et al. Nature 2014

A study in monkeys finds that treatment with the protein interferon protects against simian immunodeficiency virus, but that prolonged interferon administration exacerbates the chronic stage of the infection. **SEE LETTER P.601**

31 JULY 2014 | VOL 511 | NATURE | 537

AMALIO TELENTI

IMMUNOLOGY

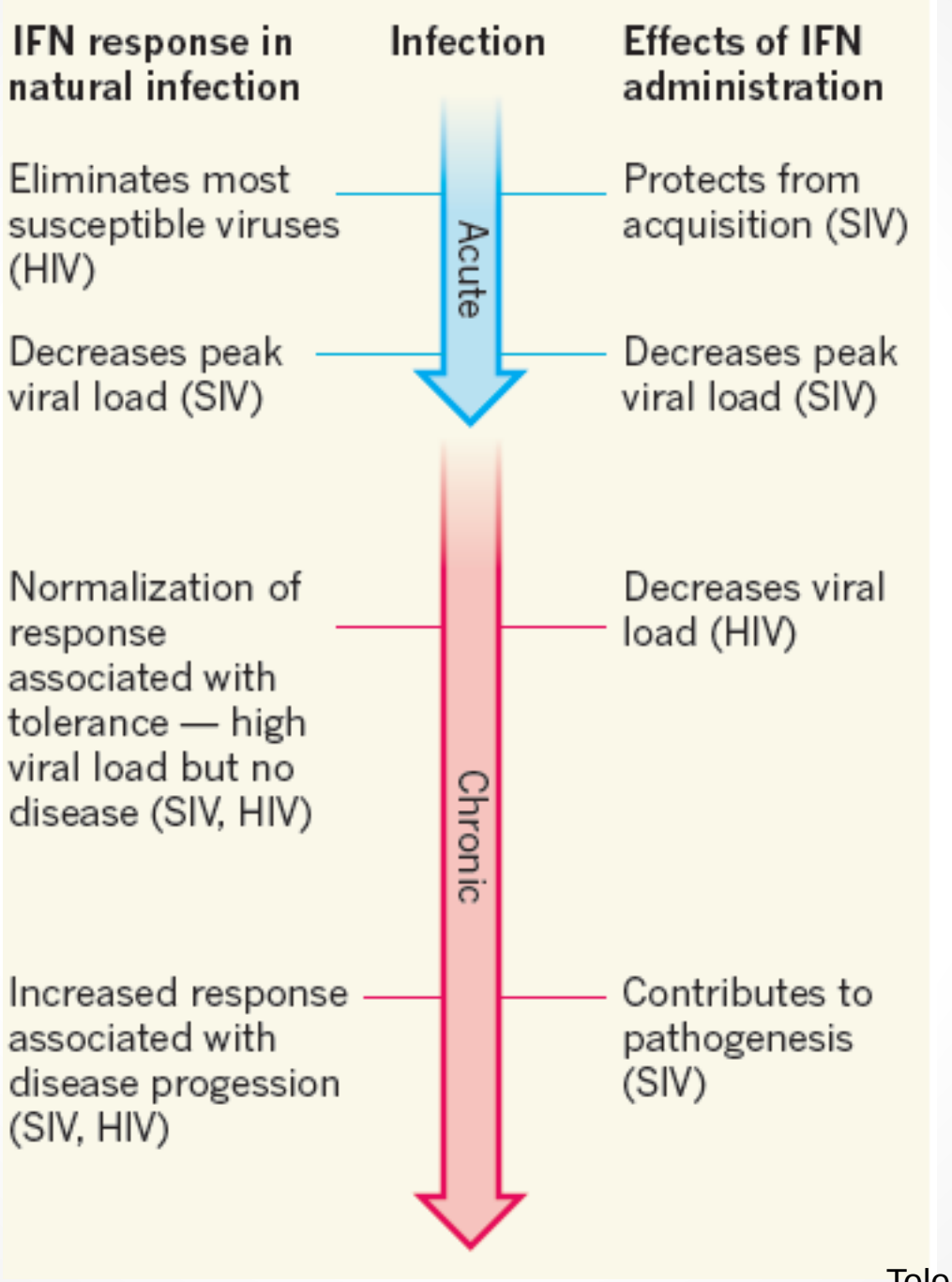
An Interferon Paradox

Interferons must balance antiviral actions against immunosuppressive effects during acute and chronic infections.

Pamela M. Odorizzi and E. John Wherry

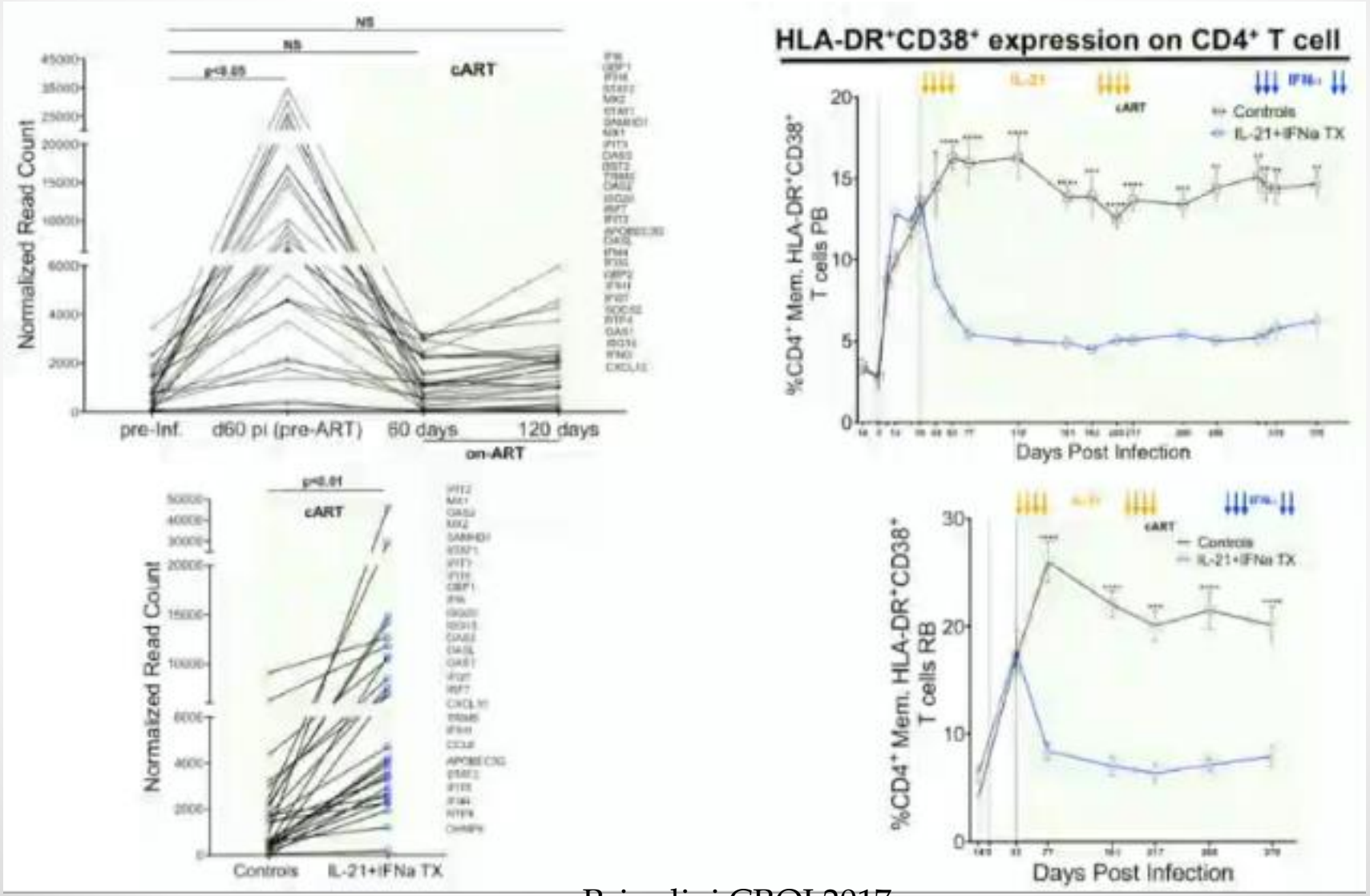
LCMV mouse model:
Wilson et al; Tejiaro et al. Science 2013

SCIENCE VOL 340 12 APRIL 2013



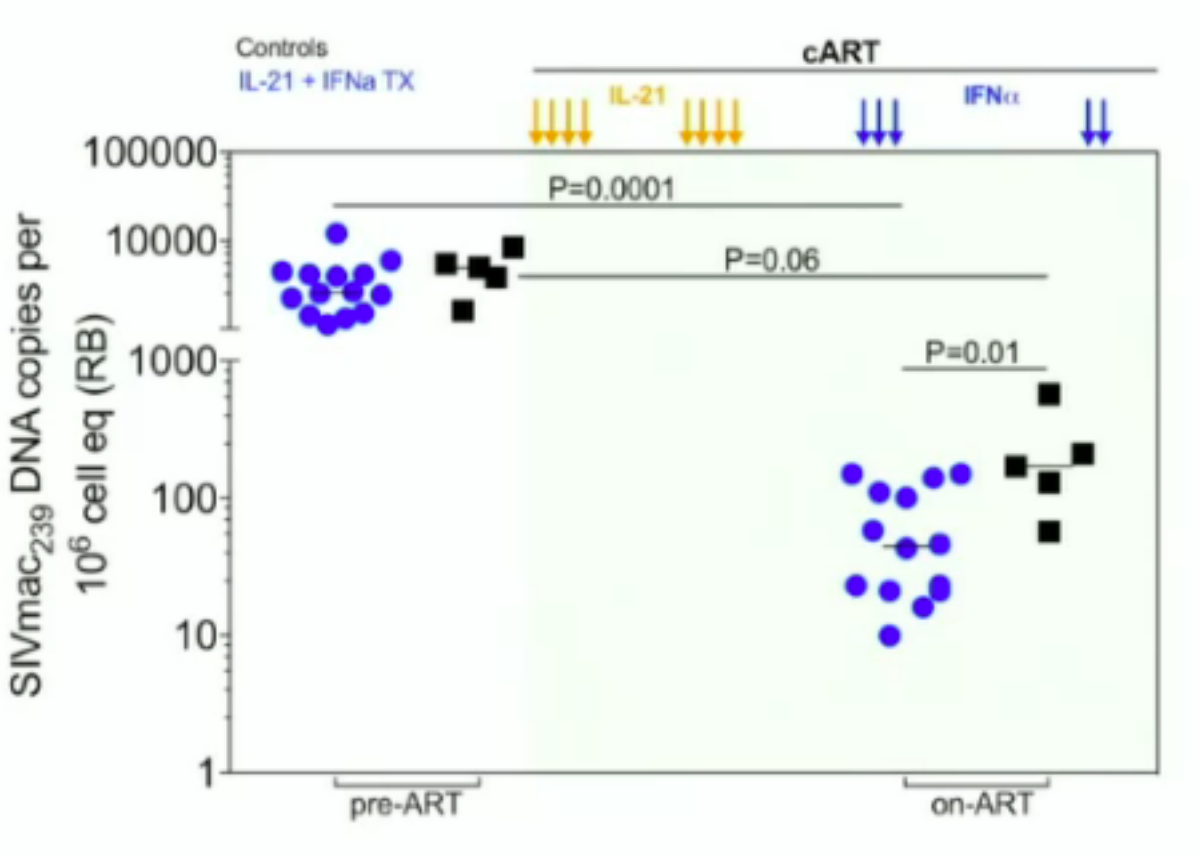
Telenti Nature 2014

IFN-a + IL-21 maintain low immune activation on cART



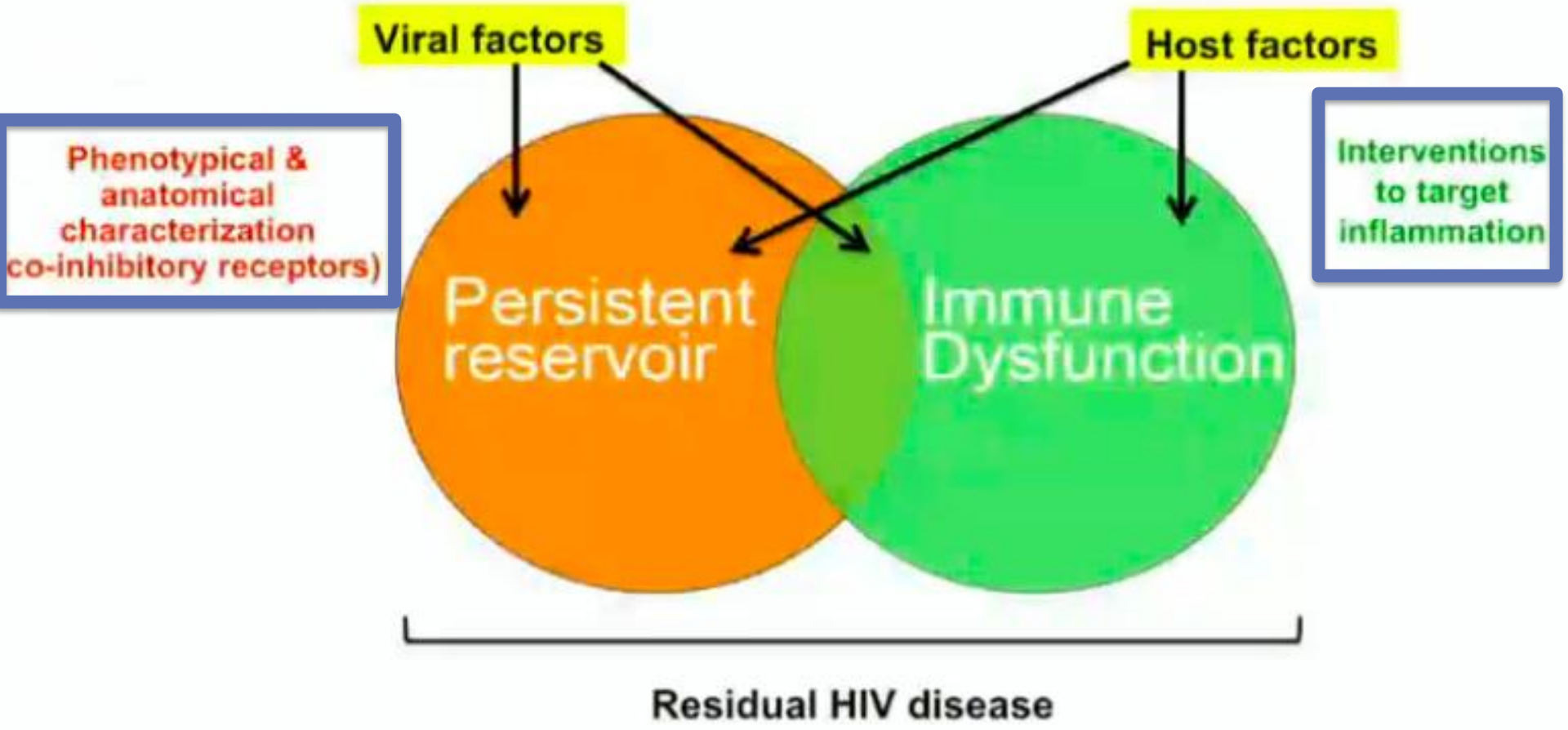
Paiardini CROI 2017

IL-21 + IFN-a reduce gut SIV-DNA



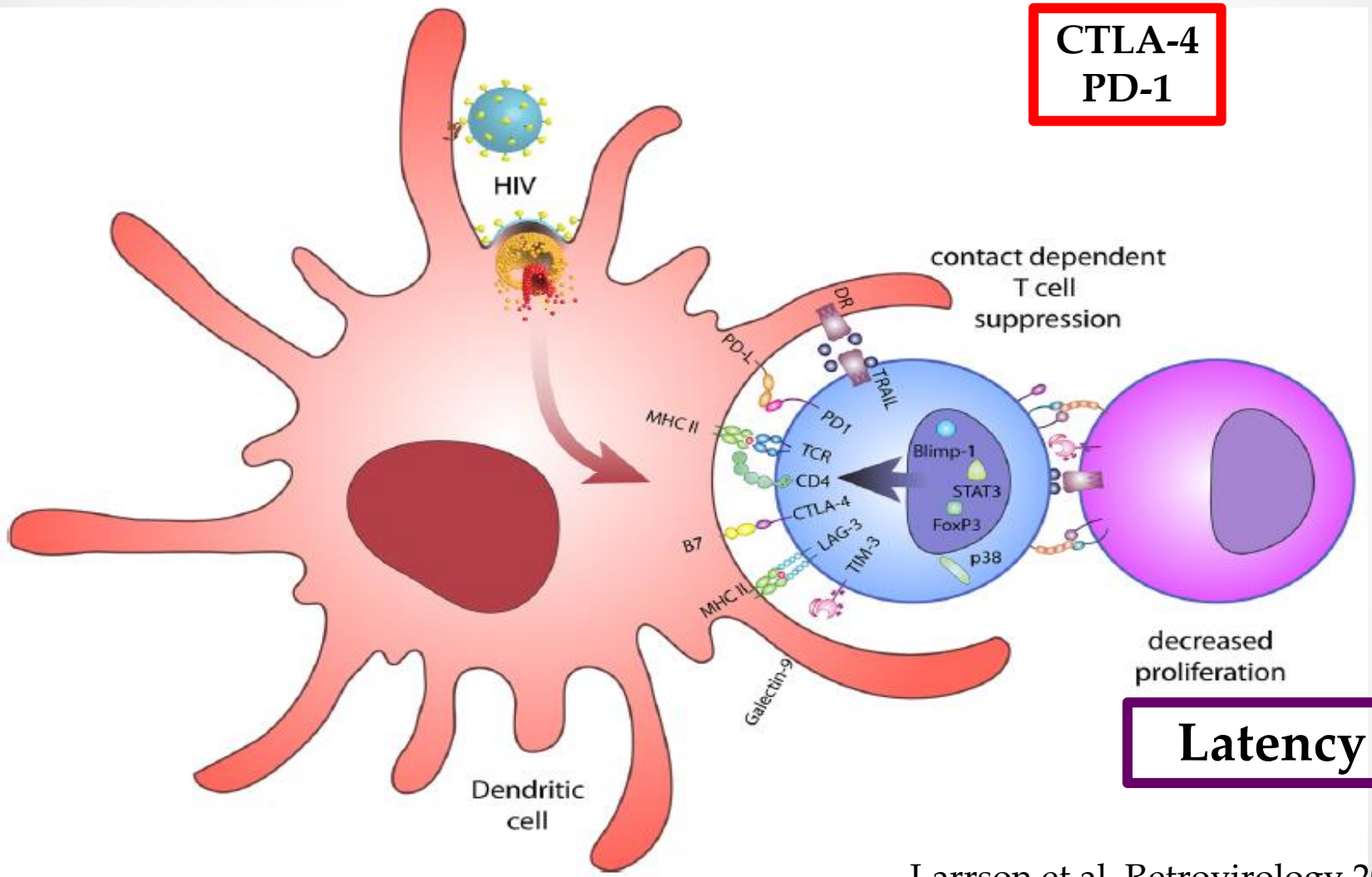
Paiardini CROI 2017

Residual disease in ART-treated HIV-infection



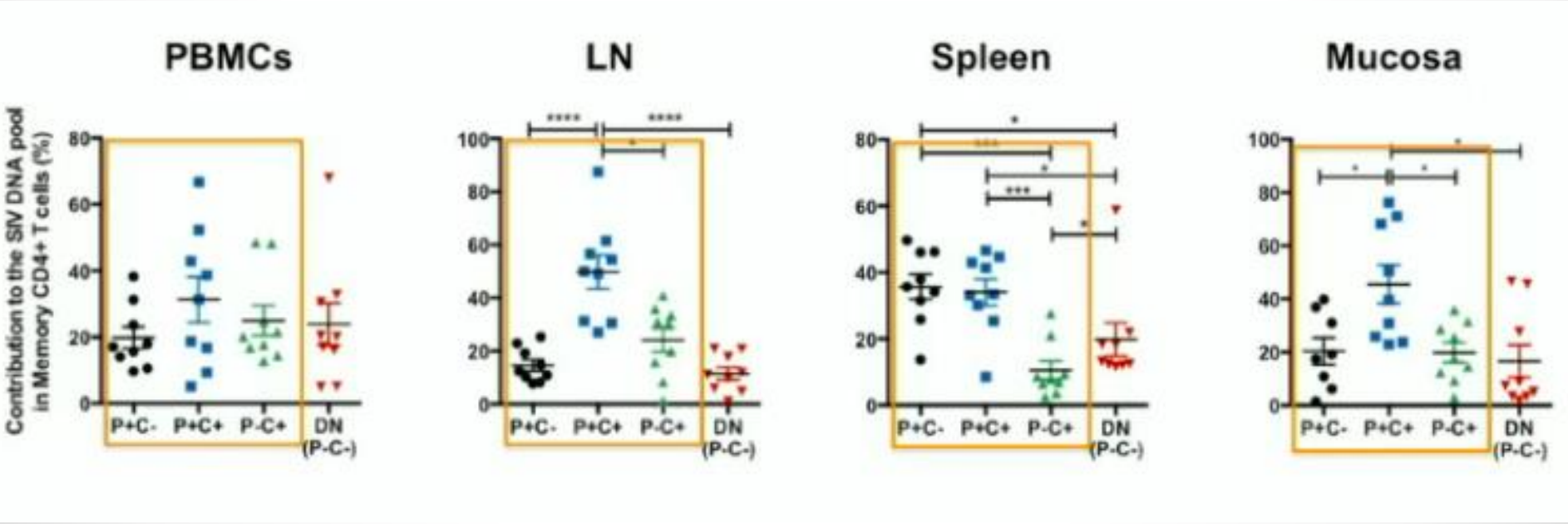
- Curing HIV infection is a virological AND immunological problem
- It is possible that eliminating the "last copy" of HIV in the body will not "cure" the immune dysfunction (inflammation, loss of mucosal integrity, immune senescence, fibrosis, etc.)

Co-inhibitors receptors and HIV

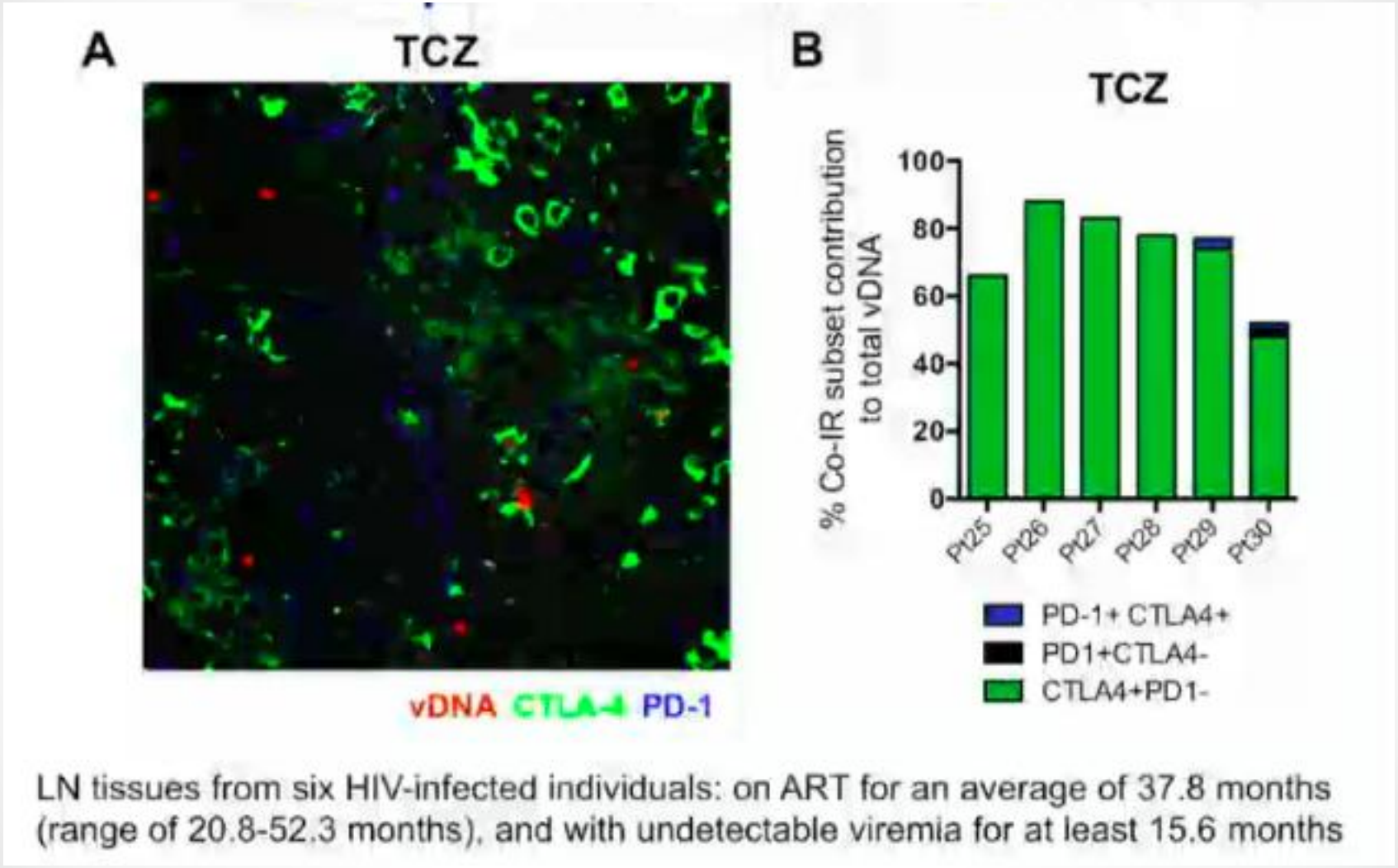


Larrson et al. Retrovirology 2013

CTLA-4 and PD-1-expressing CD4+ cells significantly contribute to SIV-DNA pool



Paiardini CROI 2017



LN tissues from six HIV-infected individuals: on ART for an average of 37.8 months (range of 20.8-52.3 months), and with undetectable viremia for at least 15.6 months

Paiardini CROI 2017

CTLA-4-pos PD-1-neg are Treg critical for viral persistence and could be target of cure strategies

Any effect for CTLA-4/PD-1 blockade on SIV persistence during ART and after ART stop?

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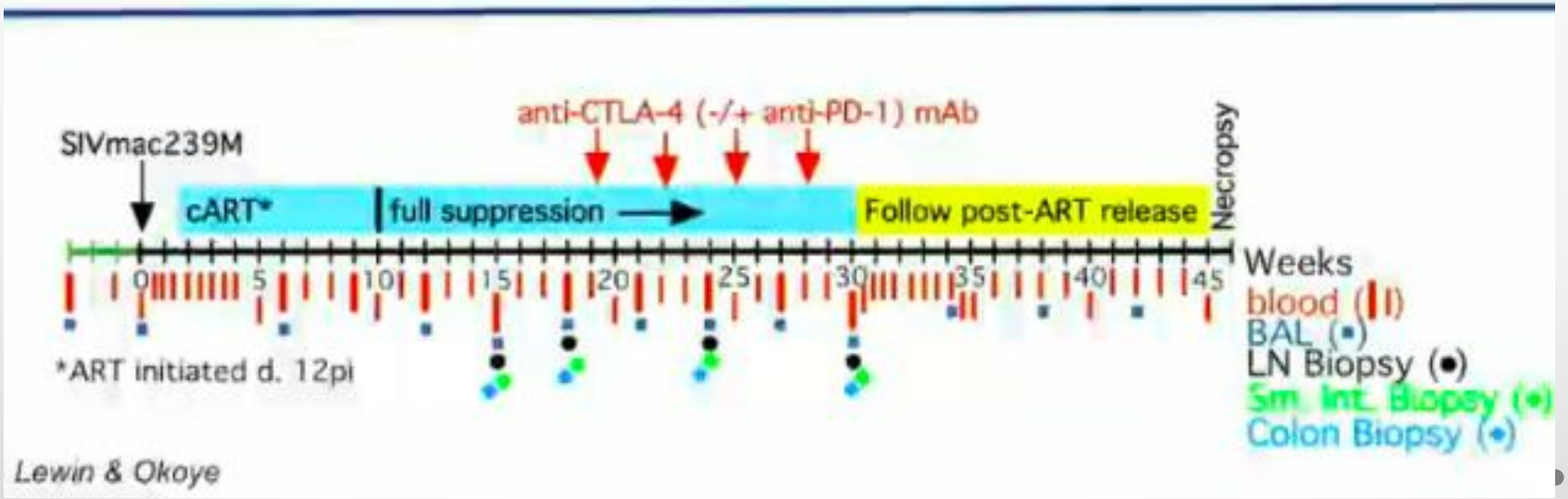


Functional cure: immune modulants as Latency Reversing Agents (LRA)?

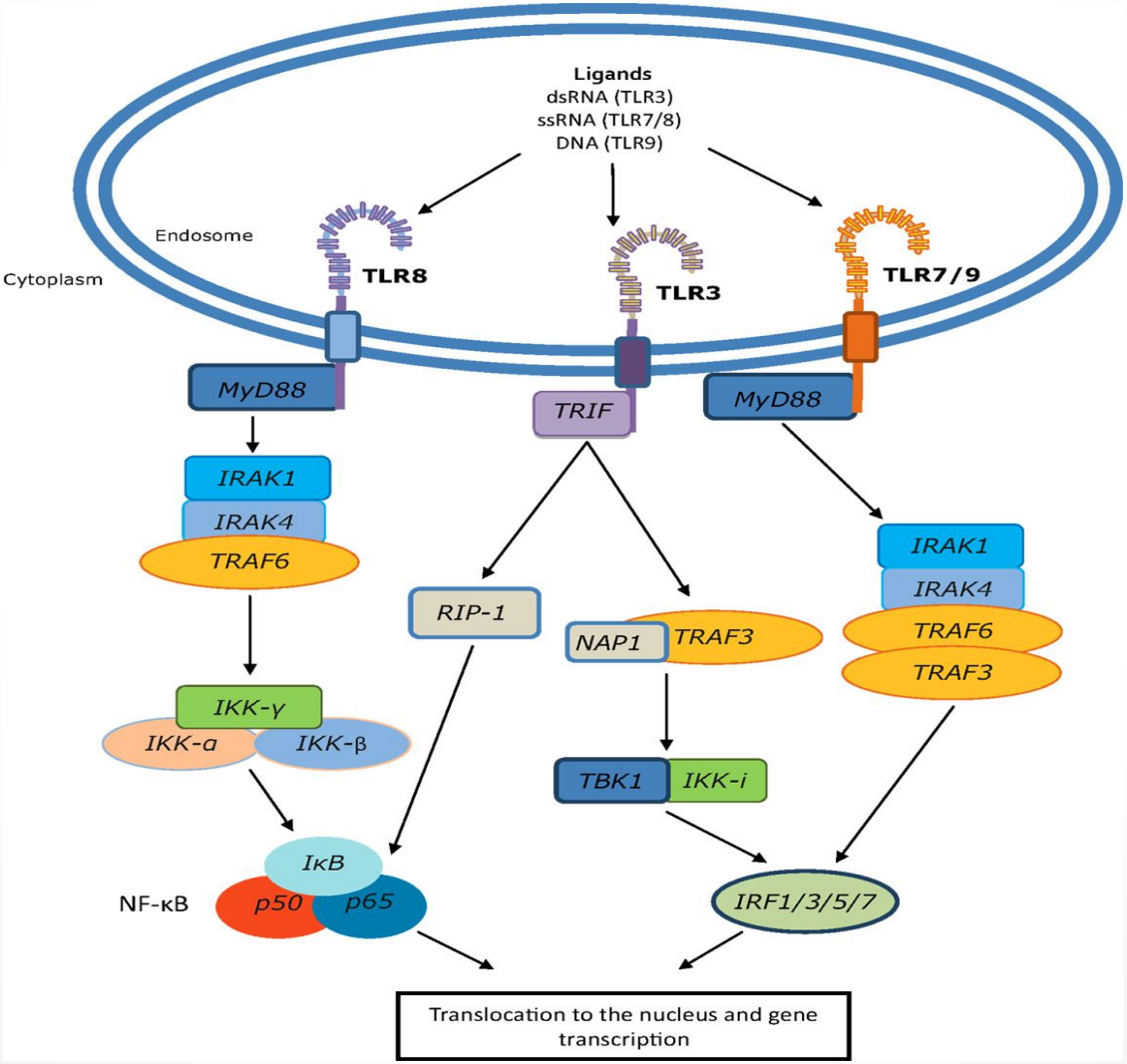
Table 1. Clinical Trials of Latency-Reversing Agents

	Drug Dosing (doses)	HIV-1 Transcription (fold > baseline)	Plasma HIV-1	Post Dosing Viral Effect	T cell Activation	Reservoir Size	Refs
Vorinostat							
Archin *et al.* (2012)	400 mg (1)	4.8	No change	ND[c]	ND	ND	[14]
Elliott *et al.* (2014)	400 mg daily (14)	2.7	No change	Yes	No change	No change	[18]
Archin *et al.* (2014)	400 mg TIW[c] (22)	1.3	No change	ND	ND	No change	[15]
Panobinostat							
Rasmussen *et al.* (2014)	20 mg TIW (12)	2.9	Increased[a]	Yes	Increased	No change	[17]
Romidepsin							
Sogaard *et al.* (2015)	5 mg/m^2 (3)	3.8	Increased	No	Increased	No change	[19]
Disulfiram							
Spivak *et al.* (2014)	500 mg daily (14)	ND	Increased[b]	Yes	ND	No change	[16]
Elliot *et al.* (2015)	Dose escalation (3)	~2	Increased	Yes	ND	ND	[20]

[a]Determined nonquantitatively by nucleic acid testing (NAT) using a transcription-mediated amplification (TMA)-based assay (Procleix Ultrio Plus®, Novartis).
[b]The subgroup of patients with a measurable metabolite had an increase in low-level viremia.
[c]Abbreviations: ND, not determined; TIW, three times a week.

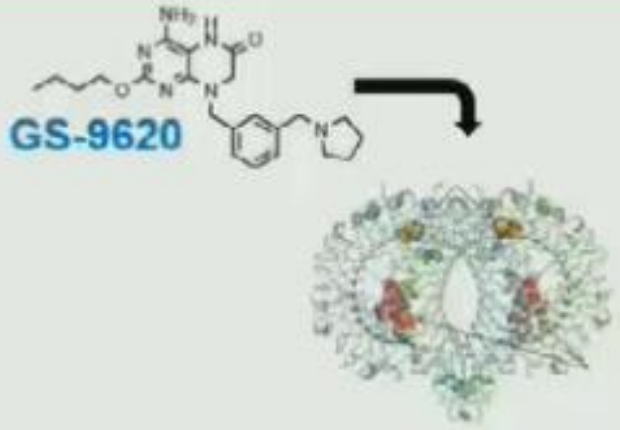
Rasmussen et al. Trends Mircobiol 2016

Toll-like receptors (TLRs) agonists

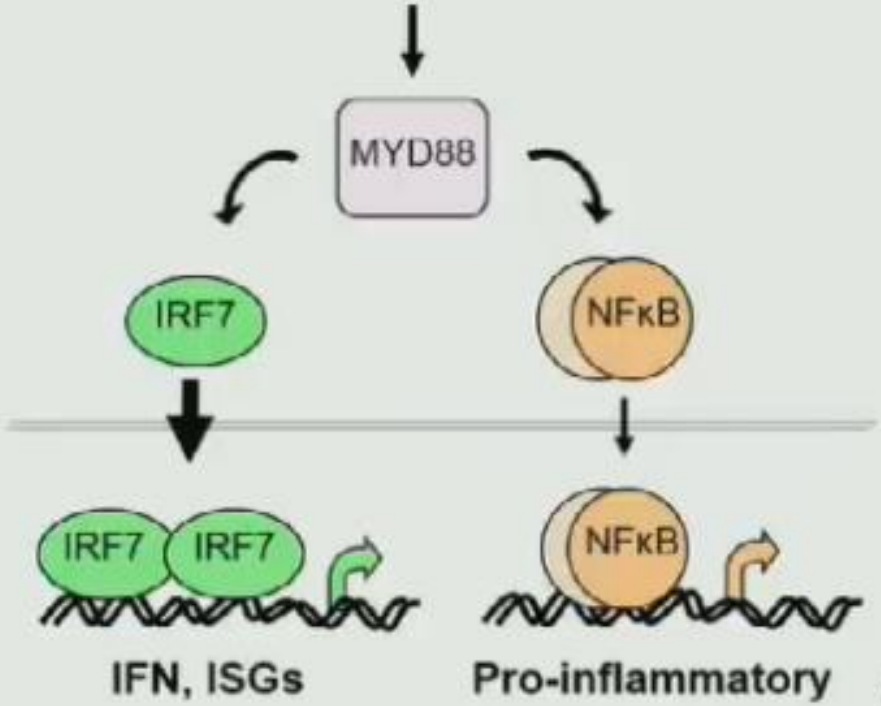


Vesatolimod: A Potent and Selective TLR7 Agonist

- Toll-like Receptor 7 (TLR7)
  - Primarily expressed on plasmacytoid DCs and B cells
  - Targeted for HBV and HCV, based on clear antiviral effects of IFN-α
- GS-9620 (Vesatolimod) is 30-fold selective for TLR7 over TLR8
- Phase 1 study in HIV+ individuals in progress

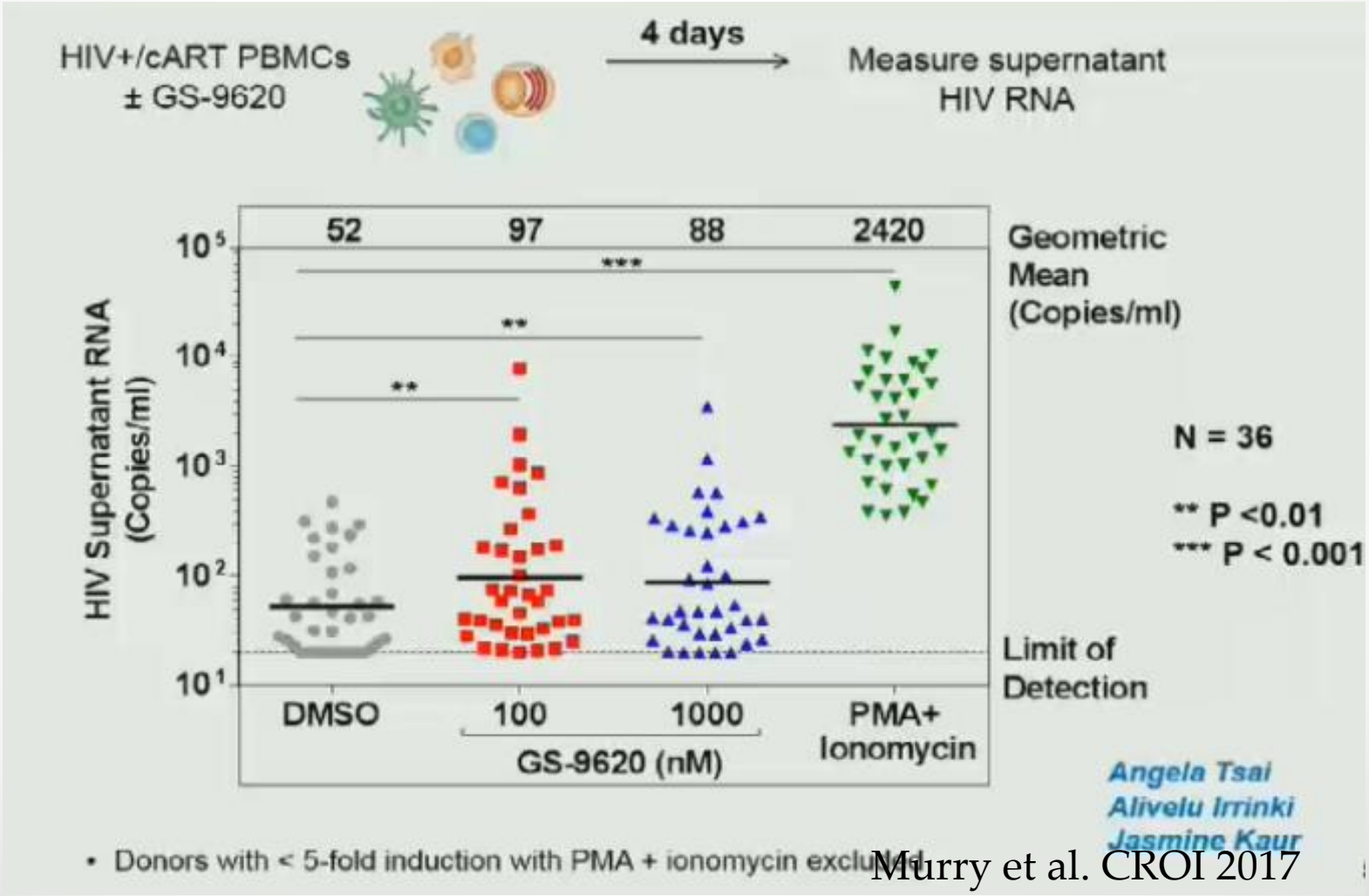


Zhang et al., Immunity, 2016



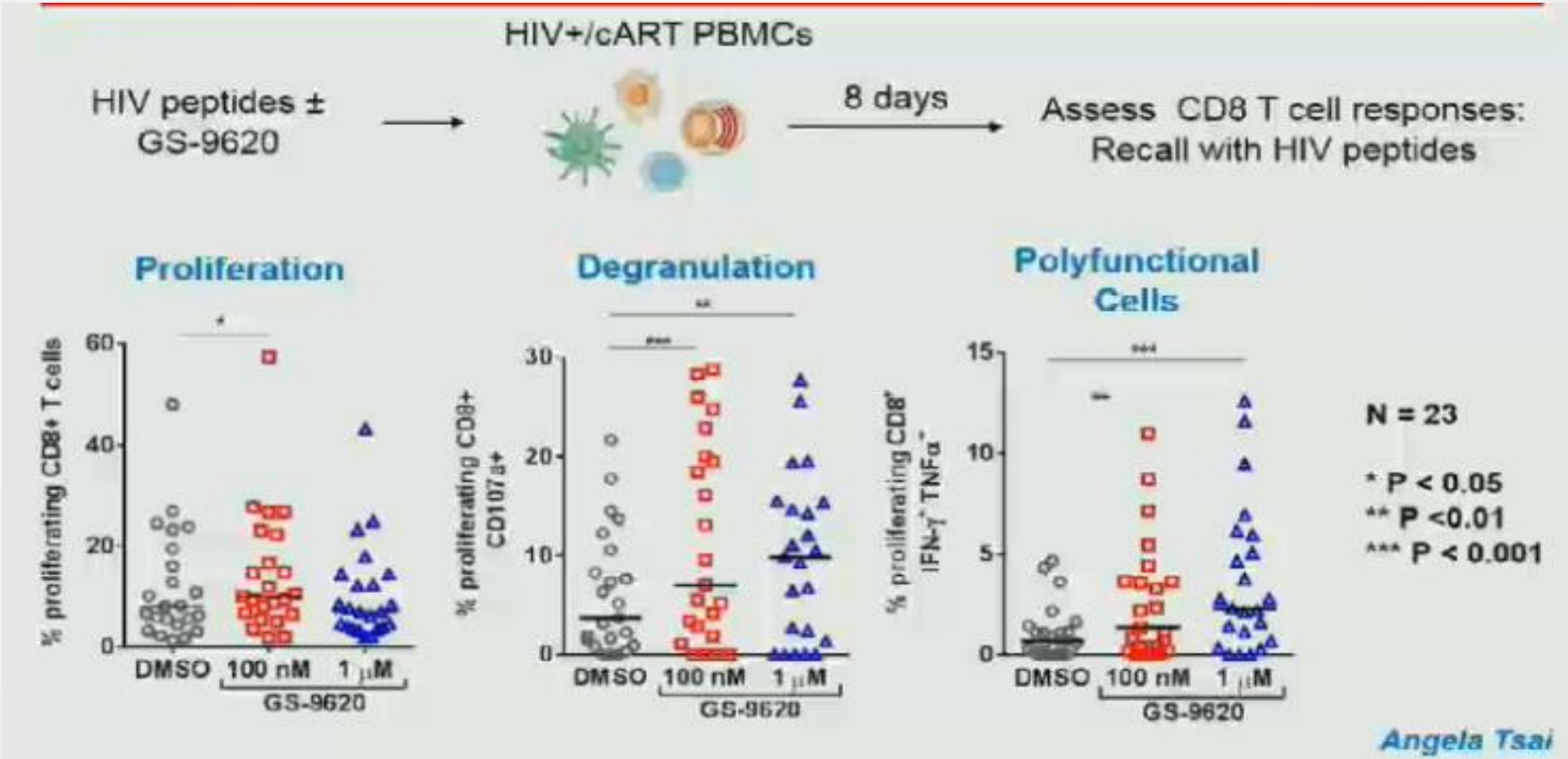
Murry et al. CROI 2017

cART-treated patients on viral suppression for >1 year



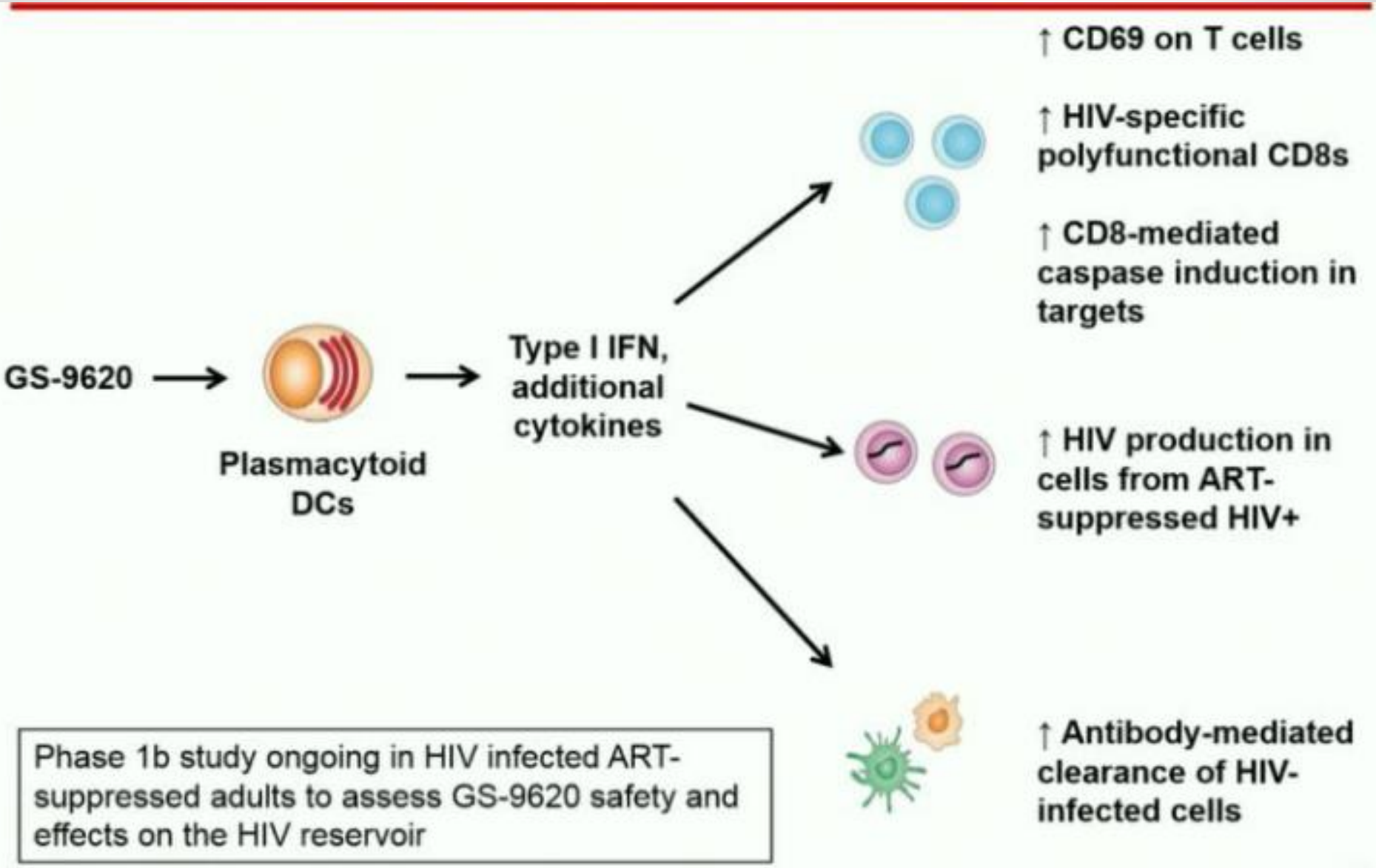
Murry et al. CROI 2017

GS-9620 Induces HIV-specific T-cell activation/proliferation



- Significant effects also found in CD4+ T cells, though to a lesser degree
- Activated response to CMV/EBV/Flu/Tetanus also seen

Murry et al. CROI 2017



Murry et al. CROI 2017

Functional cure: what contribution of therapeutic vaccination?

Therapeutic vaccination: the rationale

- Therapeutic vaccine may help to tackle HIV-1 viral diversity in the viral reservoir driven by HIV immune escape

- combination of vaccine with LRA (*kick and kill*) or other immunotherapeutic approach could synergistically act to clear HIV reservoir and enhance HIV immunity

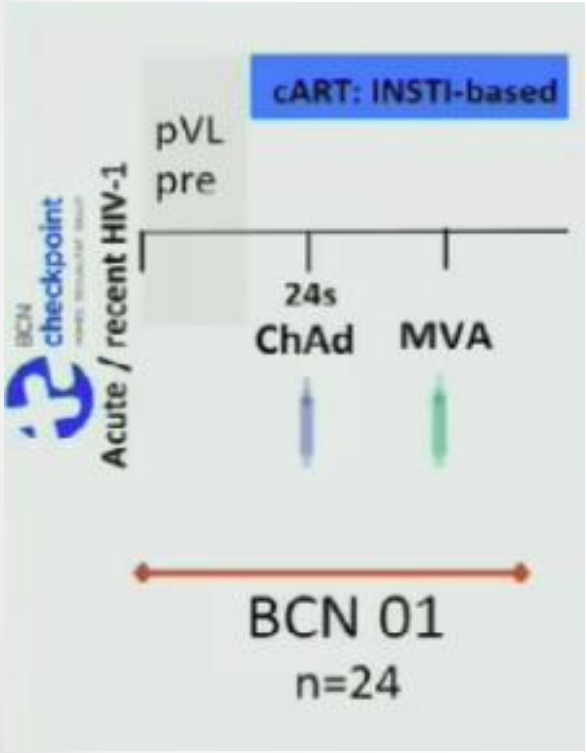
Principal therapeutic phase I/II vaccines

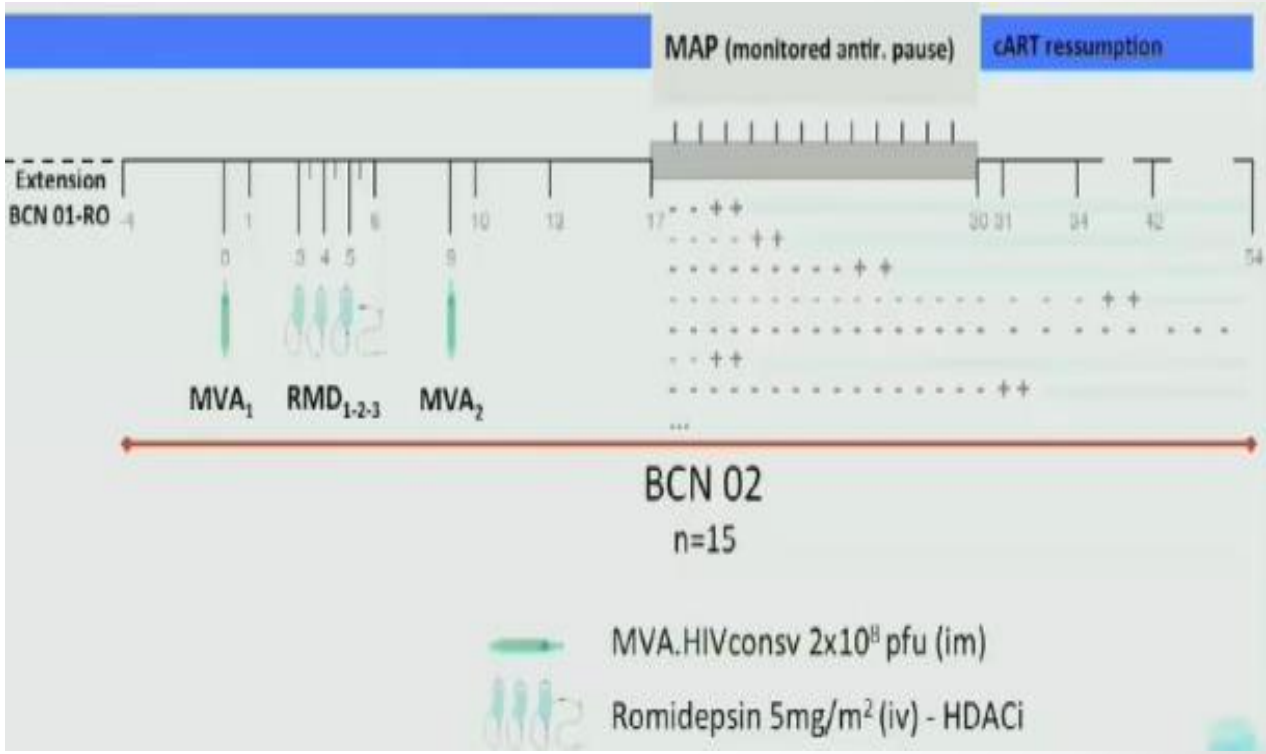
Vaccine	Additional description	Phase	Trial Registry Identifier*	Reference
vCP1452	ALVAC-based vaccine	2	NCT00056797	
MRK Ad5 HIV-1 gag	Adenovirus-based vaccine	2	NCT00080106	[56,57]
ISS T-002	HIV Tat-based vaccine	2	NCT00751595	[58,59]
GTU-multiHIV B + LIPO-5	DNA + lipopeptide vaccines	2	NCT01492985	
DermaVir LC002	DNA-based vaccine	1/2	NCT00270205	[60-62]
Synthetic vaccine	HIV Tat-based vaccine	1/2	NCT01793818	
THV01	Lentiviral-based vaccine	1/2	NCT02054286	
DNA-GTU	Plasmid DNA-based vaccine	1/2	NCT02457689	
AGS-004	Patient-derived dendritic cells + HIV antigens	1/2	NCT01069809	
Epimmune	DNA-based vaccine	1	NCT00052182	[64]
rMVA-HIV (env/gag [TBC-M358] + tat/rev/nef [TBC-M335])	Vaccina Ankara-based vaccine	1	NCT00107549	[65]
rFPV-HIV (env/gag [TBC-F357] + tat/rev/nef [TBC-F349])	Fowlpox-based vaccine	1	NCT00107549	[65]
MVA.HIVconsv	MVA-based vaccine	1	NCT01024842	
MAG pDNA + rSVIN HIV-Gag	DNA + VSV-based vaccine	1	NCT01266616	
HIVAX	Lentiviral-based vaccine	1	NCT01428596	
ChAdV63.HIVconsv + MVA.HIVconsv	Adenovirus + MVA-based vaccines	1	NCT01712425	
iHIVARNA-01	TriMix + HIV antigen naked messenger RNA	1	NCT02413645	
D-GPE DNA + M-GPE MVA	DNA and MVA viral vector vaccines	1	NCT01881581	

BCN02- pilot single-arm open lable

HIV+ treated within 3 months from acute infection, fully suppressive cART for 3yrs

- **cART interruption 8 weeks after last vaccine boost**
- **cART re-started if VL>2000**

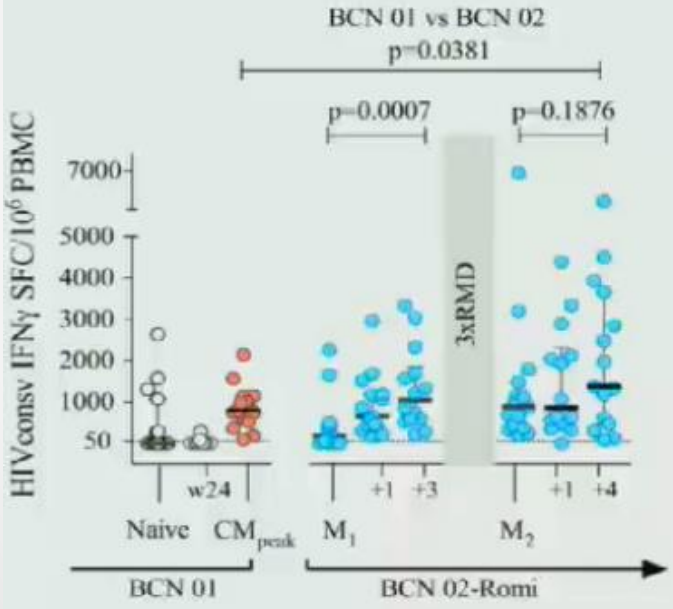




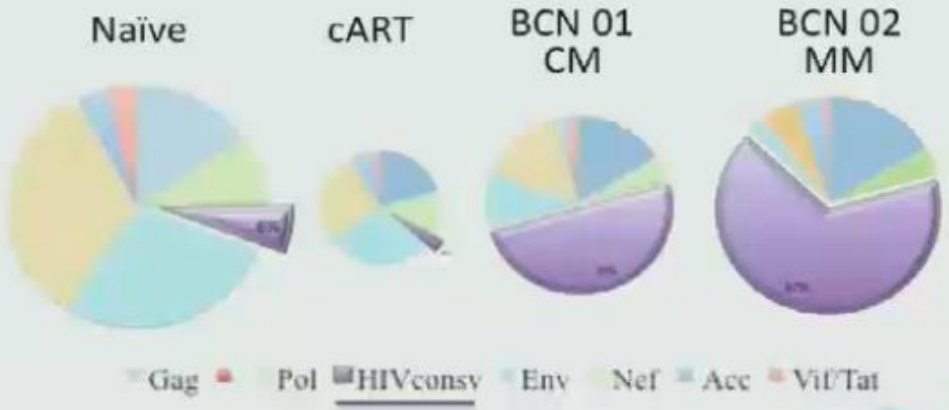
Mothe V #119 LB CROI 2017

n=15

HIVconsv responses were effectively boosted after >2years from 1st CM



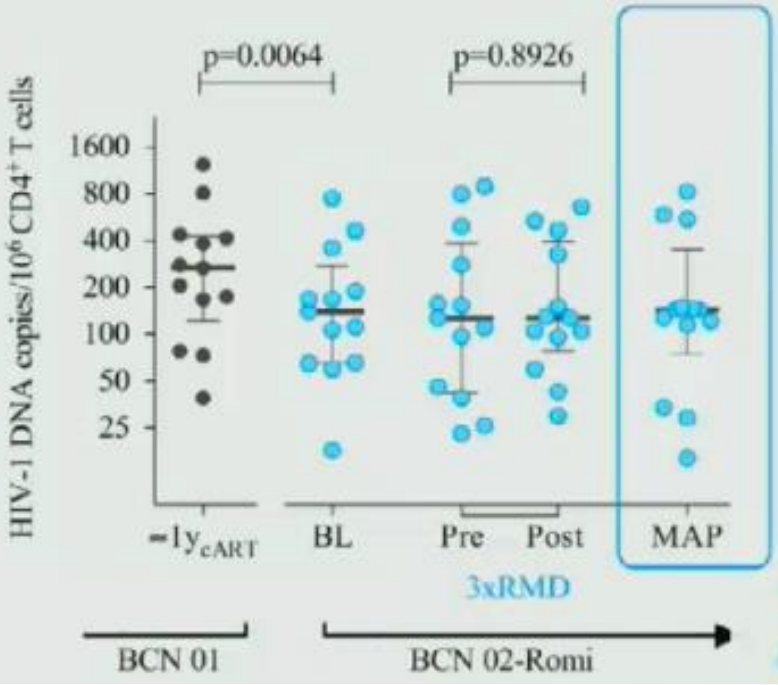
- Change in CTL immunodominance pattern towards conserved regions



Mothe V #119 LB CROI 2017

n=13
Feb 15th

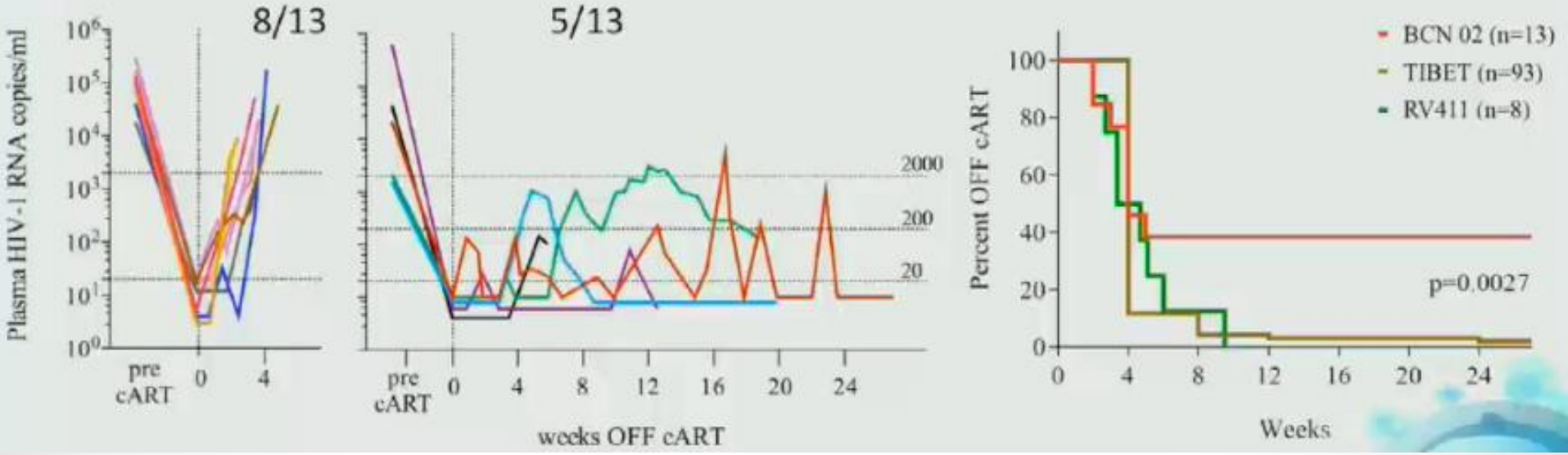
- Up to 3years on cART, continues reduction in levels of proviral DNA.
- No further decrease with RMD.
- At MAP, median (range) of
  144 (16-829) copies/10^6 $CD4^+$ T cells
- Detectable in all patients.



Mothe V #119 LB CROI 2017

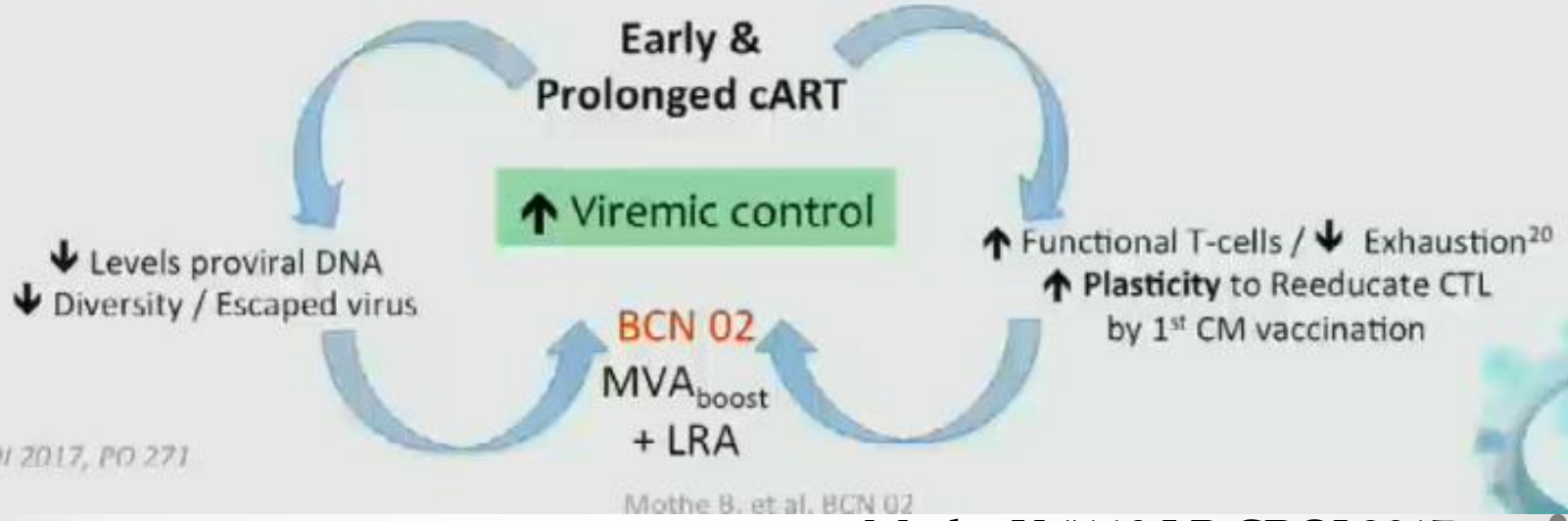
n=13
Feb 15th

- 13 participants have interrupted cART to date.



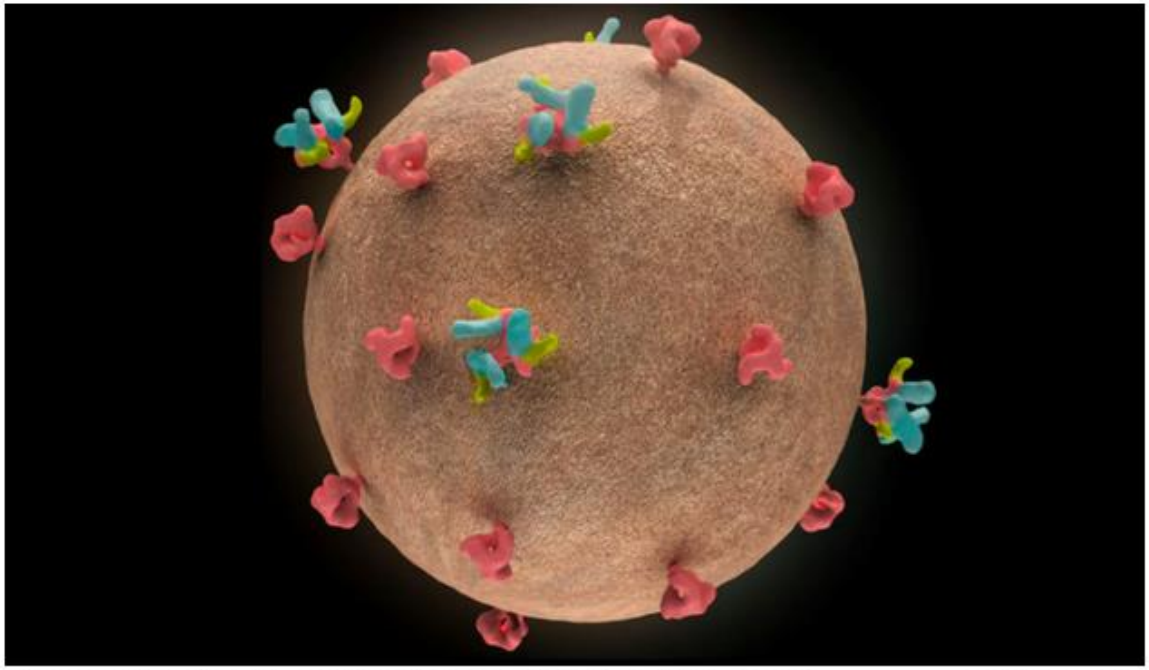
Mothe V #119 LB CROI 2017

- This is the first therapeutic vaccine trial reporting a durable control of HIV-1 after cART cessation in a substantial proportion of patients (≈35-38%, so far >12-24wks).
- BCN 02 data suggest that viral control can be achieved by an effective redirection of CTL towards conserved regions in the context of a limited viral reservoir.



Mothe V #119 LB CROI 2017

Science AAAS



HIV surface proteins (salmon) rapidly mutate to dodge antibodies (lime and blue) so some vaccines direct immune responses to viral pieces that rarely change.

Donald Bliss and Sriram Subramaniam/NIH

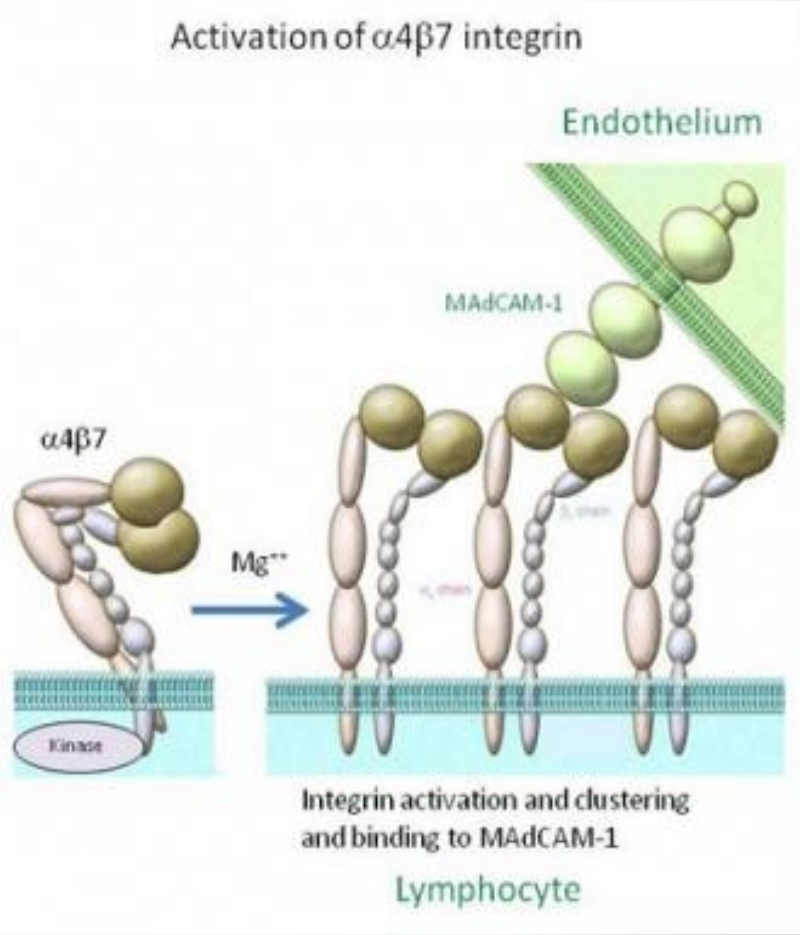
AIDS vaccine may be 'functional cure' for some

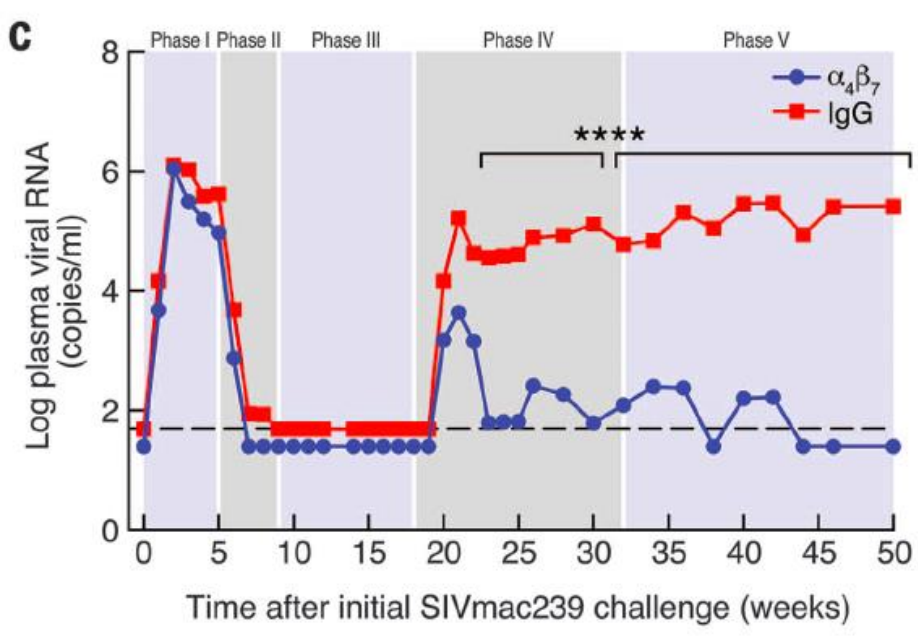
By Jon Cohen | Feb. 22, 2017 , 4:45 PM

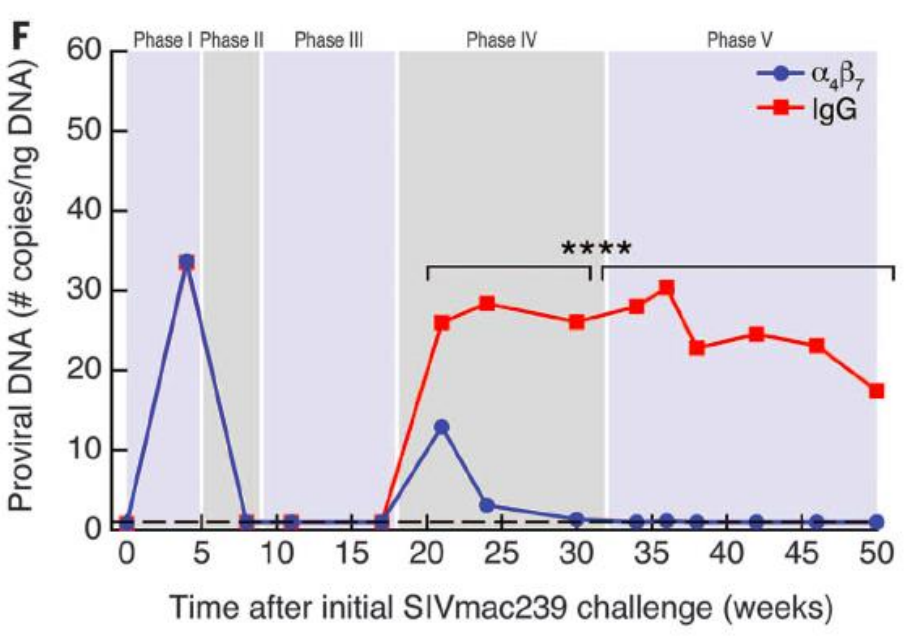
RESEARCH ARTICLE

HIV-1 THERAPY

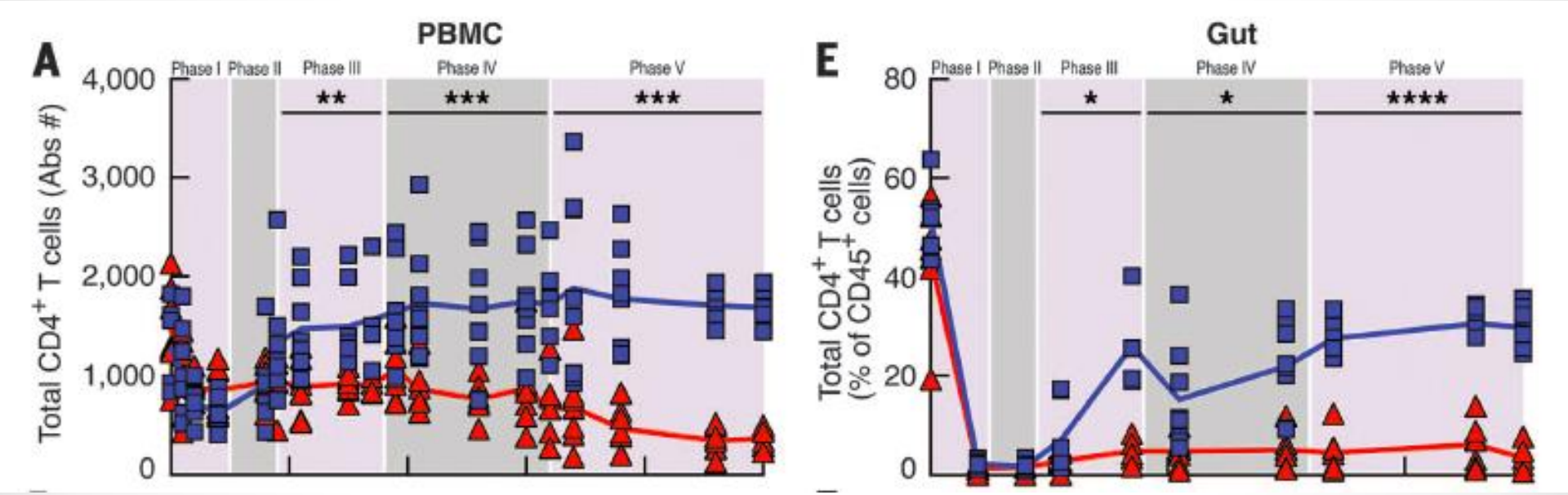
Sustained virologic control in SIV$^+$ macaques after antiretroviral and $\alpha_4\beta_7$ antibody therapy



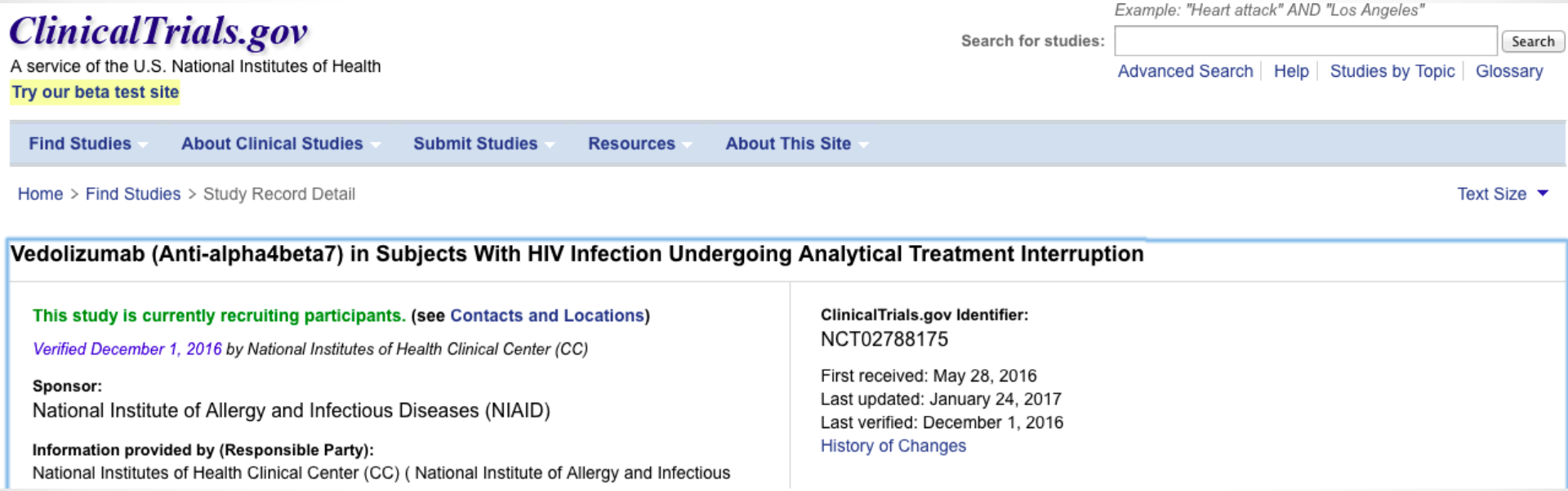




Byrareddy et al. Science 2016



Byrareddy et al. Science 2016



cART + 22-week infusion, then stop cART