CURRENT STATUS OF HIV CURE RESEARCH

Giulia Marchetti, MD, PhD

Dep of Health Sciences, Clinic of Infectious and Tropical Diseases – University of Milan – San Paolo Hospital, Milan - Italy

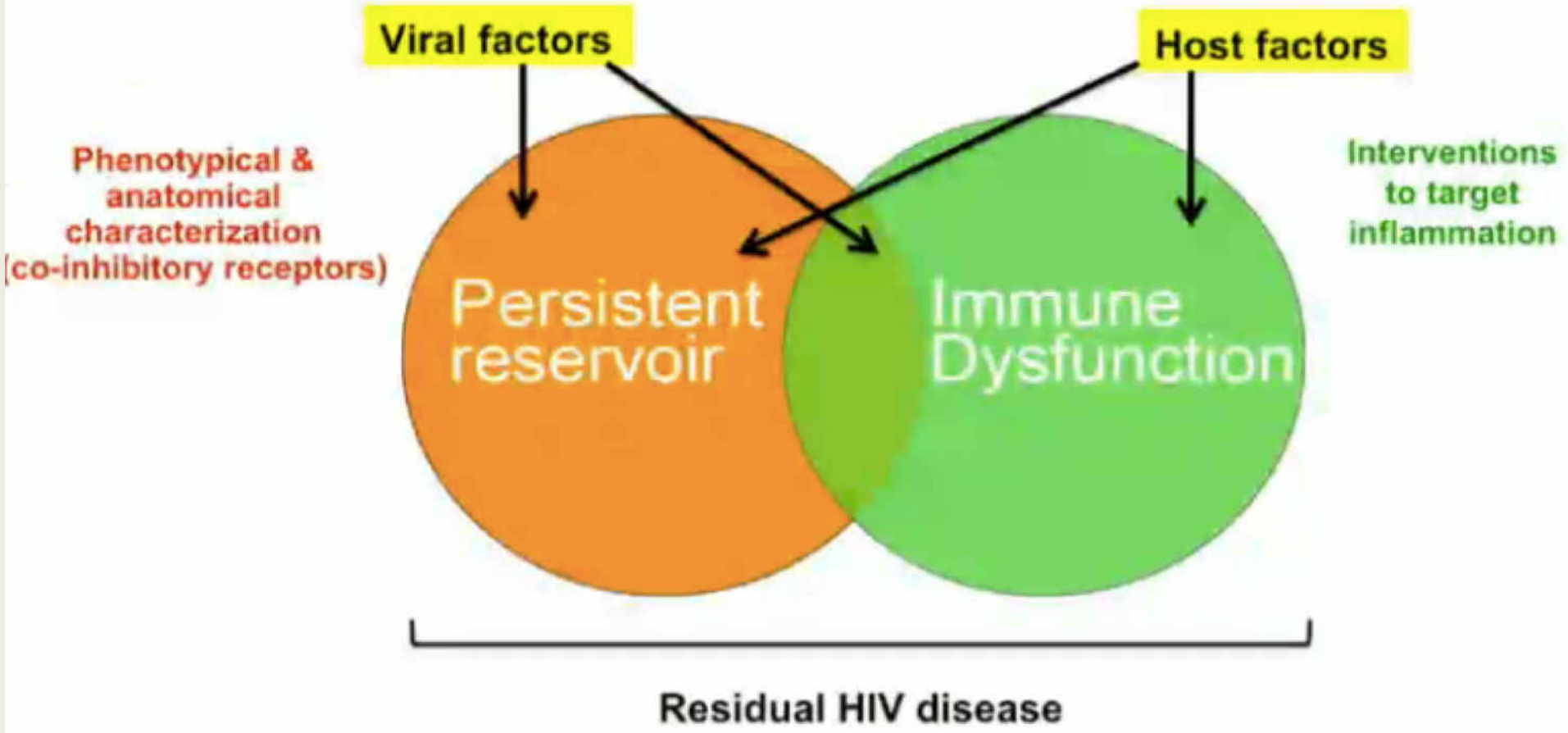
Cure or remission?

Cure
Infectious Diseases model
Elimination of all HIV-infected cells
HIV RNA < 1 copy/ml
Sterilising cure

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?

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.)

Functional cure – the assumption(s)

- LTNPs* and ECs**: high CD4 counts and/or HIV RNA control without therapy
- PTCs***: long-term virological remission following the interruption of cART started during early(est) infection

**LTNPs, long-term non progressors; **ECs, elite controllers; ***PTCs, post-treatment controllers*

Grabar et al. AIDS 2009; Saag & Deeks CID 2010; Saez-Cirion Plos Path 2013

Does early treatment approach functional cure?

The children paradigm

Parameters	Mississippi [2]	Canadian [4]	Milan [5]
Time to viral rebound	27 months	<1 month	<1 month
ART onset	30 hours	<24 hours	12 hours
Pre-ART HIV RNA. copies/ml	19,812	808	152,560
Time to HIV RNA < 50 copies/ml on ART	1 month	6 months	3 months
Time on ART before interruption	18 months	3 years	3 years
Cell-associated HIV DNA	Undetected[a]	Undetected	Undetected
Replication-competent virus	Negative viral outgrowth assay[a]	Negative viral outgrowth assay	Negative viral culture
HIV antibody	Non-reactive[a]	Non-reactive	Non-reactive
HIV-specific T cells	Undetected[a]	Not reported	Detected
Others	Normal frequencies of activated T cells[a]	Detected cell-associated HIV RNA	High frequencies of activated T cells

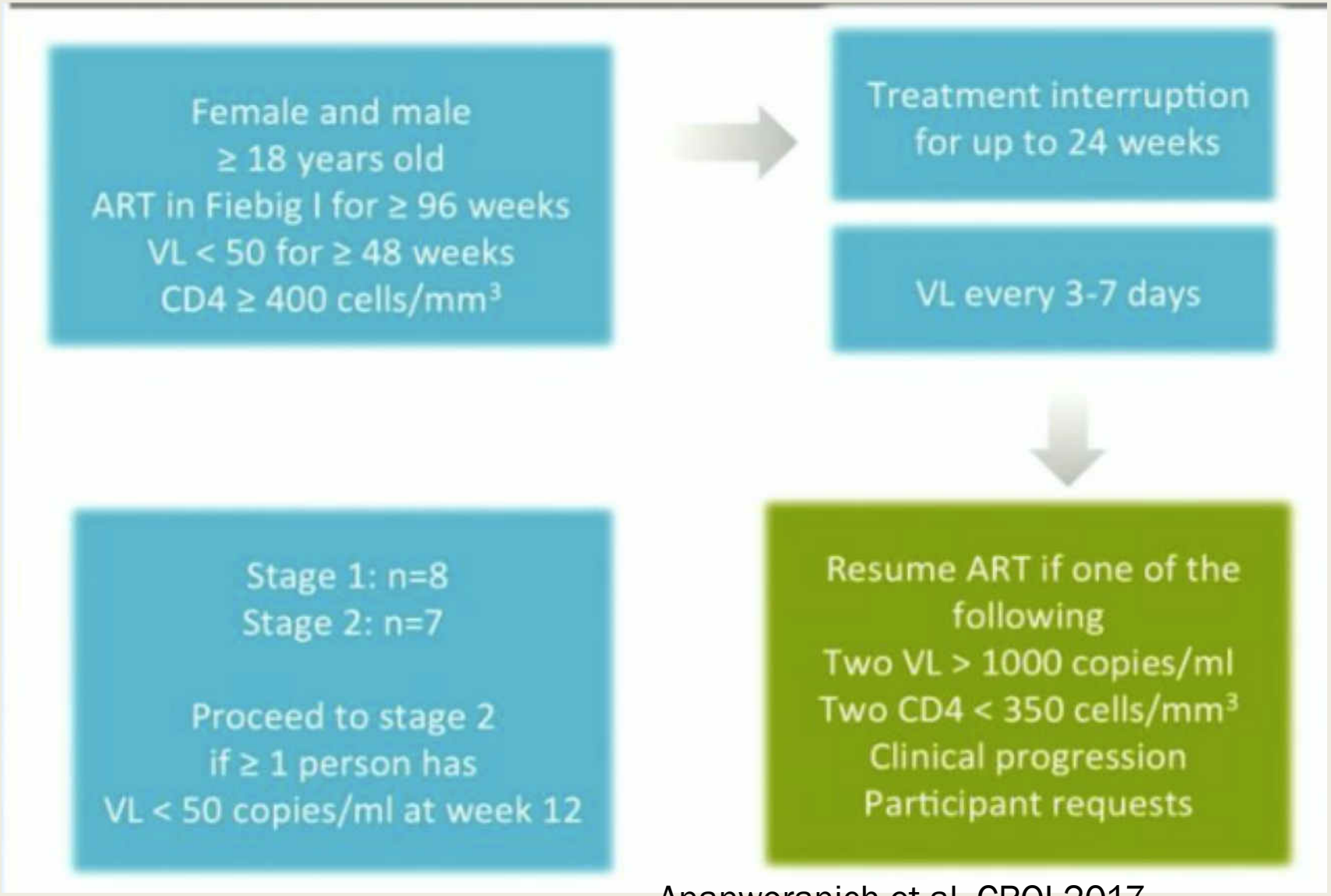
[a]The reservoir and immunity testing in the Mississippi baby were performed after ART was interrupted. The testing on the Canadian and Milan babies was performed during ART. ART: antiretroviral therapy.

Ananworanich & Robb JIAS 2014
4- Brophy J et al. 20th IAS Conference, Melbourne 2014;
5- Giacomet V et al. Lancet 2014

+ Frange et al. cART until 5yo; 11 years off cART HIV RNA<4 cp/ml, HIV DNA <2,2Logcp/10^6PBMC - IAS 2015 , Vancouver- Canada

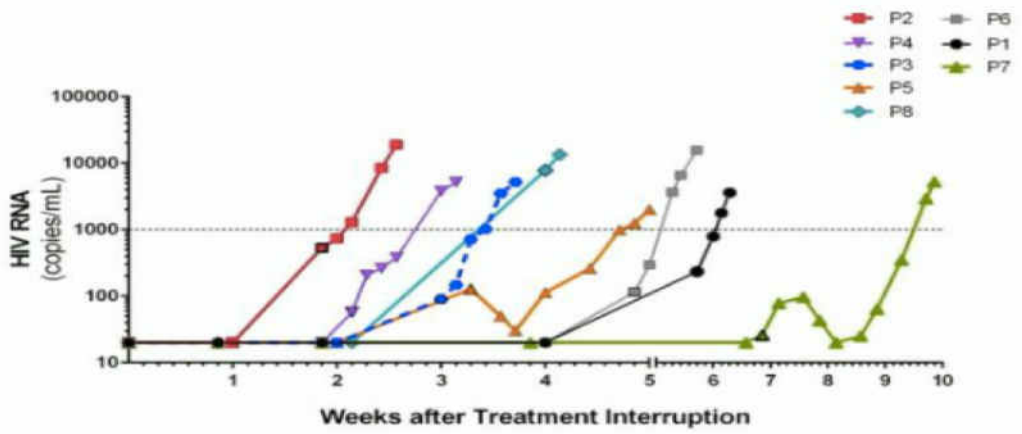
+ Violari et al. cART from 8wks until 1yo; >8 years off cART, undetectable VL/HIV-DNA, ELISA neg (weekly reactive to Gag p40) – IAS 2017, Paris

RV411

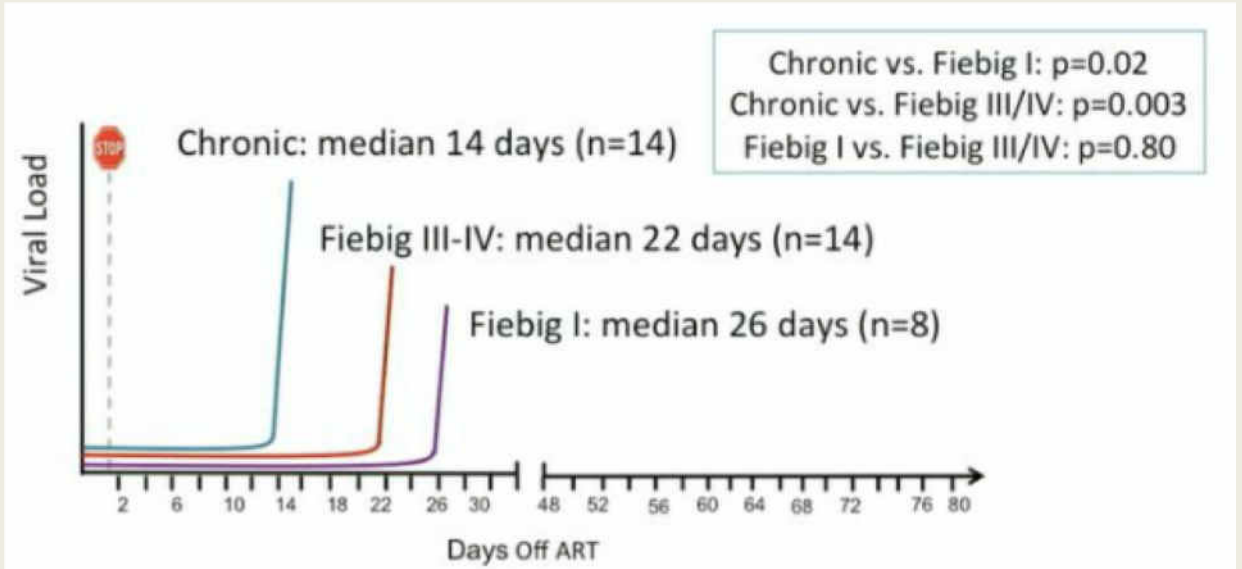


Ananworanich et al. CROI 2017

Viral Load Following Treatment Interruption



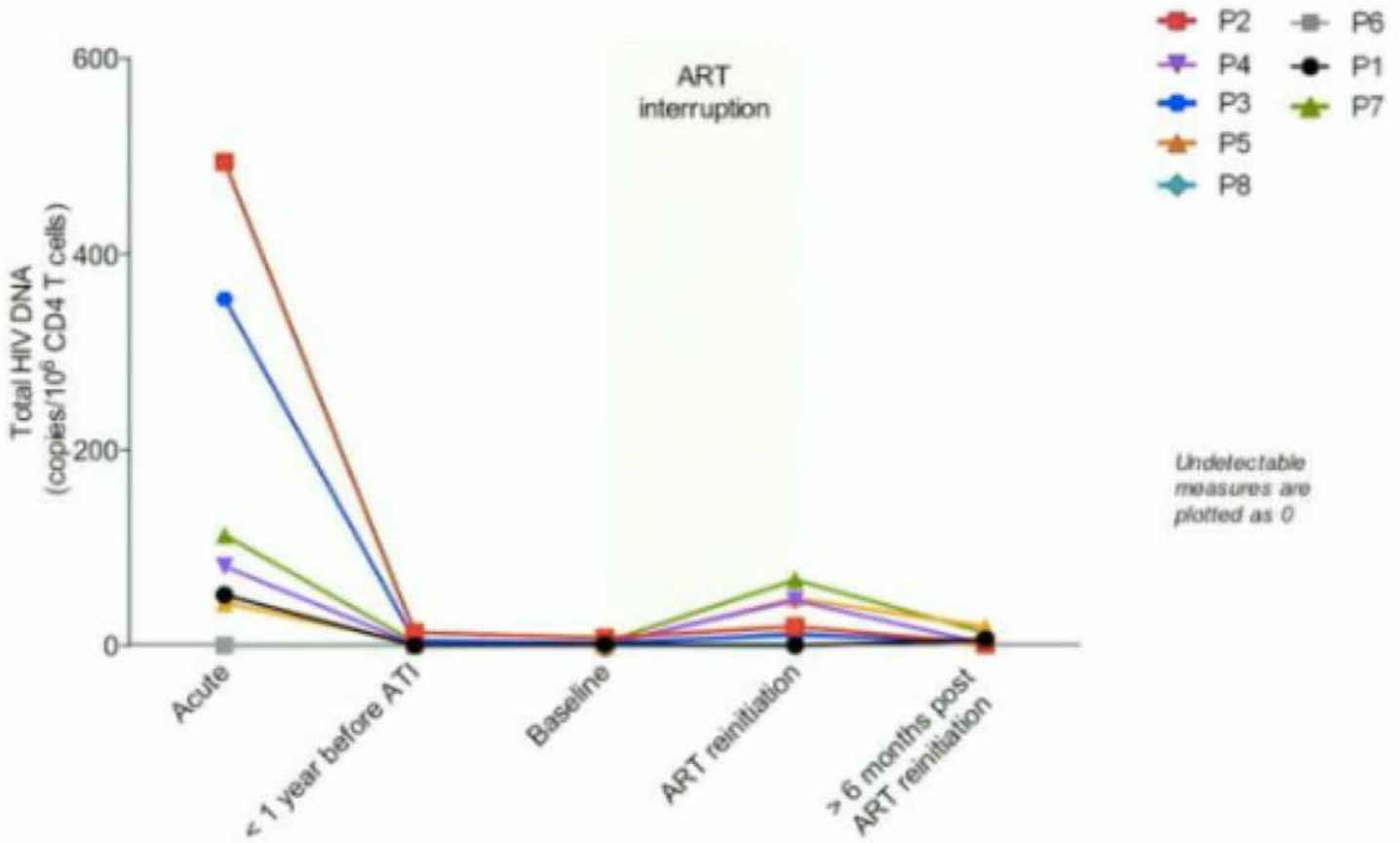
Median time to viral rebound:
26 days (range 13-48)



Chronic US: Rothenberger, Schacker, PNAS 2015
Fiebig III/IV Thai: Kroon, de Souza, IAS 2016

Ananworanich et al. CROI 2017

HIV Reservoir Size Increased during ATI and Declined to Pre-ATI Levels after ART Resumption



Ananworanich et al. CROI 2017

- ART initiated in Fiebig I acute HIV infection
  - No clinically meaningful delayed time to viral load rebound compared to chronic cohorts

- Early ART helps but alone it is not enough to induce HIV remission
  - Additional novel therapeutic strategies will be needed

Functional cure: what contribution of Latency Reversing Agents (LRA)?

"Shock and kill" strategies

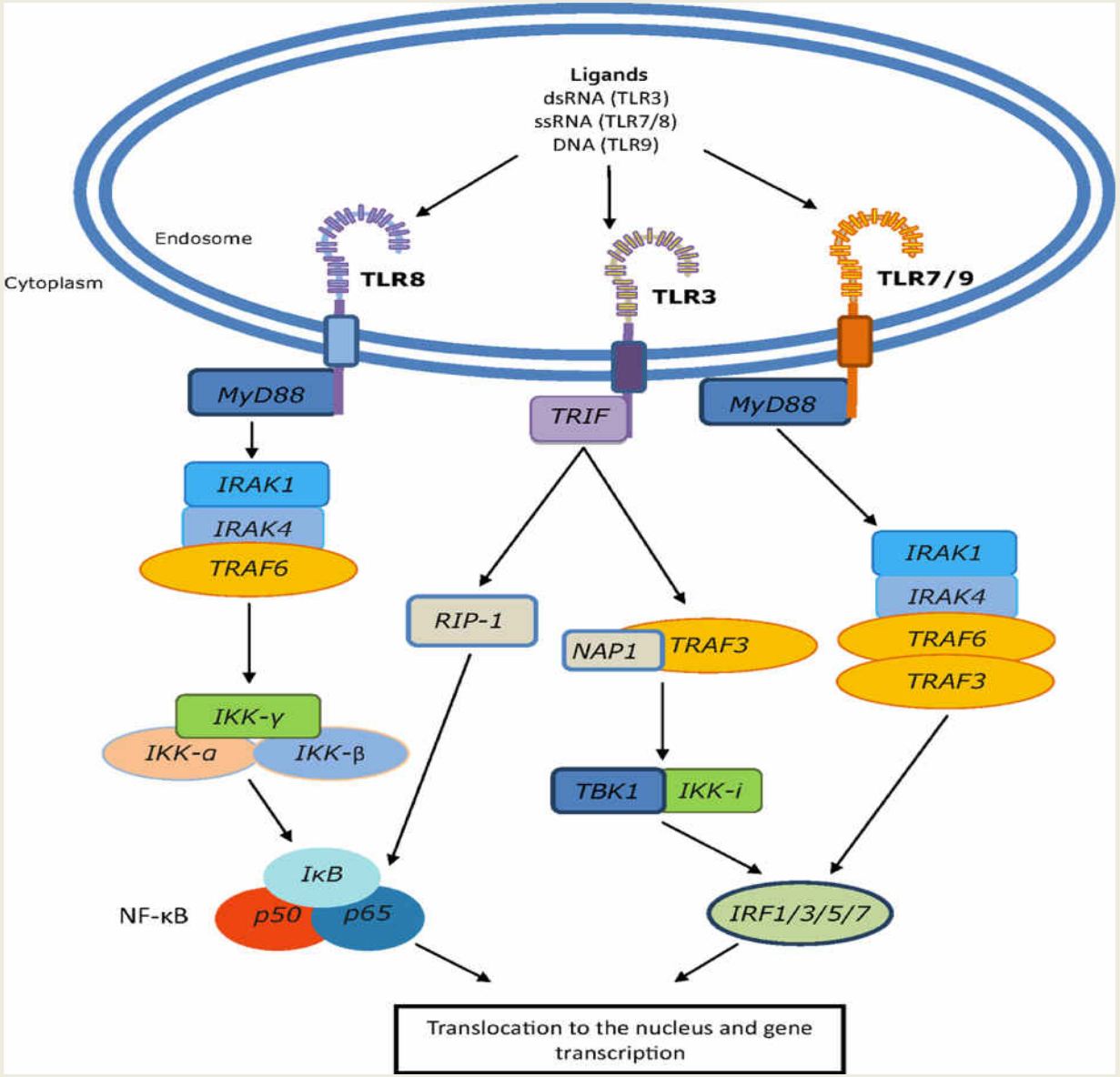
Table 1. Clinical Trials of Latency-Reversing Agents

	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.

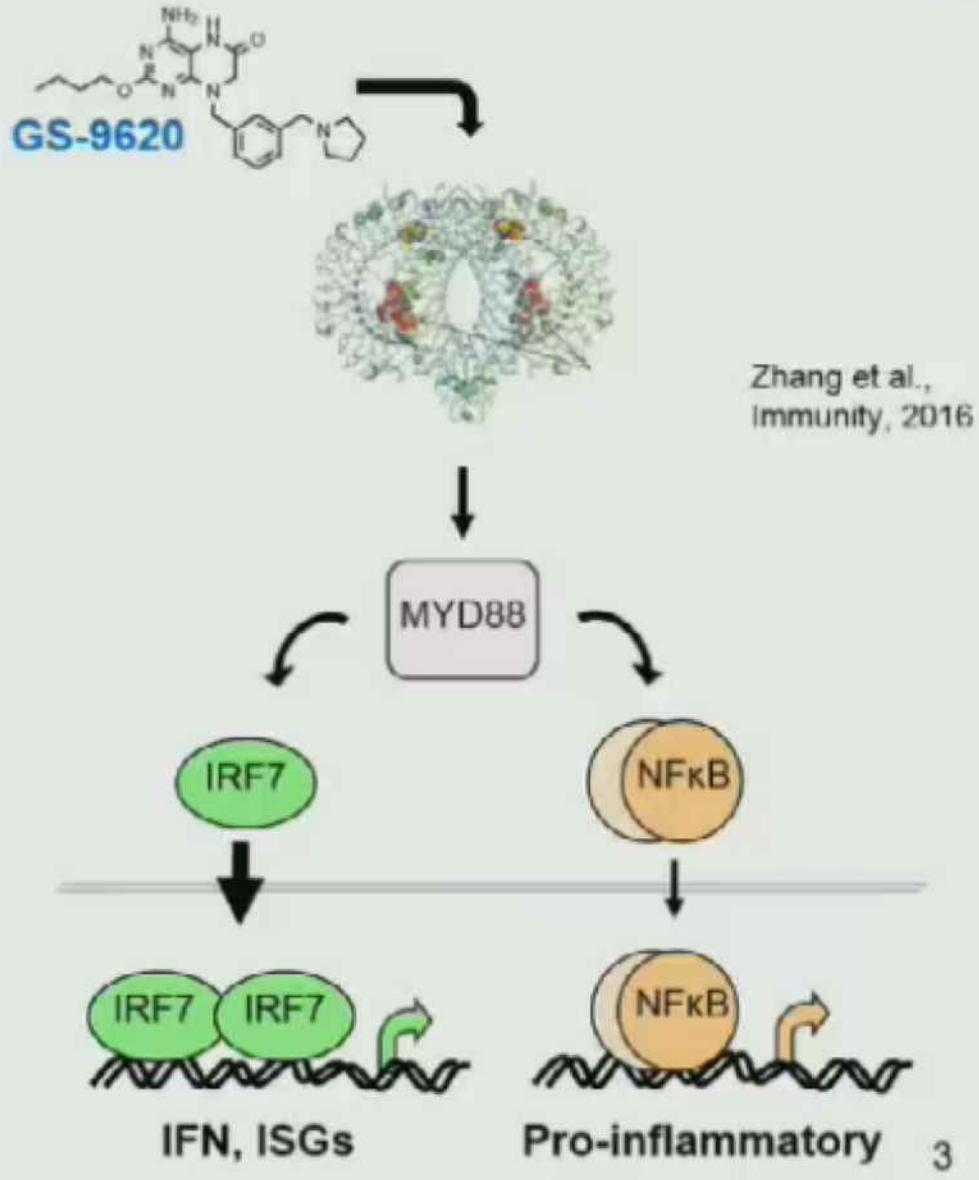
Rasmussen et al. Trends Mircobiol 2016

Toll-like receptors (TLRs) agonists



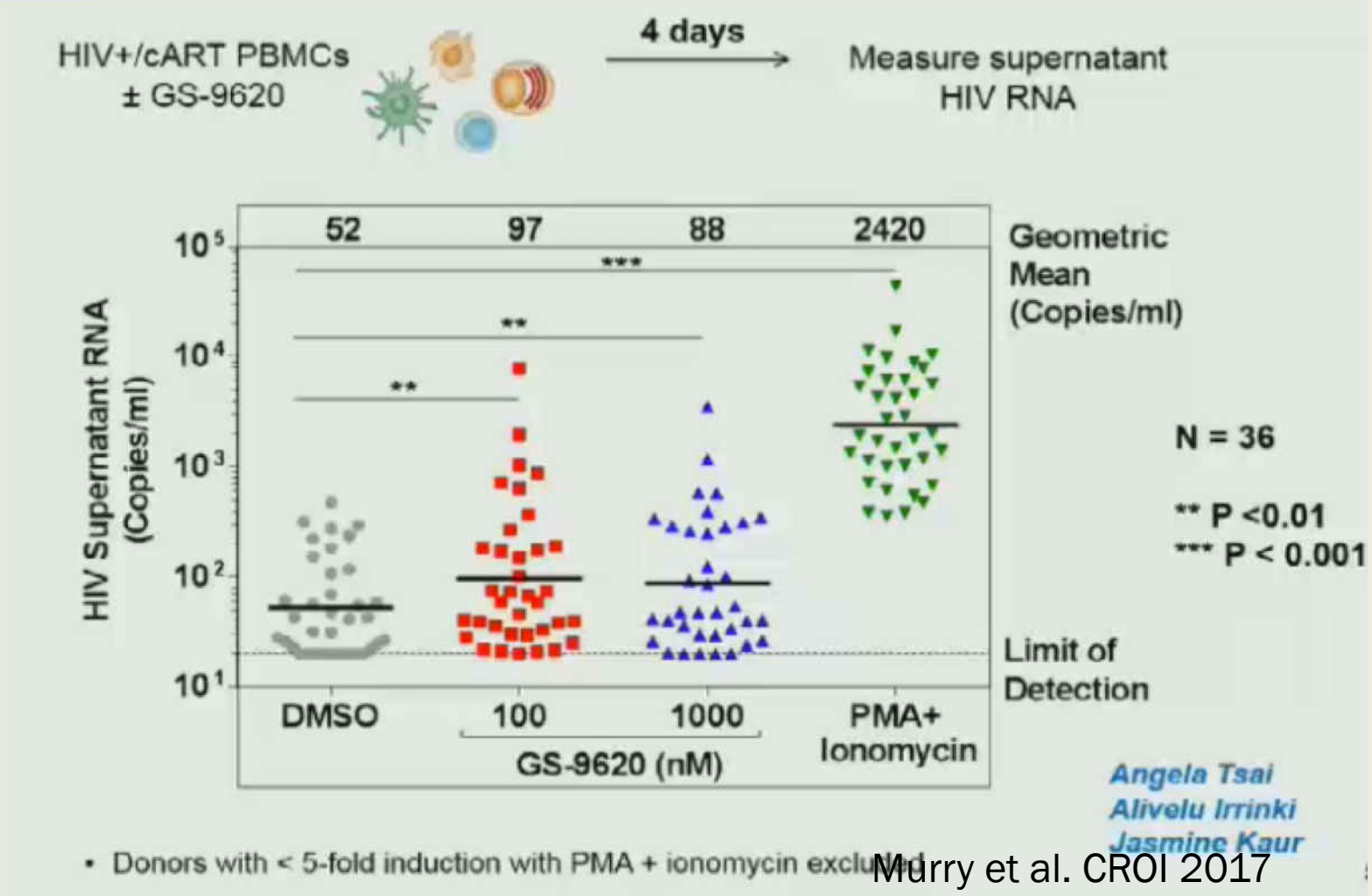
Vesatolimod: A Potent and Selective TLR7 Agonist

- 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



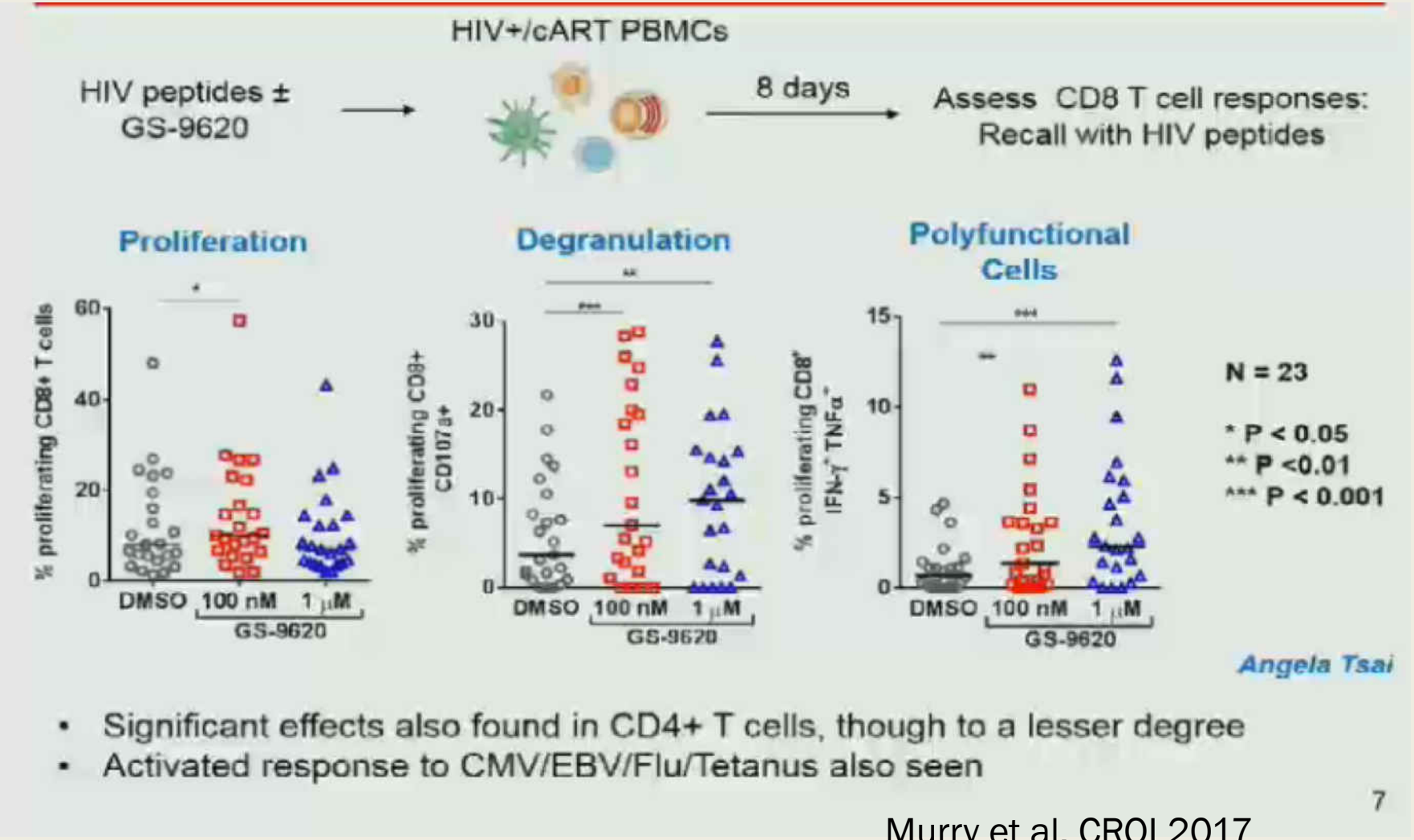
Murry et al. CROI 2017

Vesatolimod (GS-9620) Induces HIV expression in PBMC from cART-treated patients on viral suppression for >1 year

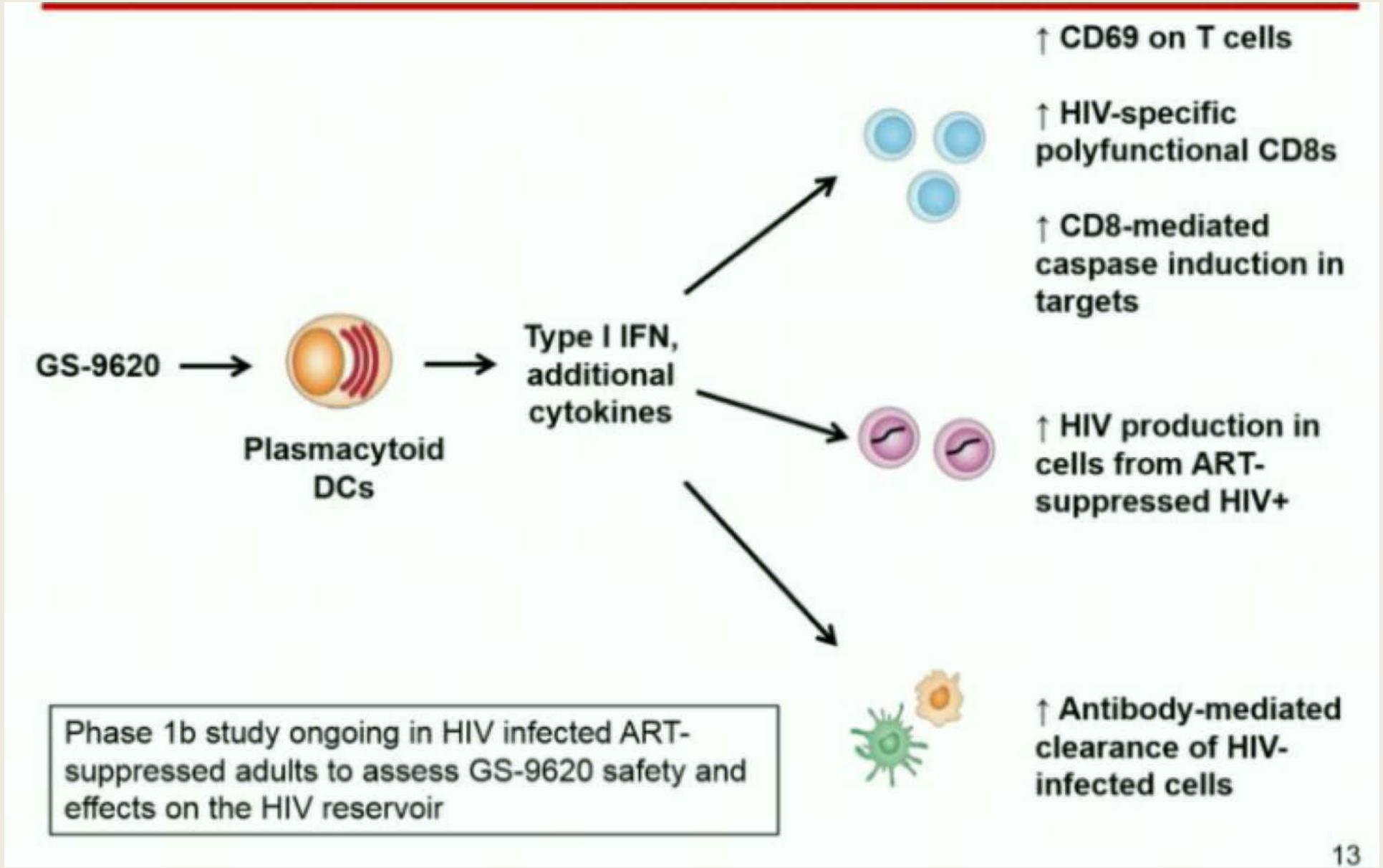


Murry et al. CROI 2017

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



Murry et al. CROI 2017



Murry et al. CROI 2017

Functional cure: what contribution of therapeutic vaccination?

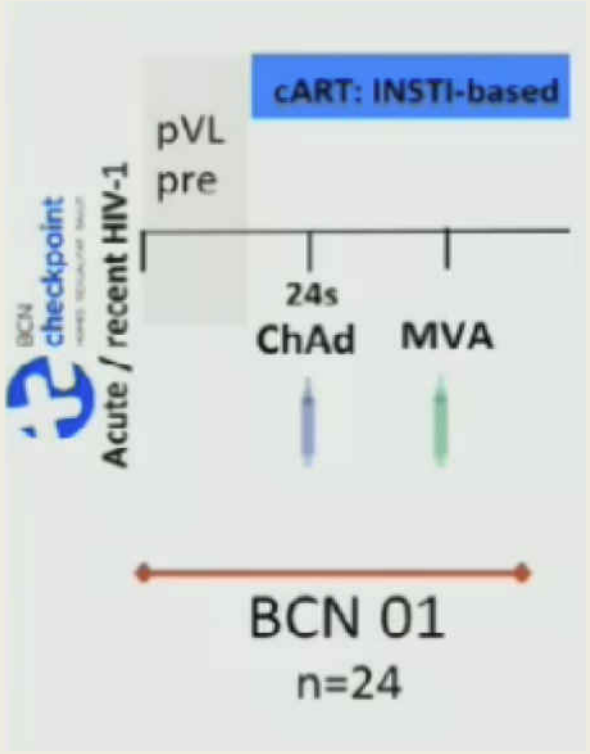
Principal therapeutic phase I/II vaccines

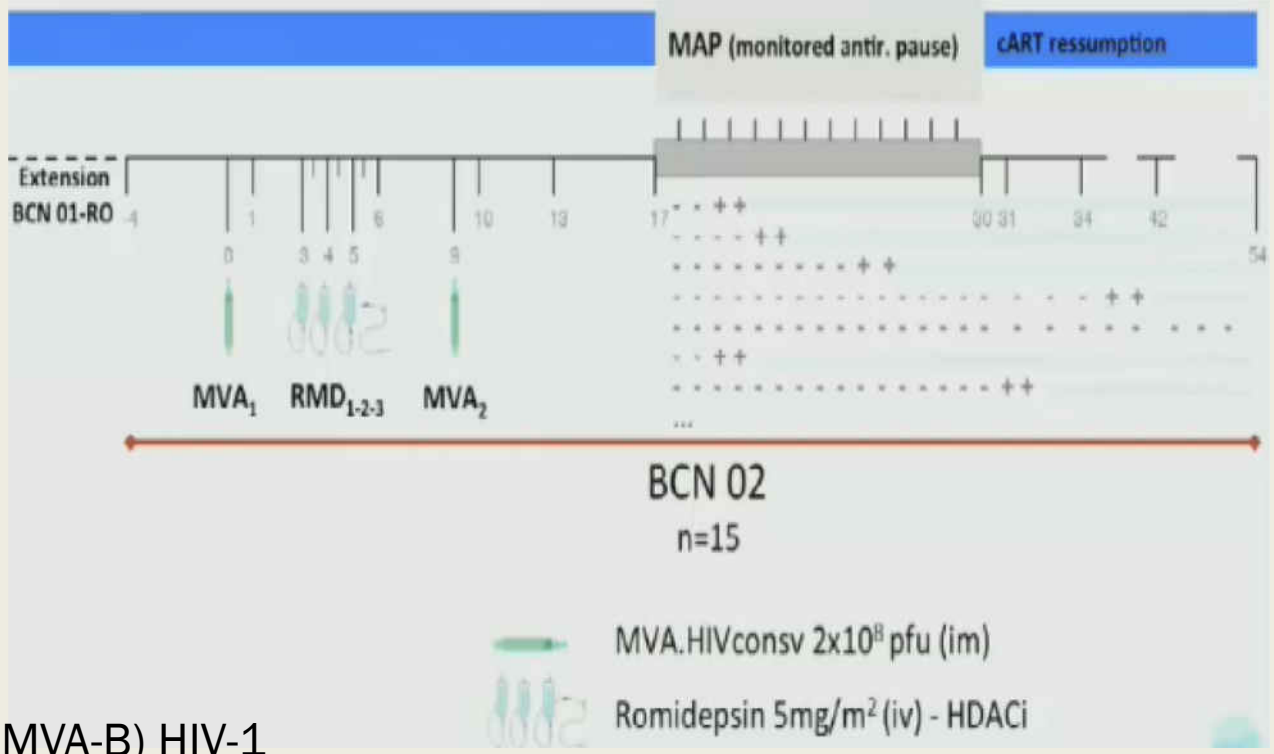
Vaccine	Additional description	Phase	Trial Registry Identifier*	Reference
vCP1452	ALVAC-based vaccine	2	NCT00056797	
MRK Ad5 HIV-1 gag	Adenovirus-based vaccine	2	NCT00080106	[56,57]
ISS T-002	HIV Tat-based vaccine	2	NCT00751595	[58,59]
GTU-multiHIV B + LIPO-5	DNA + lipopeptide vaccines	2	NCT01492985	
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



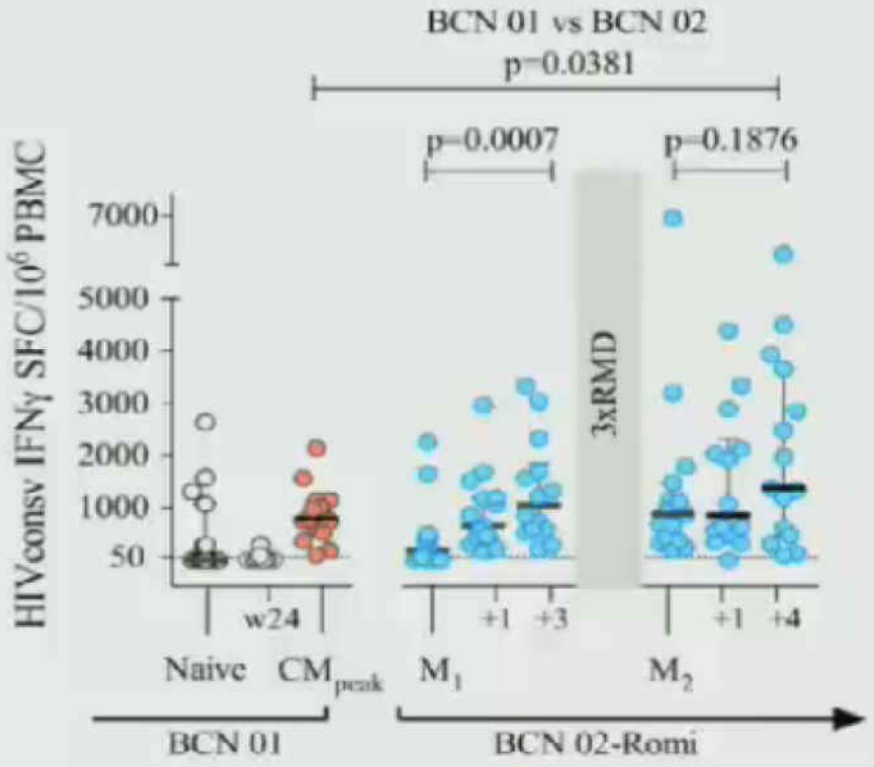


Recombinant modified Ankara-based (MVA-B) HIV-1 vaccine expressing gp120 and fused Gag-Pol-Nef polyprotein of clade B

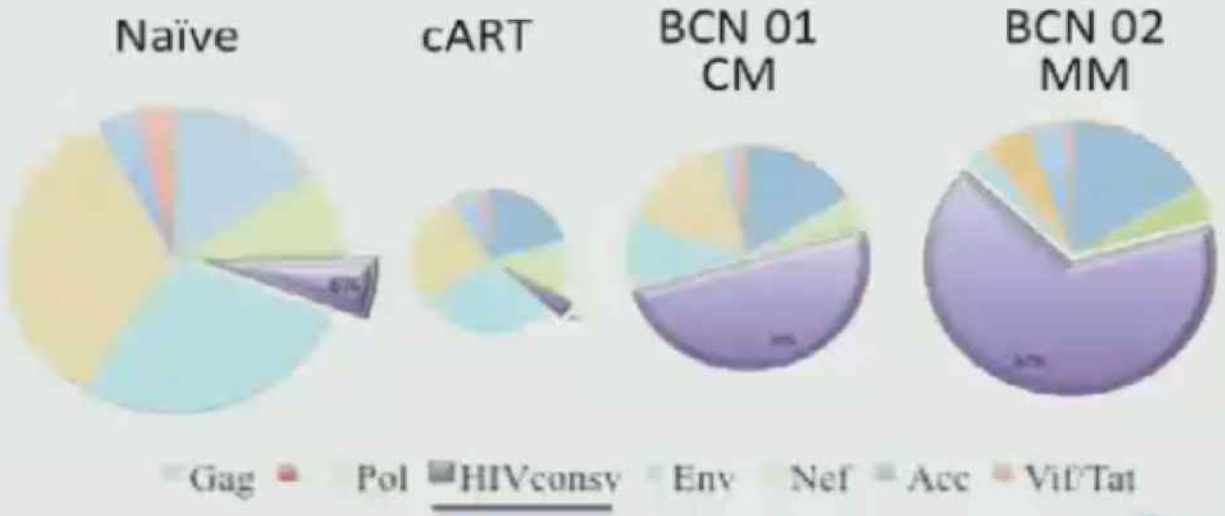
Mothe V #119 LB CROI 2017

n=15

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



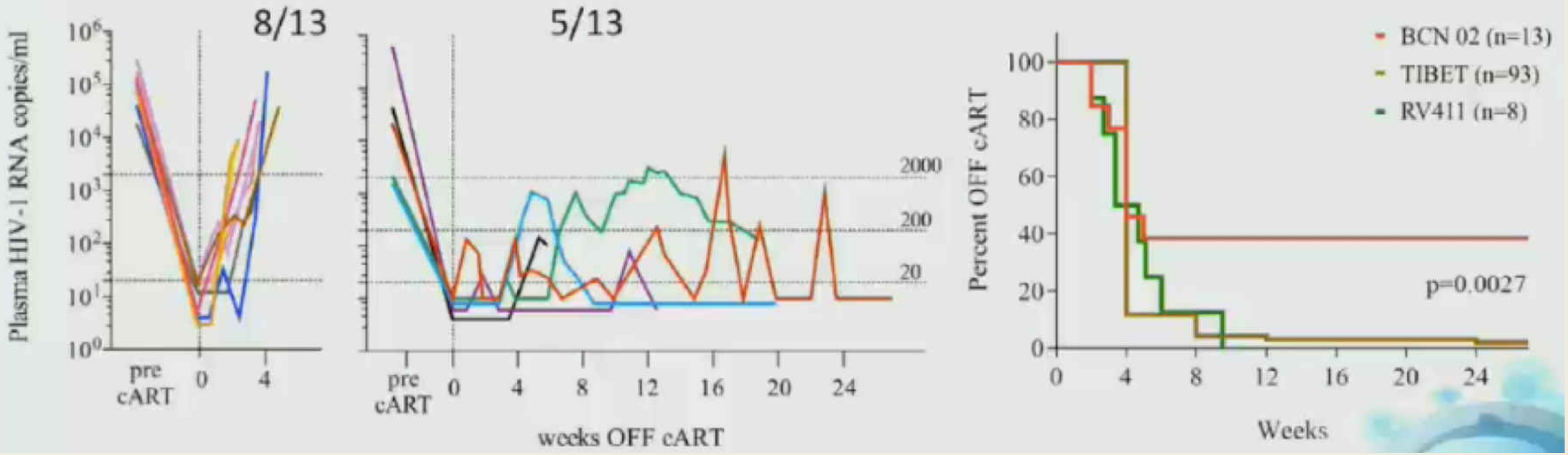
- Change in CTL immunodominance pattern towards conserved regions



Mothe V #119 LB CROI 2017

n=13
Feb 15th

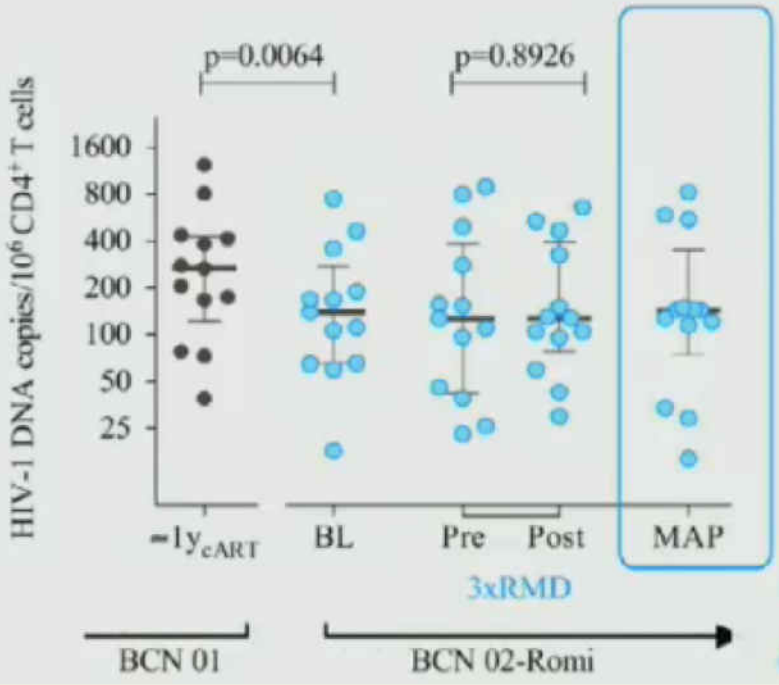
- 13 participants have interrupted cART to date.



Mothe V #119 LB CROI 2017

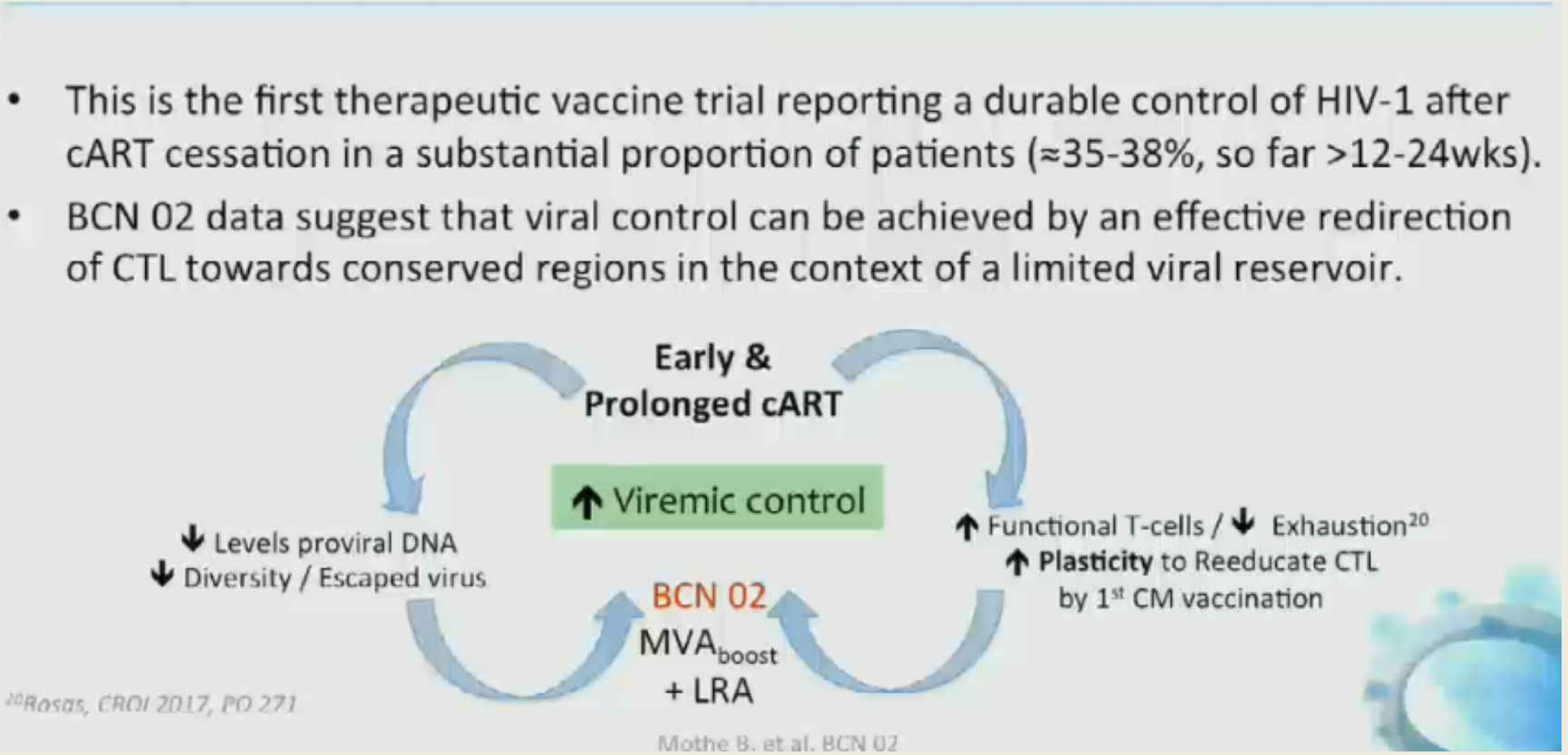
n=13
Feb 15th

- 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

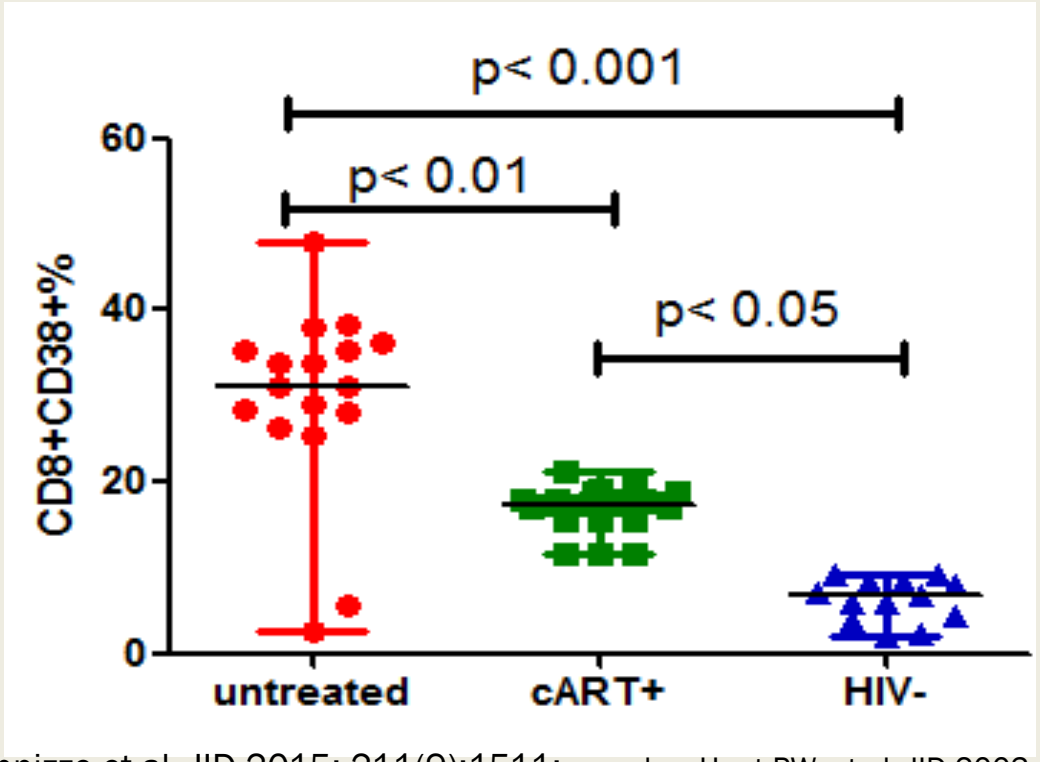
- This is the first therapeutic vaccine trial reporting a durable control of HIV-1 after cART cessation in a substantial proportion of patients (≈35-38%, so far >12-24wks).
- BCN 02 data suggest that viral control can be achieved by an effective redirection of CTL towards conserved regions in the context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

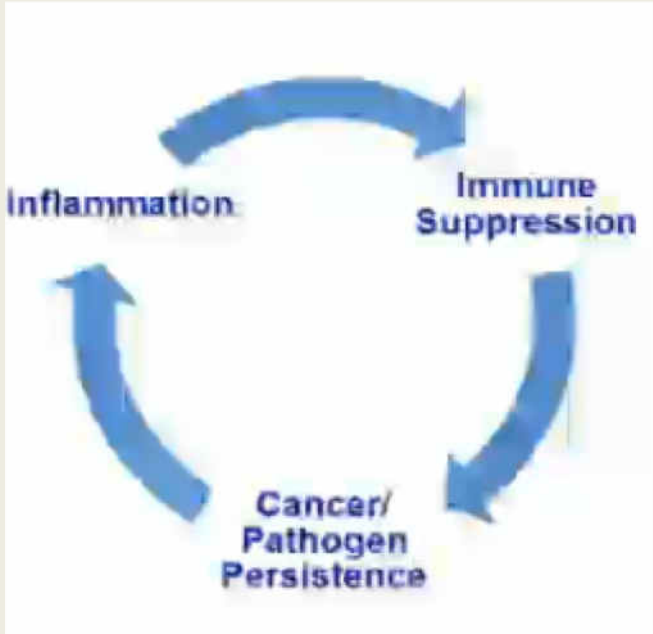


Mothe V #119 LB CROI 2017

Functional cure: what contribution of immune-based therapy?

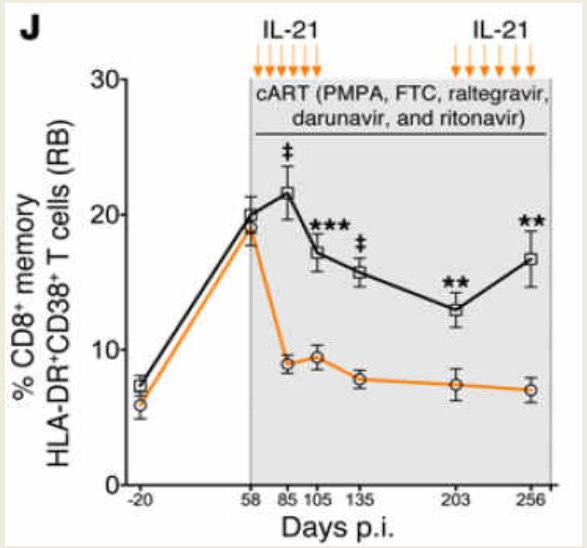
Inflammation/immune activation persists on cART and causes immune dysfunction

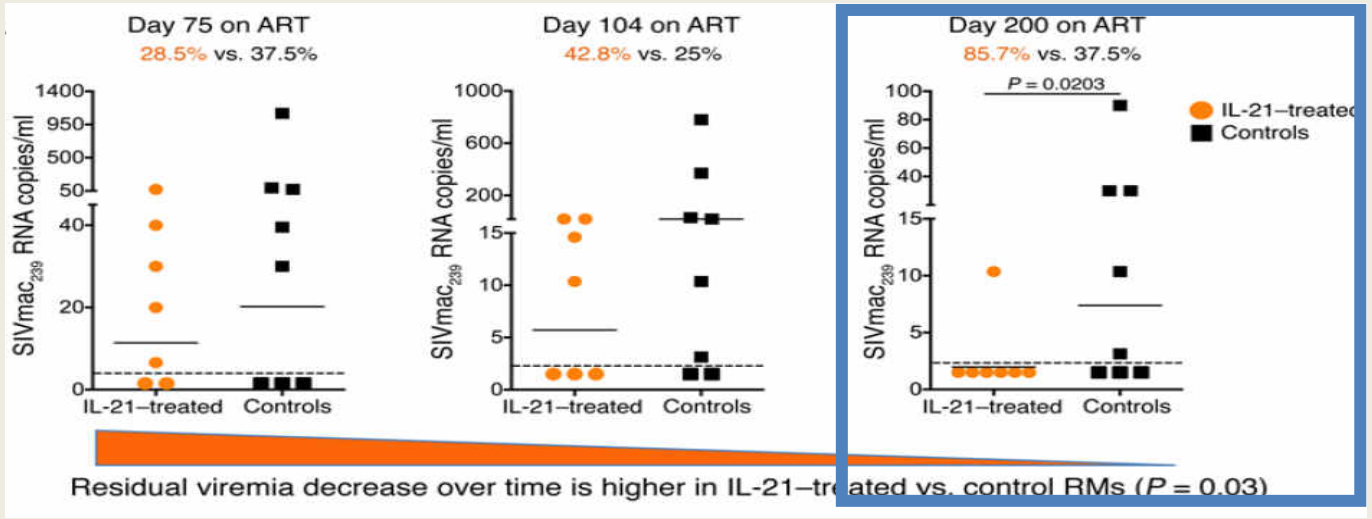




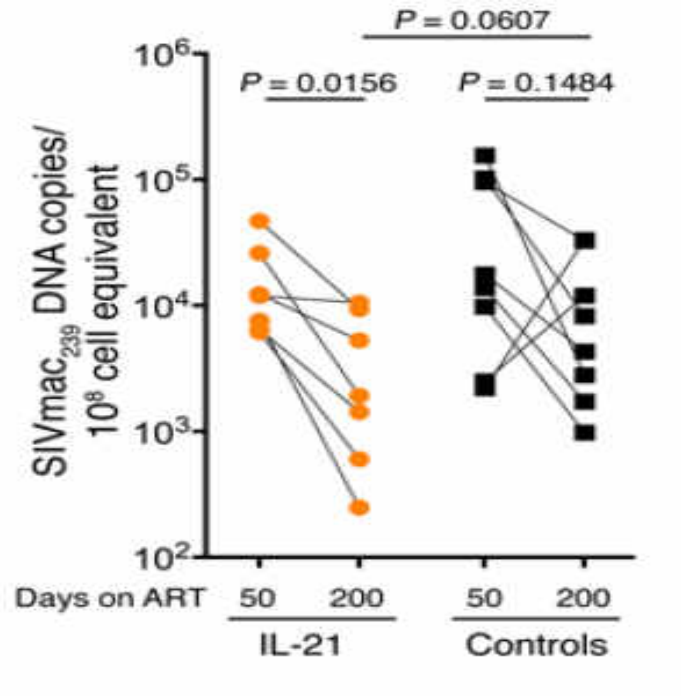
Cannizzo et al. JID 2015; 211(9):1511; see also: Hunt PW, et al. JID 2003

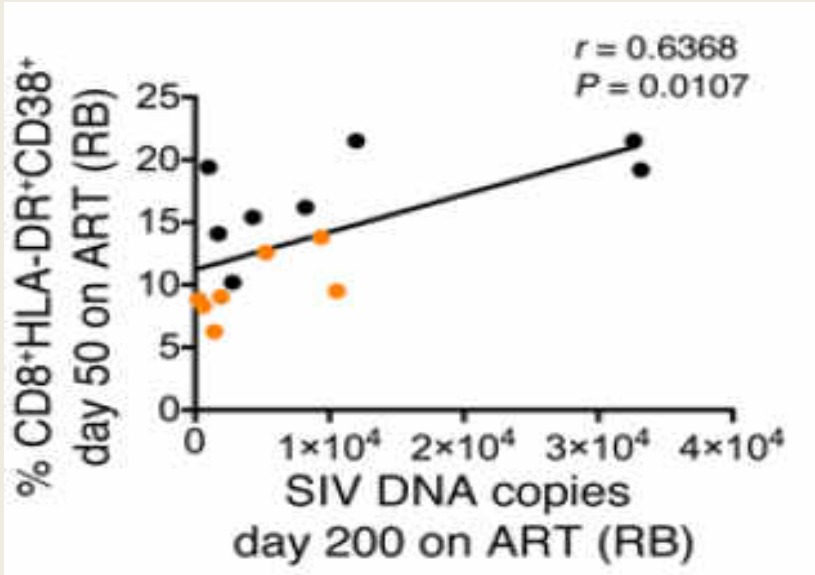
Interventions that reduce inflammation/immune suppression may also be beneficial in containing viral persistence





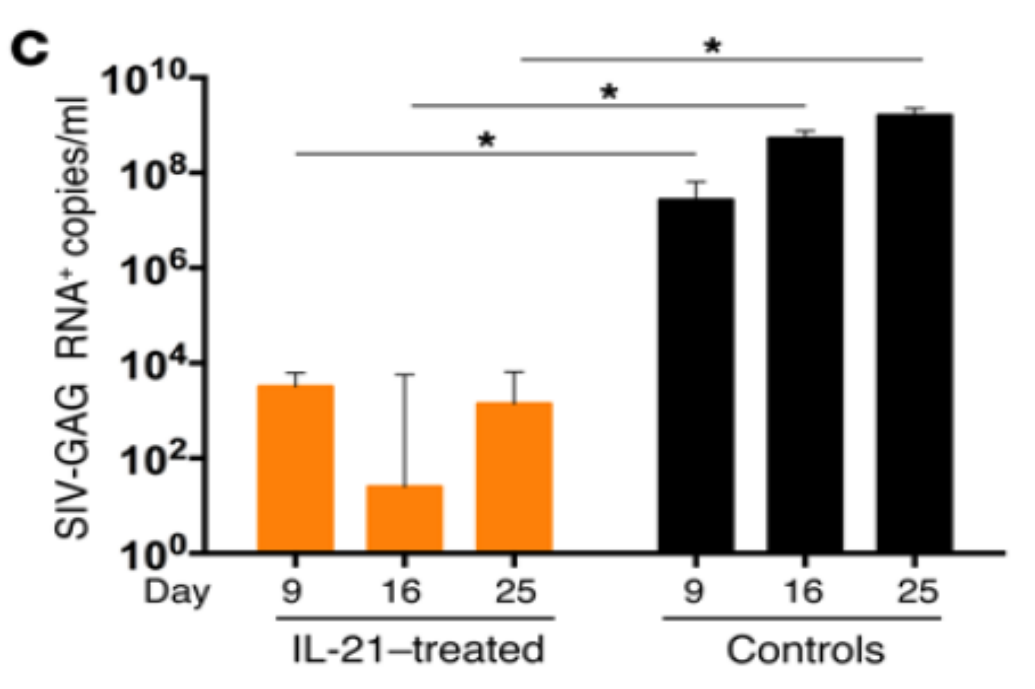
Micci et al. JCI 2015



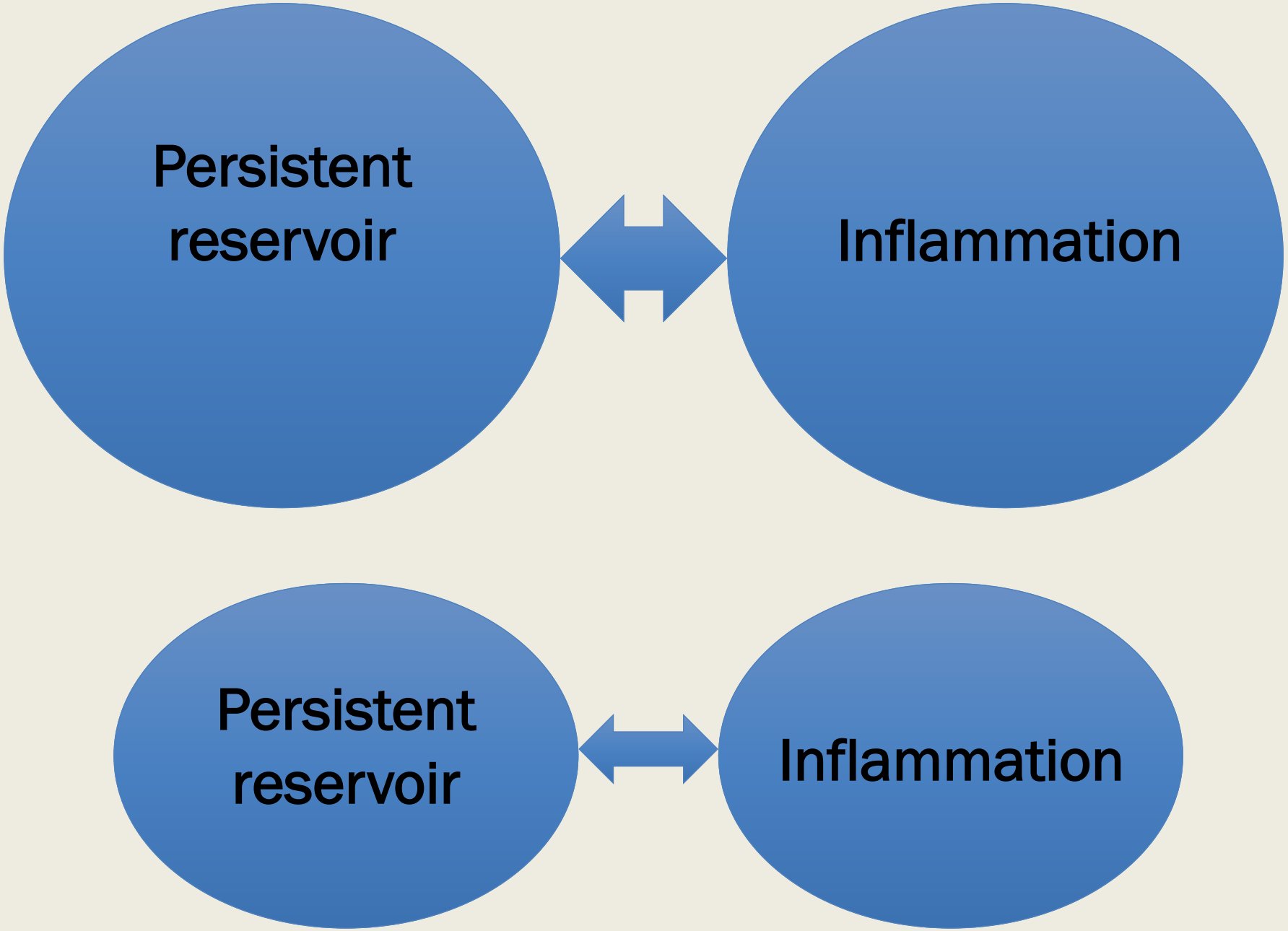


Micci et al. JCI 2015

Reduction in replication-competent virus by Il-21

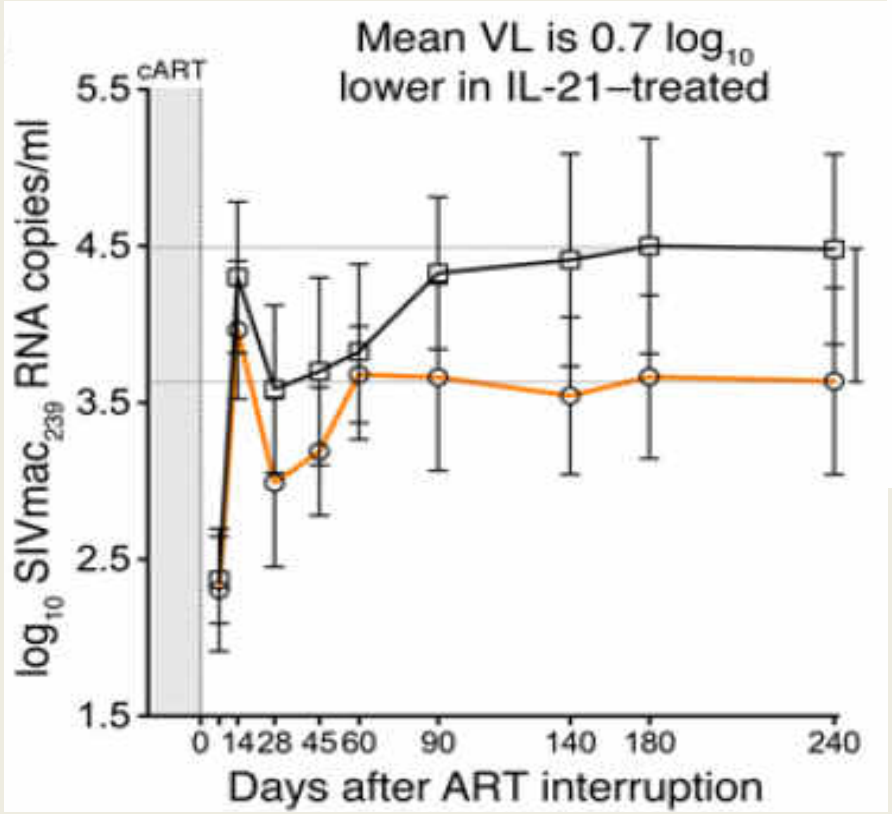


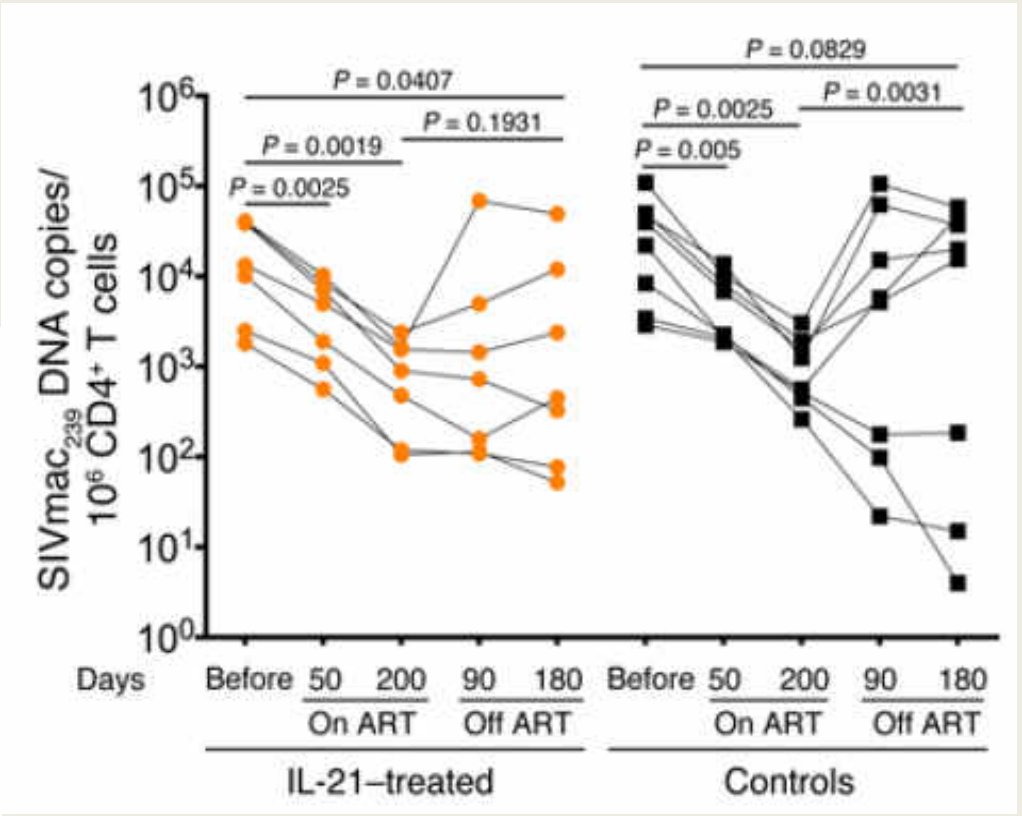
Micci et al. JCI 2015

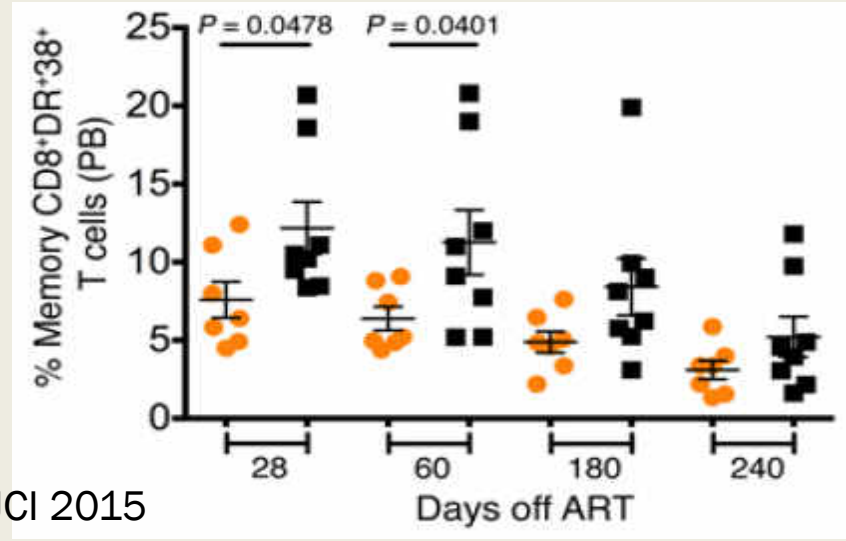

Persistent reservoir
Inflammation
Persistent reservoir
Inflammation

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

However,

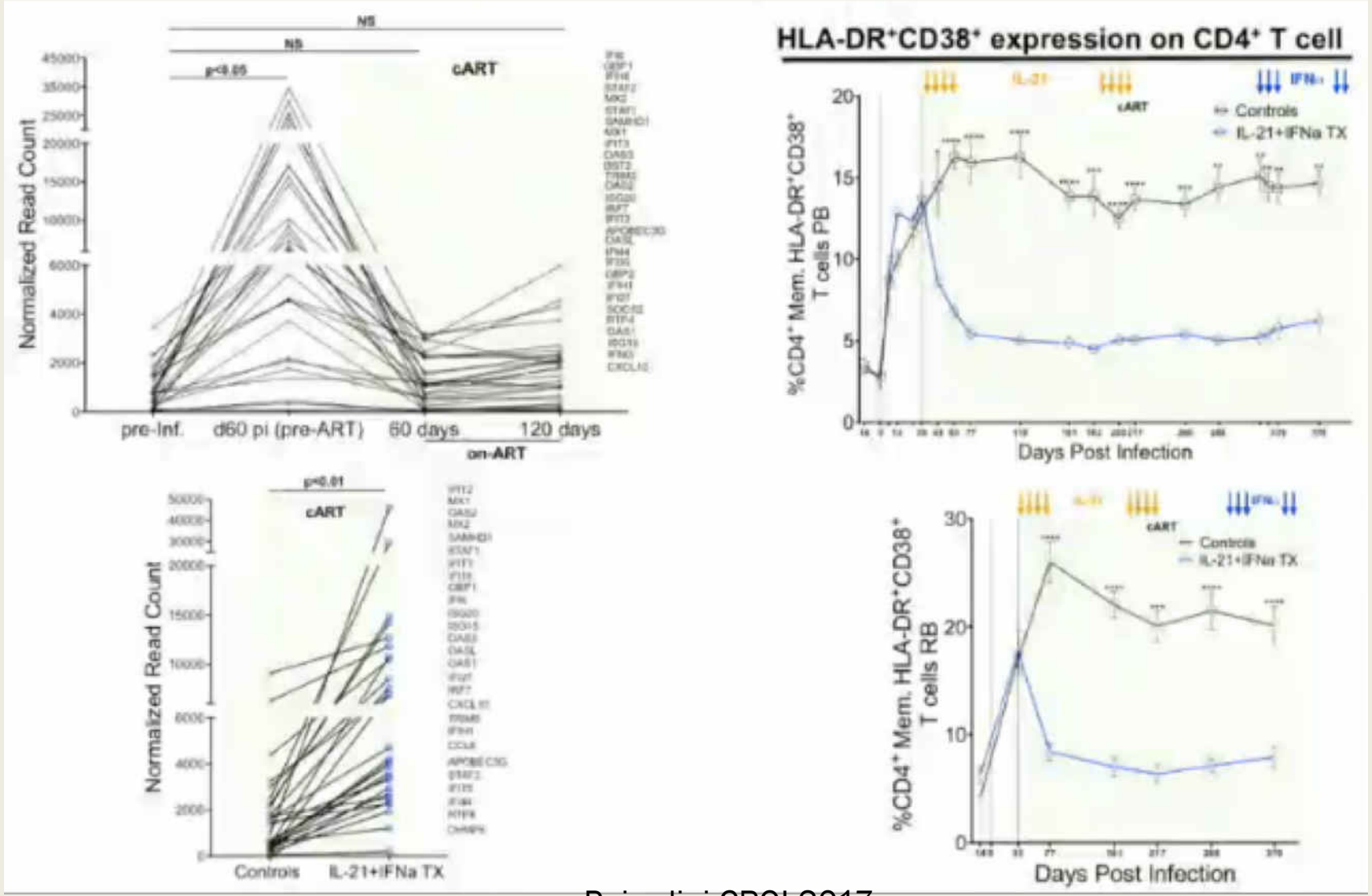




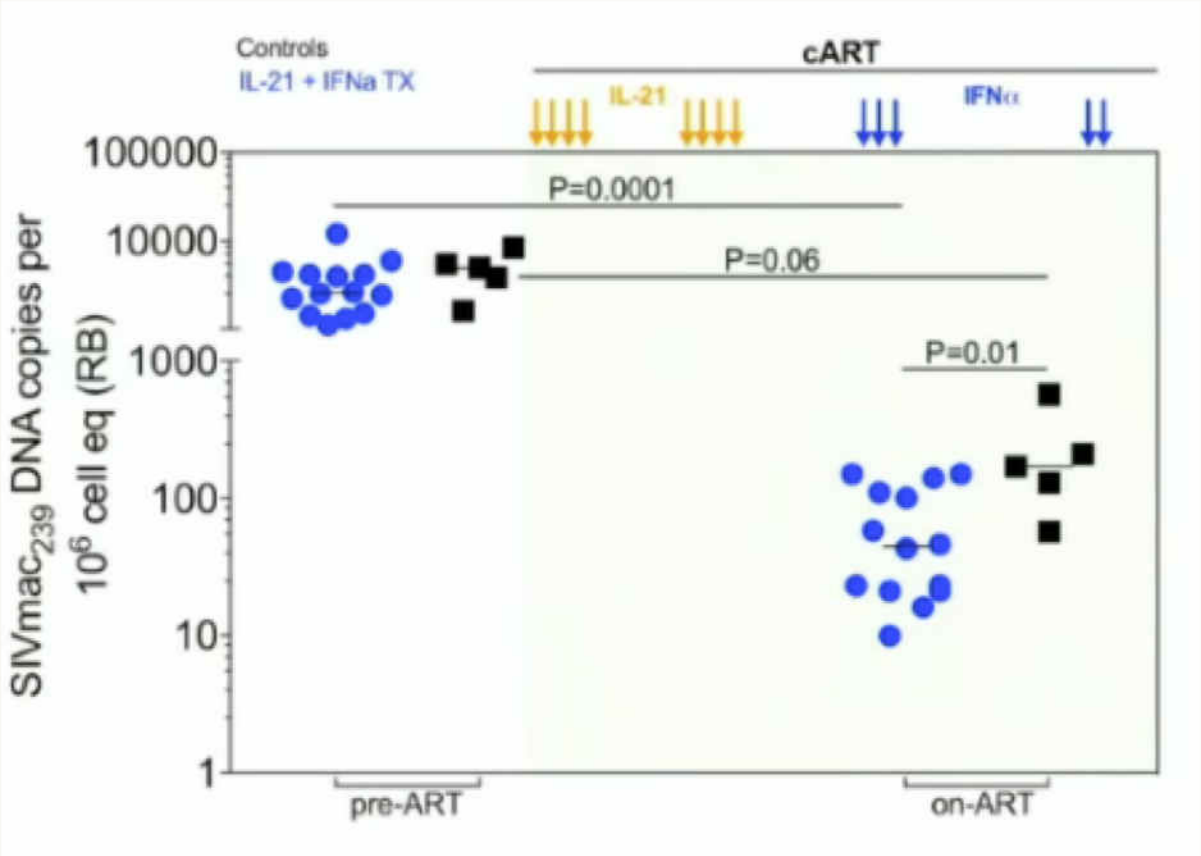


Micci et al. JCI 2015

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

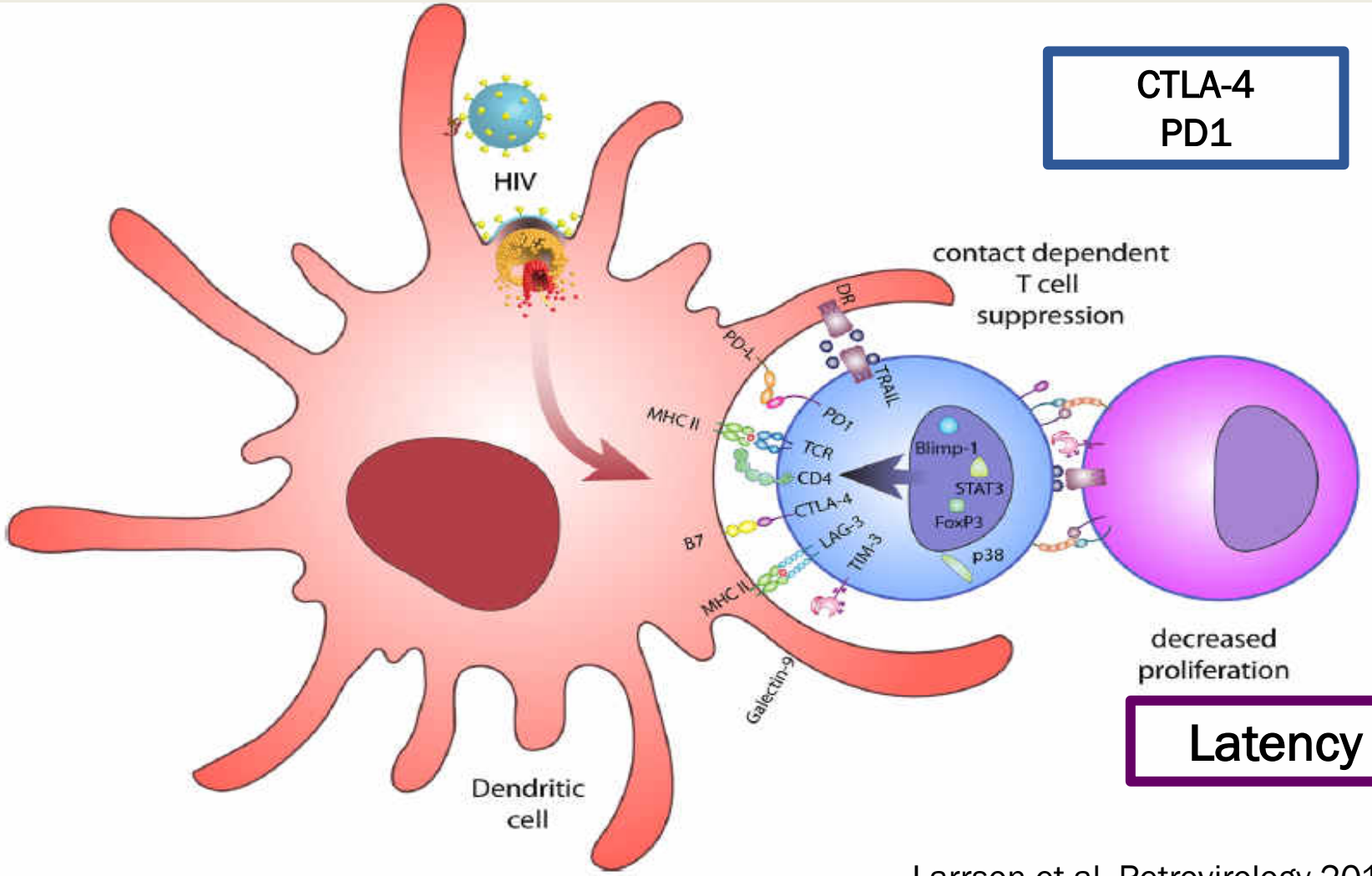


IL-21 + IFN-a reduce gut SIV-DNA



Paiardini CROI 2017

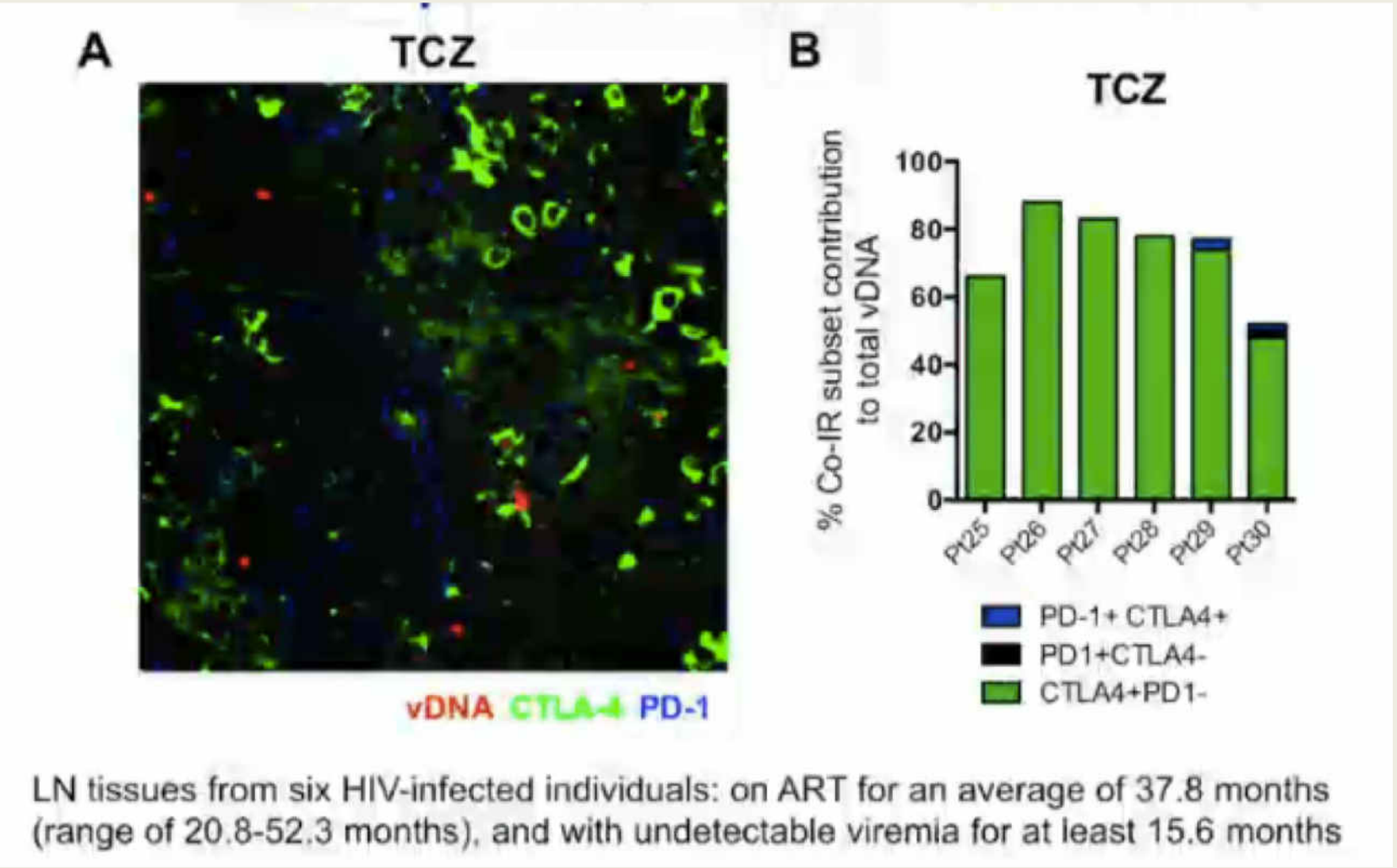
Co-inhibitors receptors and HIV



CTLA-4
PD1

Latency

Larrson et al. Retrovirology 2013

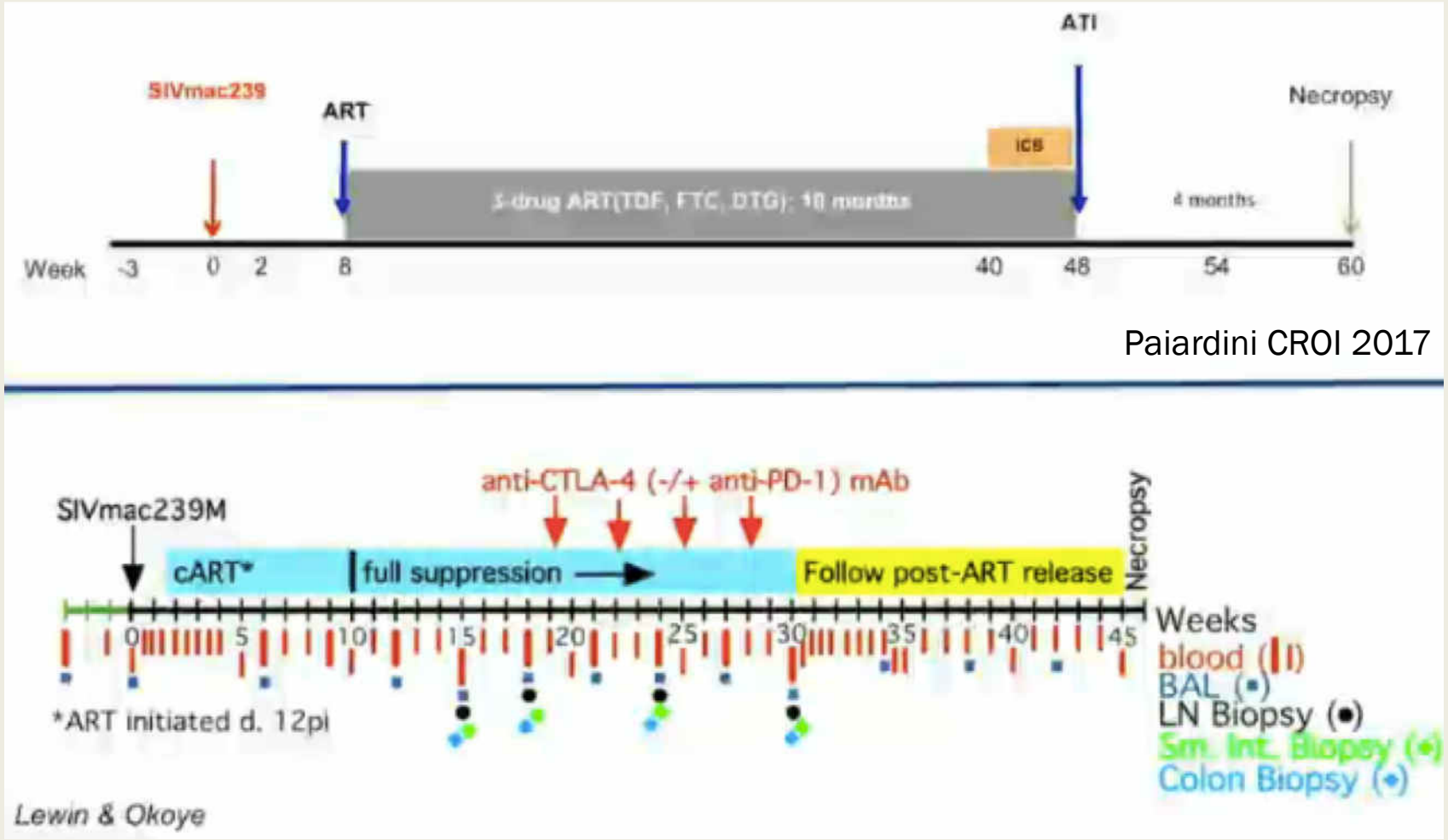


LN tissues from six HIV-infected individuals: on ART for an average of 37.8 months (range of 20.8-52.3 months), and with undetectable viremia for at least 15.6 months

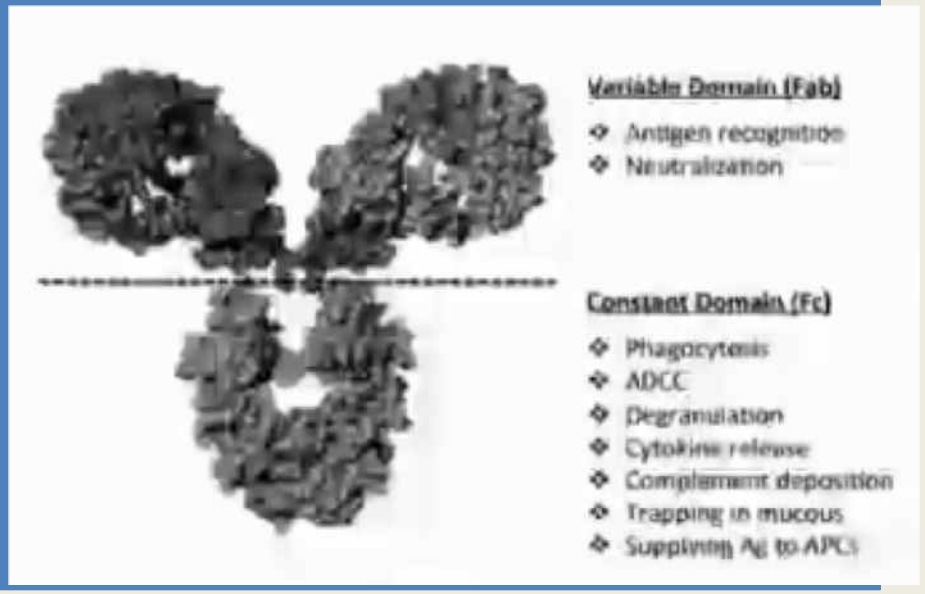
CTLA-4-pos PD-1-neg are Treg critical for viral persistence and should be target of cure strategies

Paiardini CROI 2017

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



Functional cure: what contribution of antibody therapy?



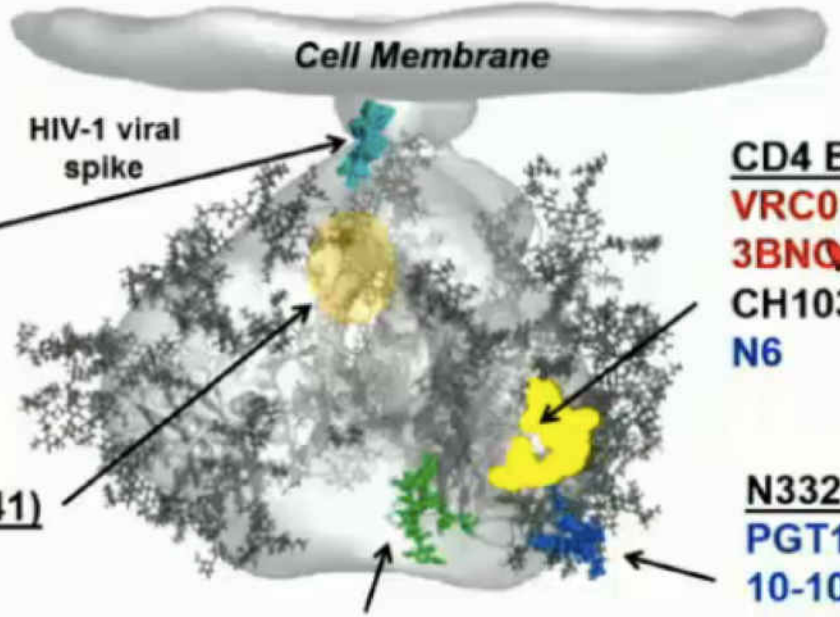
How Abs might be used for treatment?

- **Acute HIV**: with ARV, to rapidly reduce viremia and limit virus dissemination in reservoirs

- **Maintain long-term viral suppression induced by cART** (long half-life of Abs), e.g. Abs+LA-ART every 2-3 months

- **Reduce cell-associated viral reservoir**: Fc-mediated effector functions that targets cell-associated virus

Neutralizing Monoclonal Antibodies
plans for clinical trials



gp41 MPER:
2F5, 4E10
10e8

CD4 Binding Site:
VRC01, PG04, CH31
3BNC117, 12A12
CH103, VRC07-523,
N6

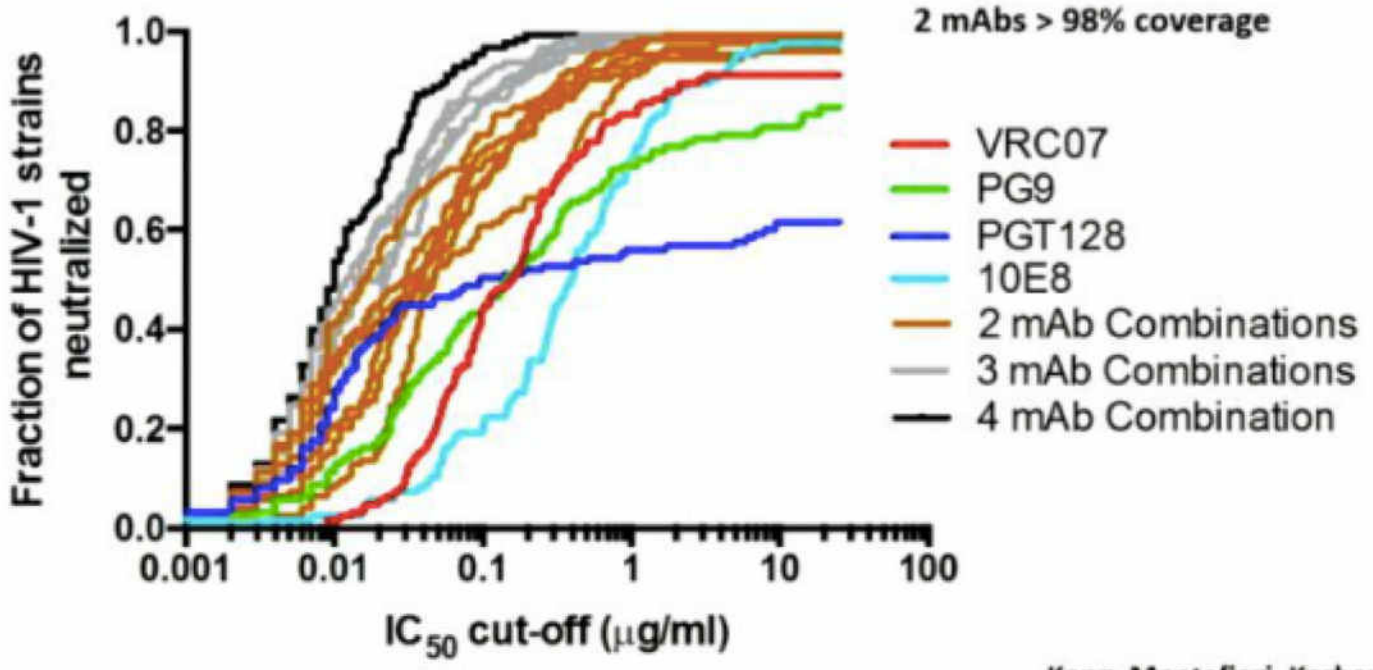
Trimer (gp120/41)
8ANC195
PGT151
35022

N332 Glycan Supersite:
PGT121, PGT128
10-1074

V1V2 Glycan:
PG6, PG16, CH01-04
PGT141-45, PGDM1400
CAP256-VRC26

Cryo-EM of viral spike by Subramaniam group. Fit with atomic level structures from Kwong and Wilson groups

Combined Antibodies:
Improved Potency and Breadth



Kong, Montefiori, Korber et al.
J. Virol (2015)

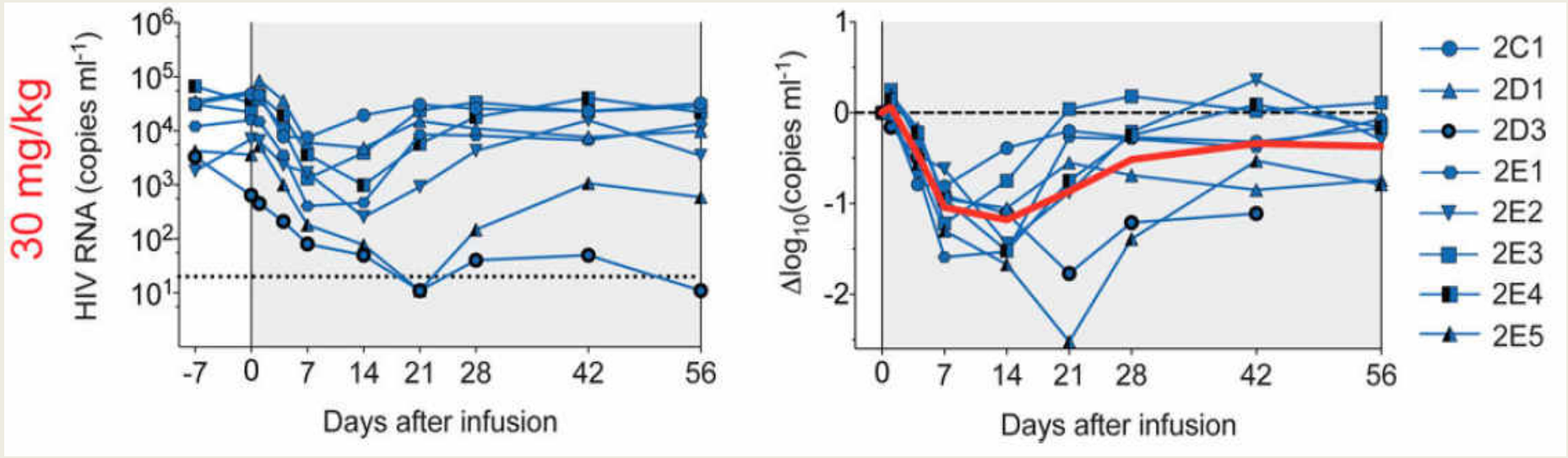
mAb 3BNC117 (CD4bs): phase I

Published in final edited form as:
Nature. 2015 June 25; 522(7557): 487–491. doi:10.1038/nature14411.

3BNC117 a Broadly Neutralizing Antibody Suppresses Viremia in HIV-1-Infected Humans

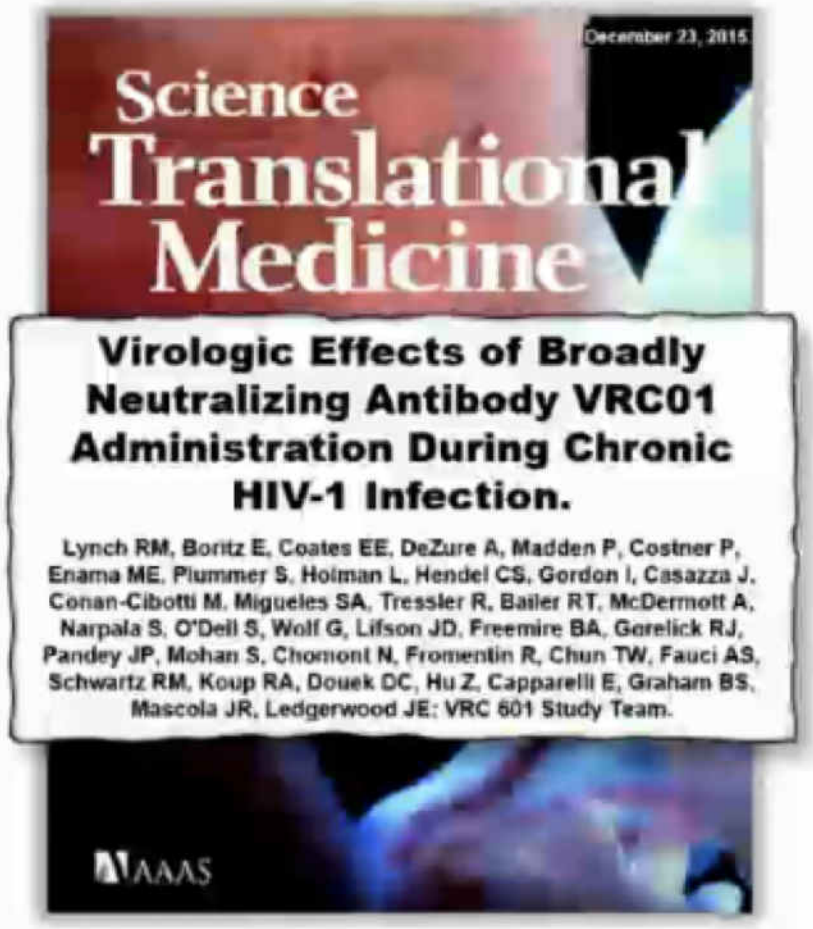
Marina Caskey[1,*], Florian Klein[1,*], Julio C. C. Lorenzi[1], Michael S. Seaman[2], Anthony P. West Jr[3], Noreen Buckley[1], Gisela Kremer[4,5], Lilian Nogueira[1], Malte Braunschweig[1,6], Johannes F. Scheid[1], Joshua A. Horwitz[1], Irina Shimeliovich[1], Sivan Ben Avraham-Shulman[1], Maggi Witmer-Pack[1], Martin Platten[4,7], Clara Lehmann[4,7], Leah A. Burke[1,8], Thomas Hawthorne[9], Robert J. Gorelick[10], Bruce D. Walker[11], Tibor Keler[9], Roy M. Gulick[8], Gerd Fätkenheuer[4,7], Sarah J. Schlesinger[1], and Michel C. Nussenzweig[1,12]

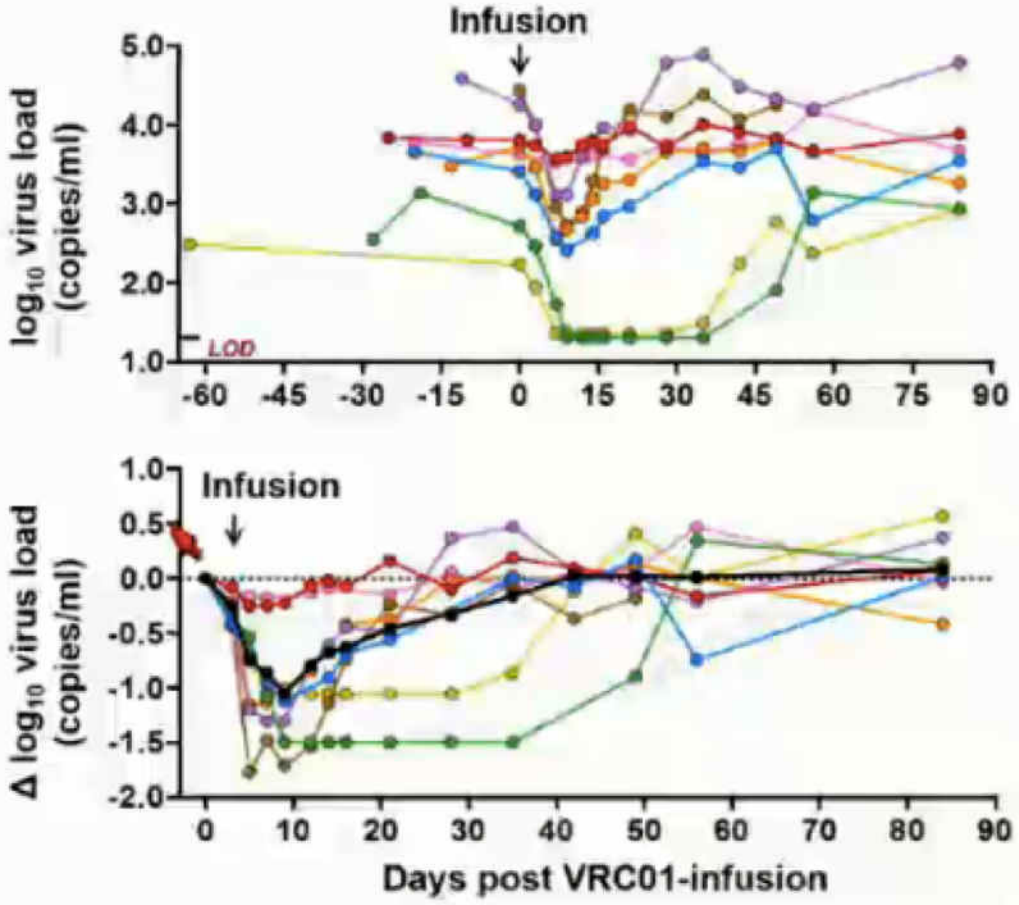
17 HIV+, ARV-naïve 15



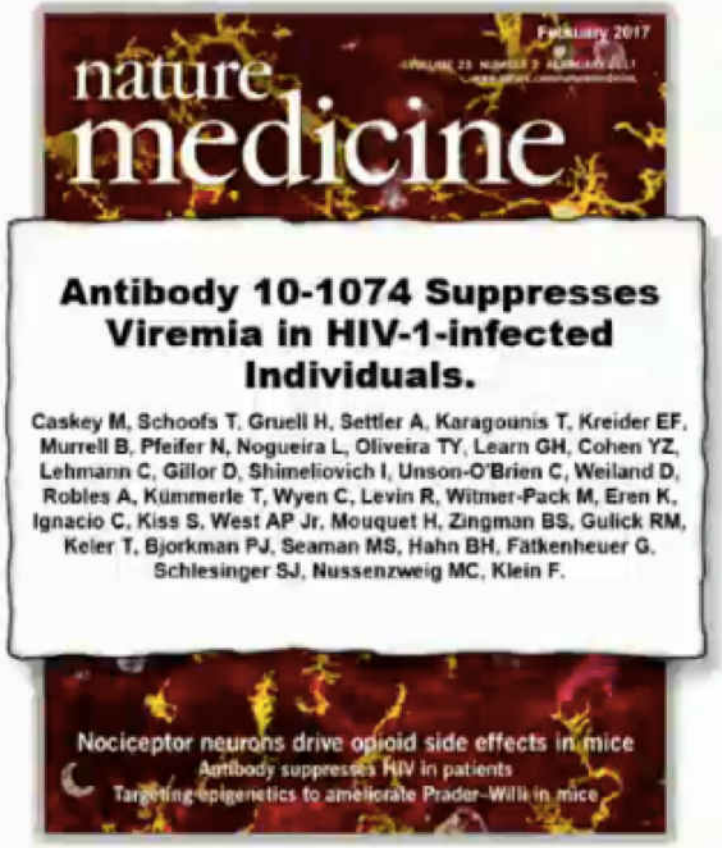
VRC01 Phase I Trial

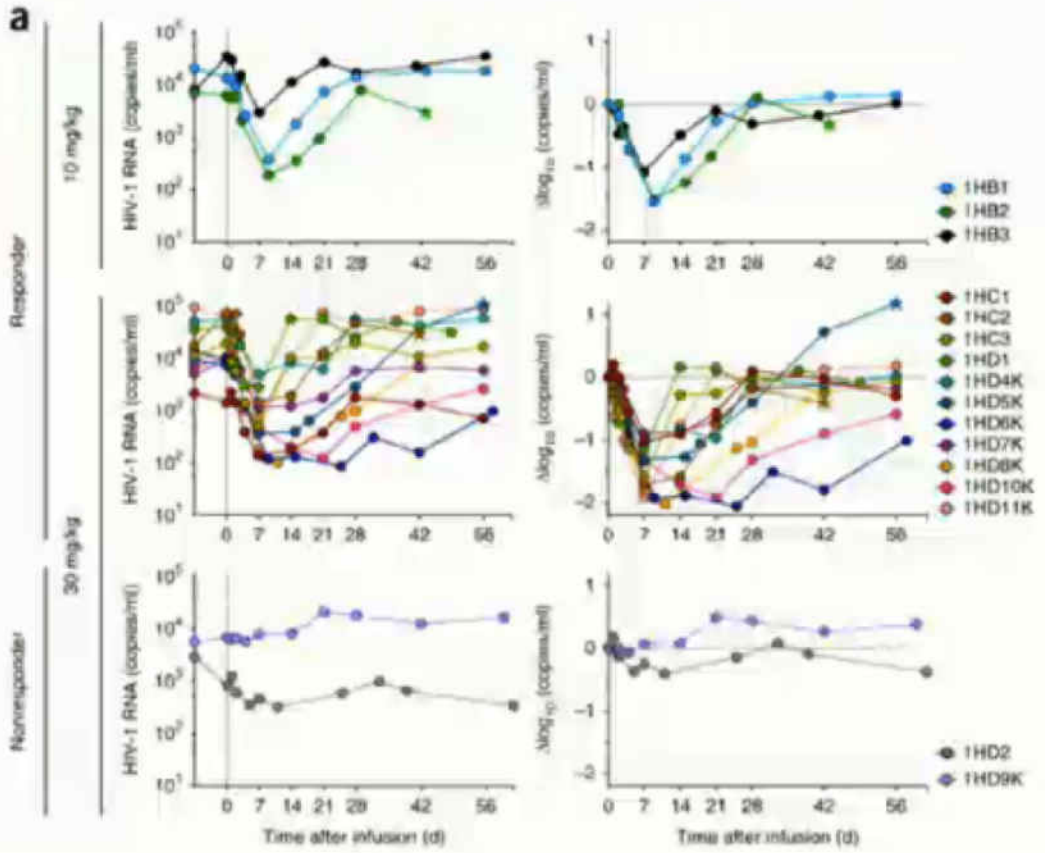
8 HIV-1 infected subjects





mAb 10-1074 (Glycan V3): phase I





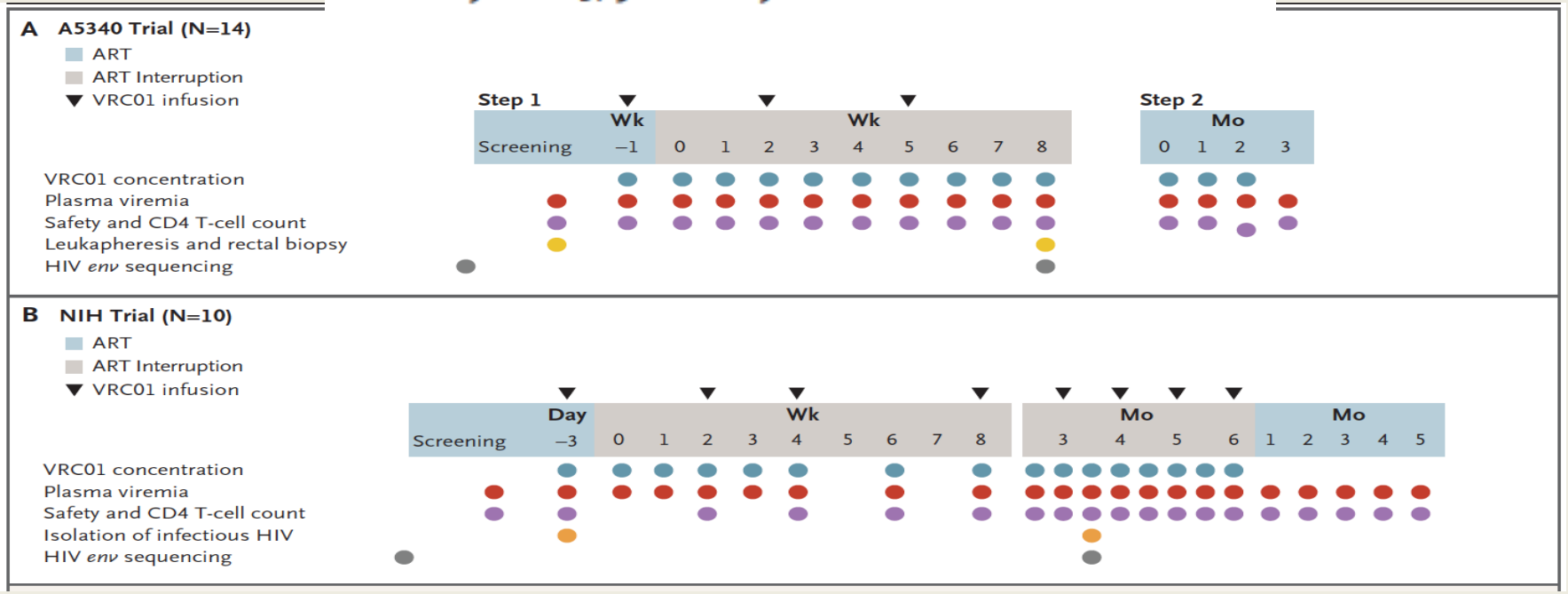
The NEW ENGLAND JOURNAL of MEDICINE

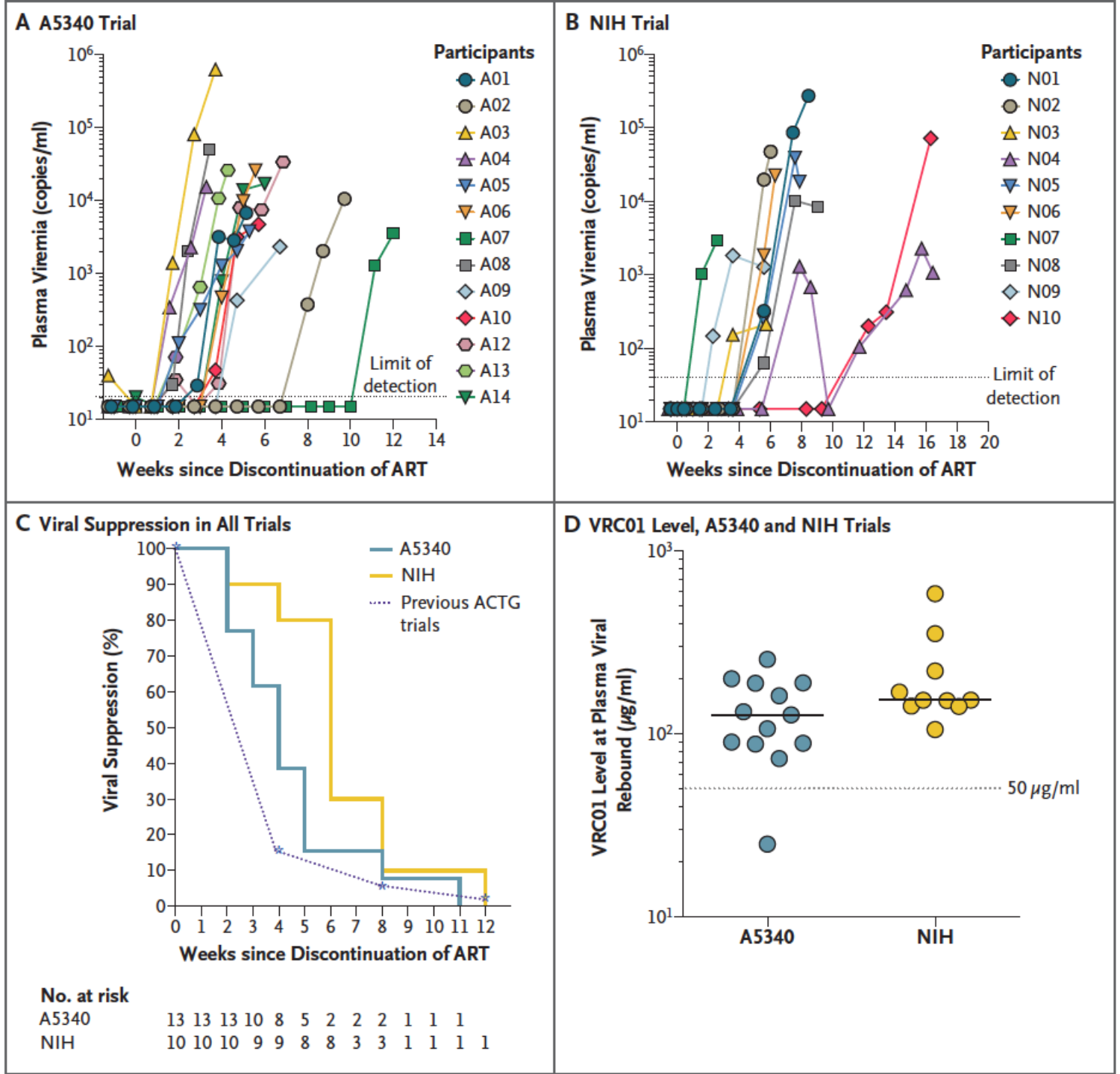
ORIGINAL ARTICLE

Effect of HIV Antibody VRC01 on Viral Rebound after Treatment Interruption

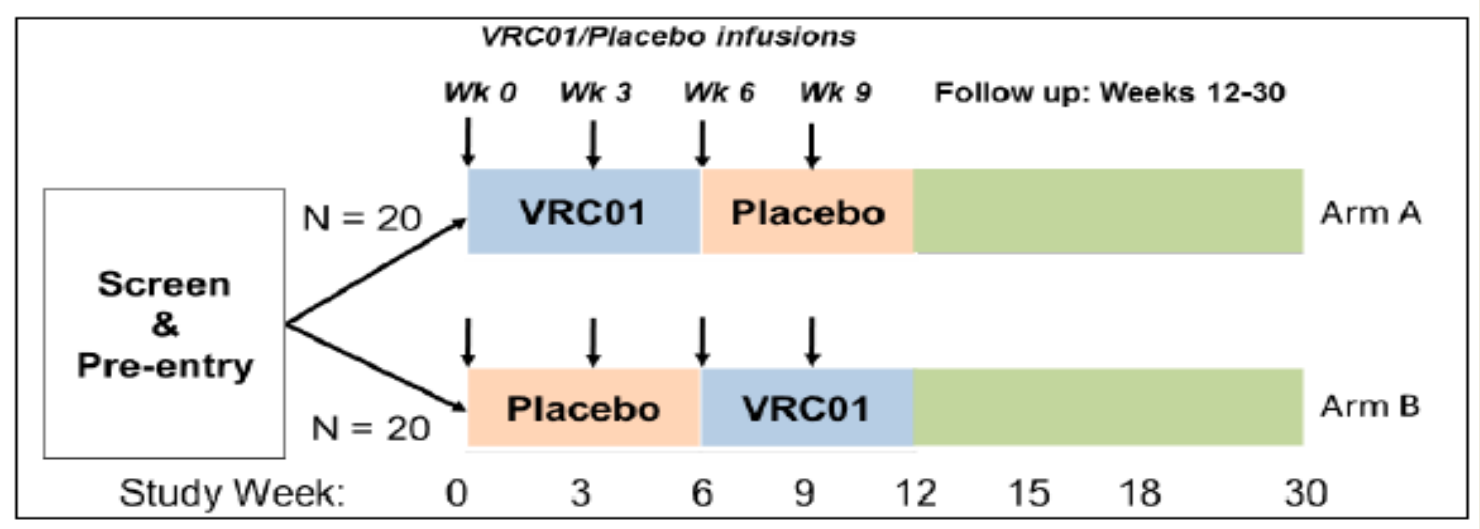
K.J. Bar, M.C. Sneller, L.J. Harrison, J.S. Justement, E.T. Overton, M.E. Petrone, D.B. Salantes, C.A. Seamon, B. Scheinfeld, R.W. Kwan, G.H. Learn, M.A. Proschan, E.F. Kreider, J. Blazkova, M. Bardsley, E.W. Refsland, M. Messer, K.E. Clarridge, N.B. Tustin, P.J. Madden, K.S. Oden, S.J. O'Dell, B. Jarocki, A.R. Shiakolas, R.L. Tressler, N.A. Doria-Rose, R.T. Bailer, J.E. Ledgerwood, E.V. Capparelli, R.M. Lynch, B.S. Graham, S. Moir, R.A. Koup, J.R. Mascola, J.A. Hoxie, A.S. Fauci, P. Tebas, and T.-W. Chun

N ENGL J MED 375;21 NEJM.ORG NOVEMBER 24, 2016

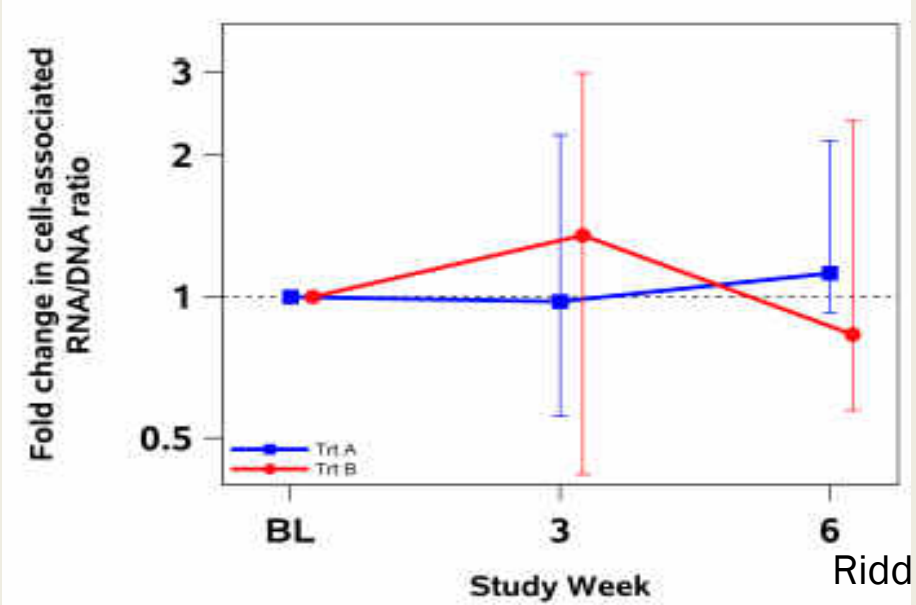



A A5340 Trial
Plasma Viremia (copies/ml)
Participants
A01
A02
A03
A04
A05
A06
A07
A08
A09
A10
A12
A13
A14
Limit of detection
Weeks since Discontinuation of ART
B NIH Trial
Plasma Viremia (copies/ml)
Participants
N01
N02
N03
N04
N05
N06
N07
N08
N09
N10
Limit of detection
Weeks since Discontinuation of ART
C Viral Suppression in All Trials
A5340
NIH
Previous ACTG trials
Viral Suppression (%)
Weeks since Discontinuation of ART
No. at risk
A5340 13 13 13 10 8 5 2 2 2 1 1 1
NIH 10 10 10 9 9 8 8 3 3 1 1 1 1
D VRC01 Level, A5340 and NIH Trials
VRC01 Level at Plasma Viral Rebound (μg/ml)
50 μg/ml
A5340
NIH

VRC01: no effect on viral persistence on virally-suppressed patients



40 HIV+ on virally-suppressive cART



Riddler S LB 330 CROI 2017

- In individuals with chronic ART-suppressed HIV infection, VRC01 infusions were safe and well tolerated.
- Two high-dose infusions of VRC01 did not affect virologic outcomes including:
  - Residual plasma viremia
  - Cell-associated HIV RNA/DNA levels
  - Total stimulated virus production from CD4+T-cells.
- Potential mechanisms being evaluated to explain the lack of response include viral resistance to VRC01, poor penetration of VRC01 to sites of virus expression, or inherent inability of VRC01 to clear virus particles or virus-expressing cells.

Functional cure: what contribution of stem cell transplantation?

Timothy Ray Brown, shown in May 2011 with his dog Jack in San Francisco, is the only man ever known to have been fully cured from AIDS. Brown is known as the "Berlin patient" because he had a bone marrow transplant in a German hospital five years ago.

July 2012, npr.org

BRIEF REPORT

Long-Term Control of HIV by *CCR5* Delta32/Delta32 Stem-Cell Transplantation

Gero Hütter, M.D., Daniel Nowak, M.D., Maximilian Mossner, B.S., Susanne Ganepola, M.D., Arne Müßig, M.D., Kristina Allers, Ph.D., Thomas Schneider, M.D., Ph.D., Jörg Hofmann, Ph.D., Claudia Kücherer, M.D., Olga Blau, M.D., Igor W. Blau, M.D., Wolf K. Hofmann, M.D., and Eckhard Thiel, M.D.

SUMMARY

Infection with the human immunodeficiency virus type 1 (HIV-1) requires the presence of a CD4 receptor and a chemokine receptor, principally chemokine receptor 5 (CCR5). Homozygosity for a 32-bp deletion in the *CCR5* allele provides resistance against HIV-1 acquisition. We transplanted stem cells from a donor who was homozygous for *CCR5* delta32 in a patient with acute myeloid leukemia and HIV-1 infection. The patient remained without viral rebound 20 months after transplantation and discontinuation of antiretroviral therapy. This outcome demonstrates the critical role *CCR5* plays in maintaining HIV-1 infection.

N Engl J Med 2009;360:692-8.

The “Boston” patients: the story

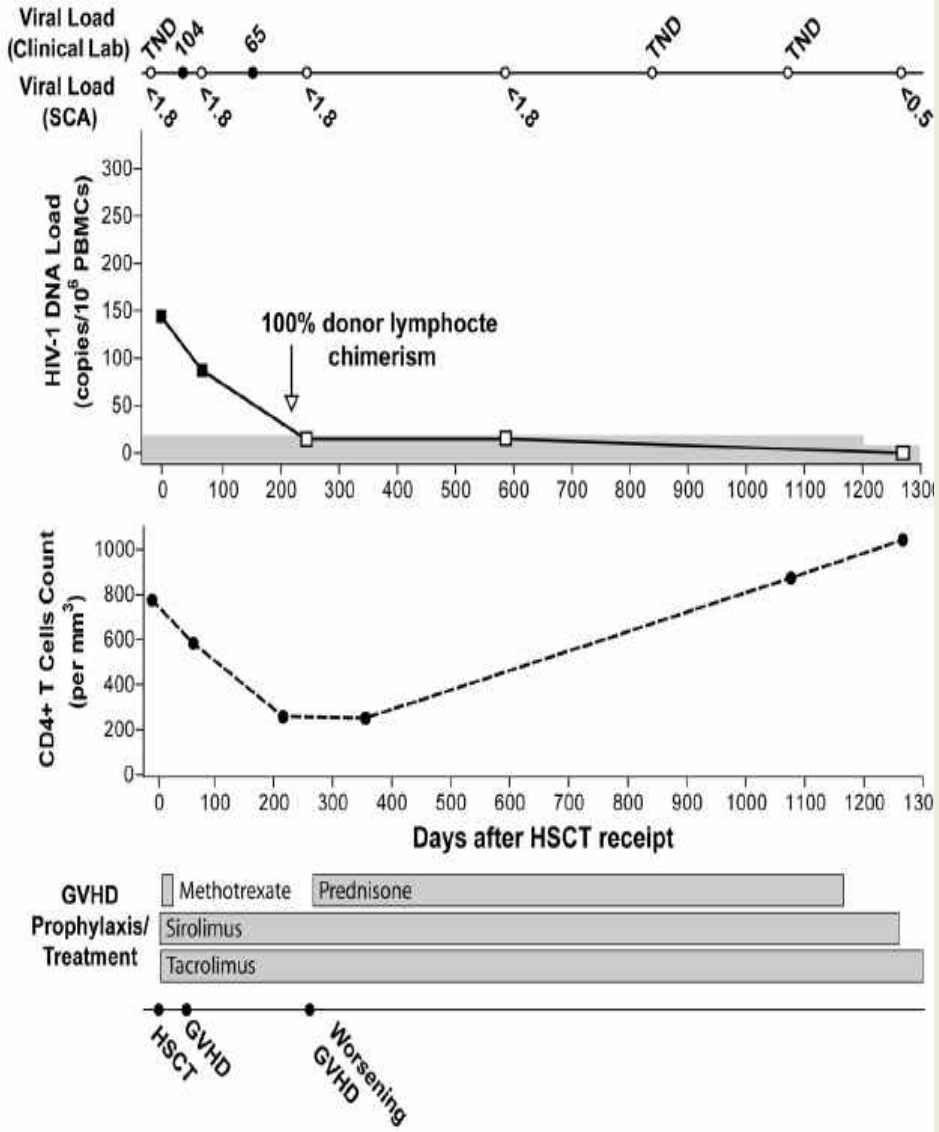
Long-Term Reduction in Peripheral Blood HIV Type 1 Reservoirs Following Reduced-Intensity Conditioning Allogeneic Stem Cell Transplantation

Timothy J. Henrich,[1,2] Zixin Hu,[1,2] Jonathan Z. Li,[1,2] Gaia Sciaranghella,[3,a] Michael P. Busch,[6,7] Sheila M. Keating,[6,7] Sebastien Gallien,[1,8] Nina H. Lin,[2,4] Francoise F. Giguel,[4] Laura Lavoie,[4] Vincent T. Ho,[2,5] Philippe Armand,[2,5] Robert J. Soiffer,[2,5] Manish Sagar,[1,2,a] Ann S. LaCasce,[2,5] and Daniel R. Kuritzkes[1,2]

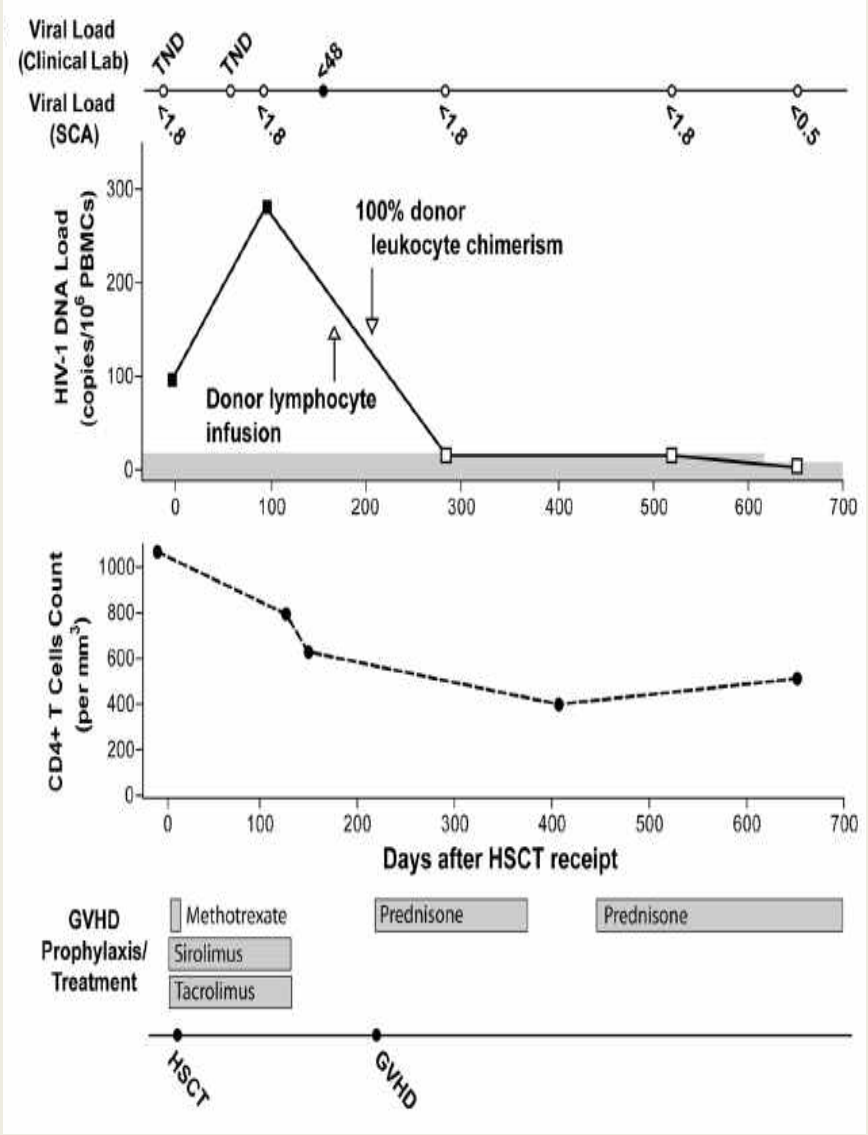
The Journal of Infectious Diseases 2013;207:1694–702

- Effects of a reduced-intensity conditioning allogeneic HSCT from donors with wildtype–CCR5+ cells on HIV-1 peripheral blood reservoirs in 2 patients heterozygous for the ccr5Δ32 mutation

A: Male with perinatal HIV on TDF/FTC/EFV (recurrent Hodgkin lymphoma)



B: Male with sexually-acquired HIV on ART since 2003 (NHL+HL)



The “Boston” blues

- Analytical Treatment Interruption (ATI) to determine full impact of allogeneic HSCT on HIV persistence (restart HAART if VL >1000cp/ml or confirmed >200cp/ml)

- Viral rebound occurred despite a reduction in HIV reservoir (PBMC DNA) of at least 3log10; rebound plasma viremia was mono/oligophyletic

- Rebound in the context of an HIV-naive (donor) immune system resembled acute infection
  - *Moderately severe symptoms including CNS*
  - *Rapid kinetics of viral replication*

Henrich et al. Ann Intern Med 2014

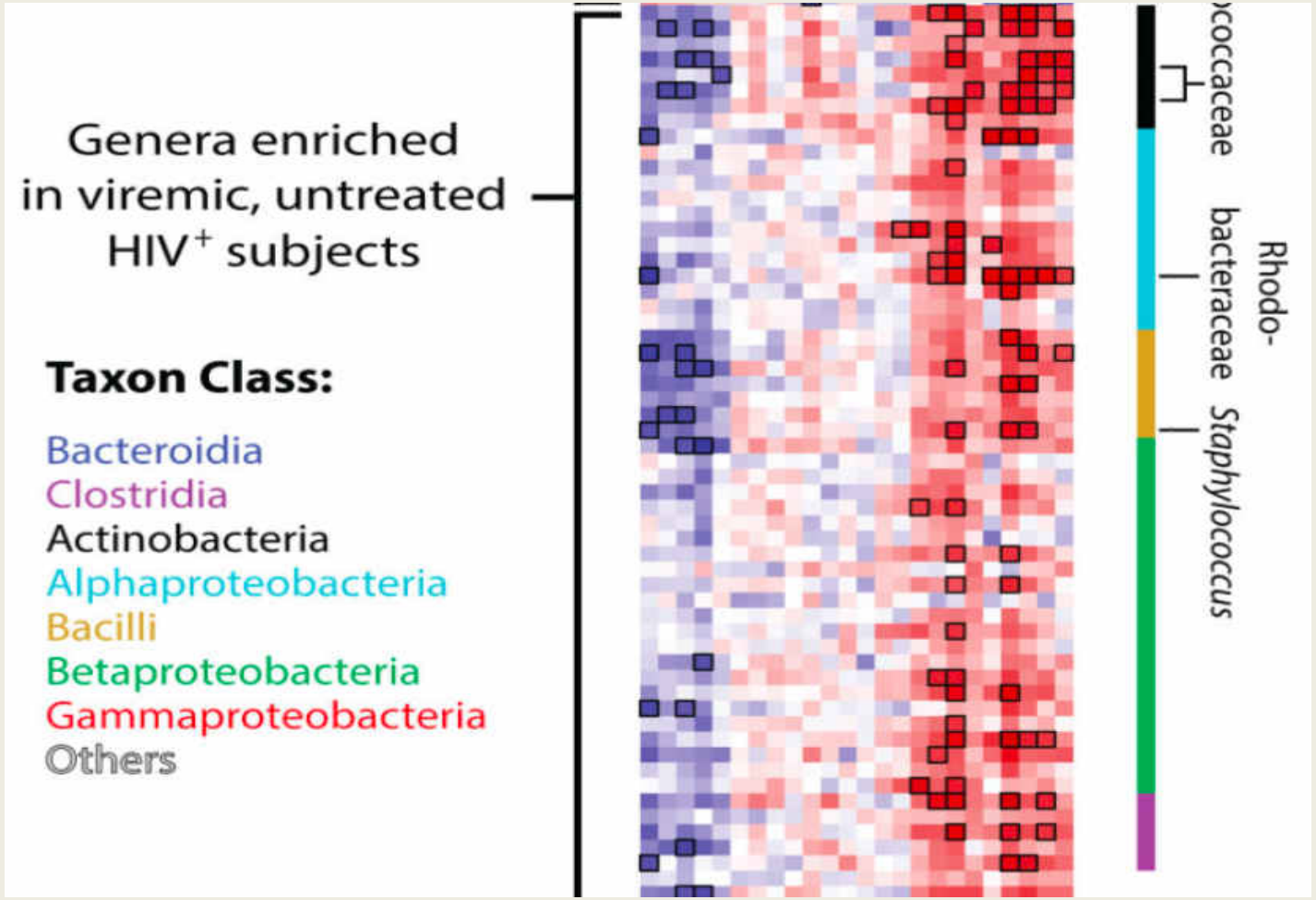
Graft versus host effect may not be powerful enough to clear all sanctuaries

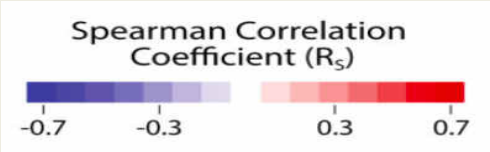
Targeting the microbiome for HIV cure?

Altered gut microbioma in HIV is associated to increased immune activation

Gut-barrier- enhancing cytokine secretion (IL-17, IL-22)

T-cell activation in blood and GALT, serum inflammatory markers





Vujkovic-Cvijin et al., Sci Transl Med, 2013; Also: Ellis et al. JAIDS 2011, Dillon et al., Mucosal Immunol, 2014

Vujkovic-Cvijin et al., Sci Transl Med, 2013

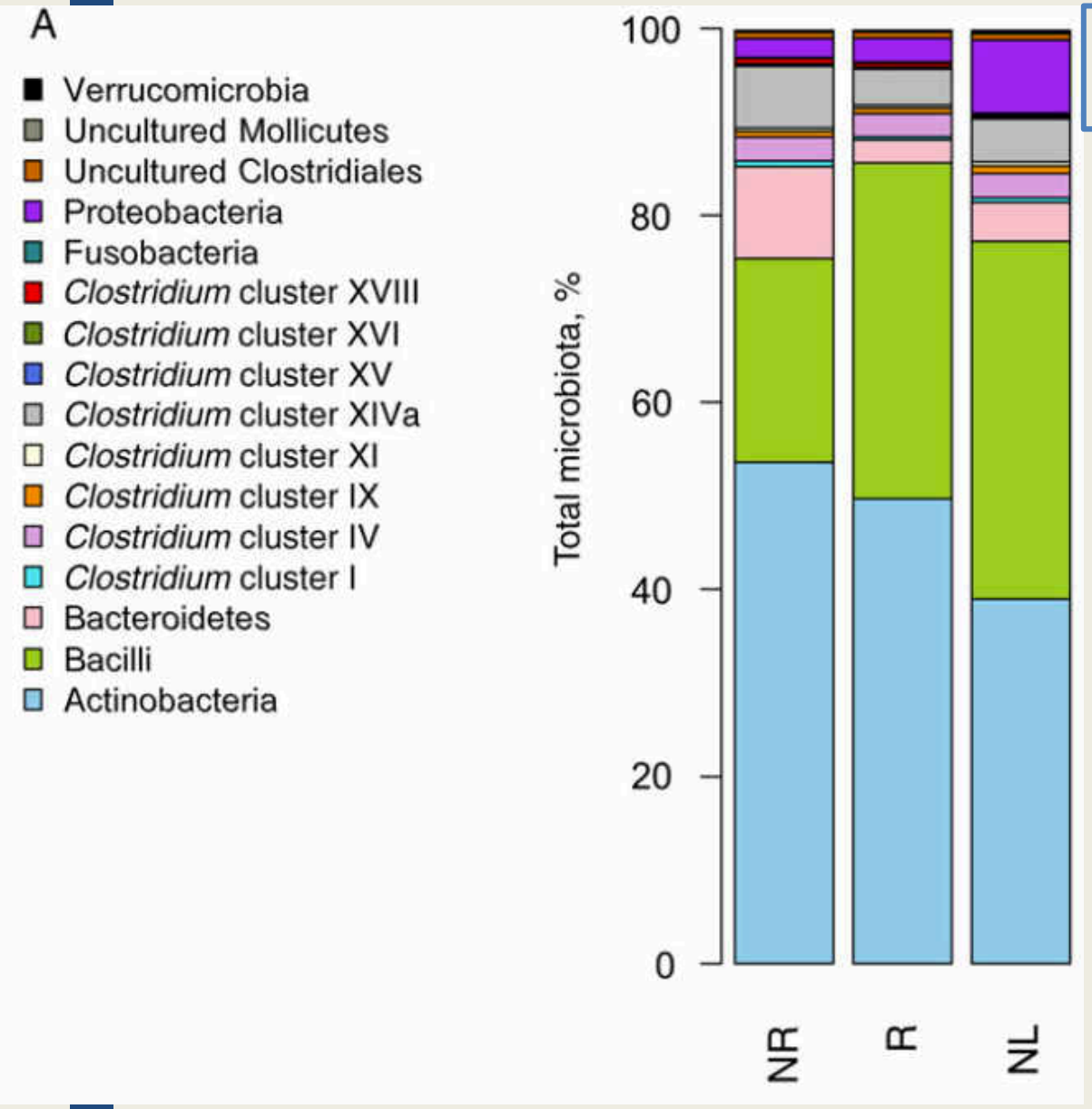
“More physiologic” microbiome in exposed uninfected infants and ECs

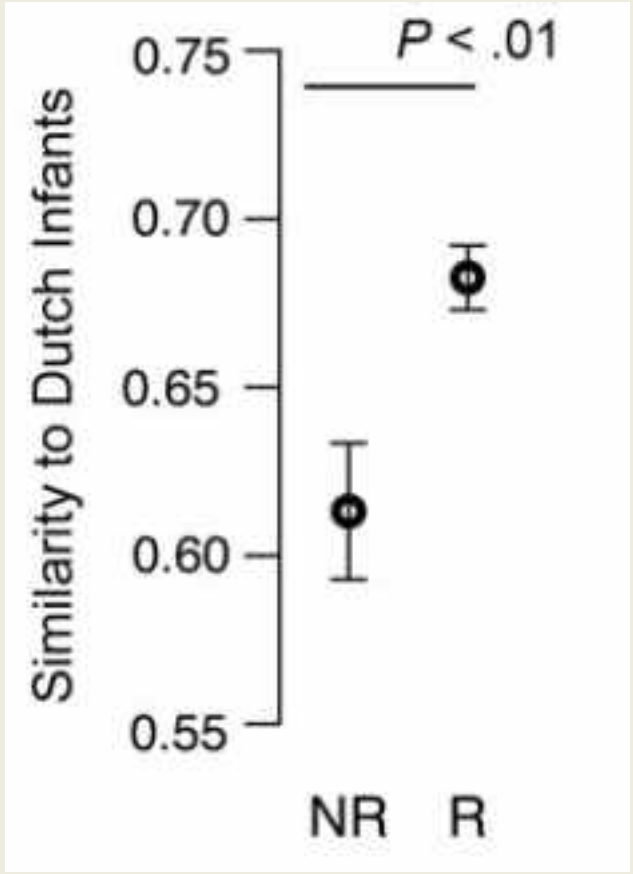
	Year	Location	Sample size	Population of interest	Comparison group	Enriched	Depleted	Summary
HEU infants								
Bender *et al.* [44▪▪]	2016	Haiti	25 HEU; 25 HUU	HEU infants	HUU infants	Pseudomonadaceae Oxalobacterae Rhodobacteraceae Thermaceae Bacillaceae Corynebacteriaceae Chloroacidobacteria Alicyclobacilaceae Sphingomonadaceae Enterobacteriaceae	Prevotellaceae Alcaligenaceae Desulfovibrionaceae Tissierellaceae Bacteroidiaceae Paraprevotellaceae Porphyromonadaceae Campylobacteraceae Erysipelotrichaceae Gemellaceae Bacilli (class)	Maternal HIV infection is associated with changes in the microbiome of HEU infants. Human breast milk oligosaccharides differ in mothers depending on their HIV status, and is associated with bacterial species found in the infant’s gut microbiome.
Elite controllers								
Vesterbacka *et al.* [43▪▪]	2017	Sweden	16 EC, 32 HIV-infected (HIV+) ART-naïve, 16 HIV-uninfected (HIV-)	EC adults	HIV+ ART naïve, HIV-	EC compared to ART naïve and HIV-: *Succinivibrio* *Sutterella* EC compared to ART naïve: *Rhizobium* *Delftia* *Anaerofilum* *Oscillospira*	EC compared to ART naïve: *Blautia* *Anaerostipes*	ECs have a richer gut microbiota than untreated HIV adults, and their microbiome is more similar to HIV-uninfected adults than untreated HIV adults.
Nowak *et al.* [45]	2015	Sweden	28 HIV+, 3 EC, 9 HIV-	EC adults	HIV+, HIV-	EC compared to HIV+ Bacteroidetes[45]	EC compared to HIV+ Actinobacteria	The microbiome of ECs is significantly different from viremic

Wei Li et al. Curr Opin HIV AIDS 2018

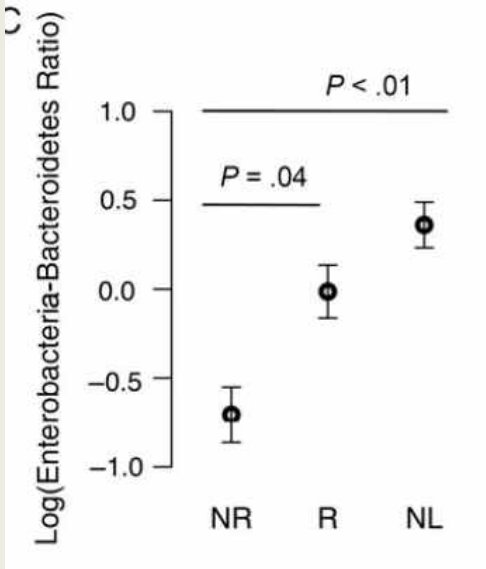
Impact of gut microbiome on response to Rotavirus vaccination

78, 6-week old Ghanaian receiving Rotavirus vaccine: 39/78 R
154 Dutch age-matched, all R

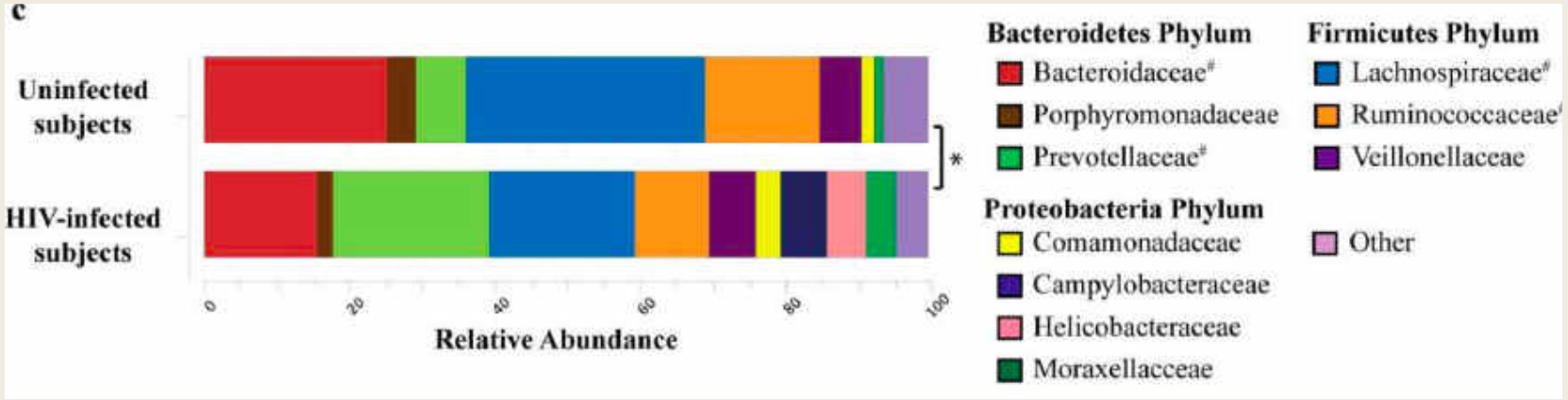




Harris et al. JID 2017

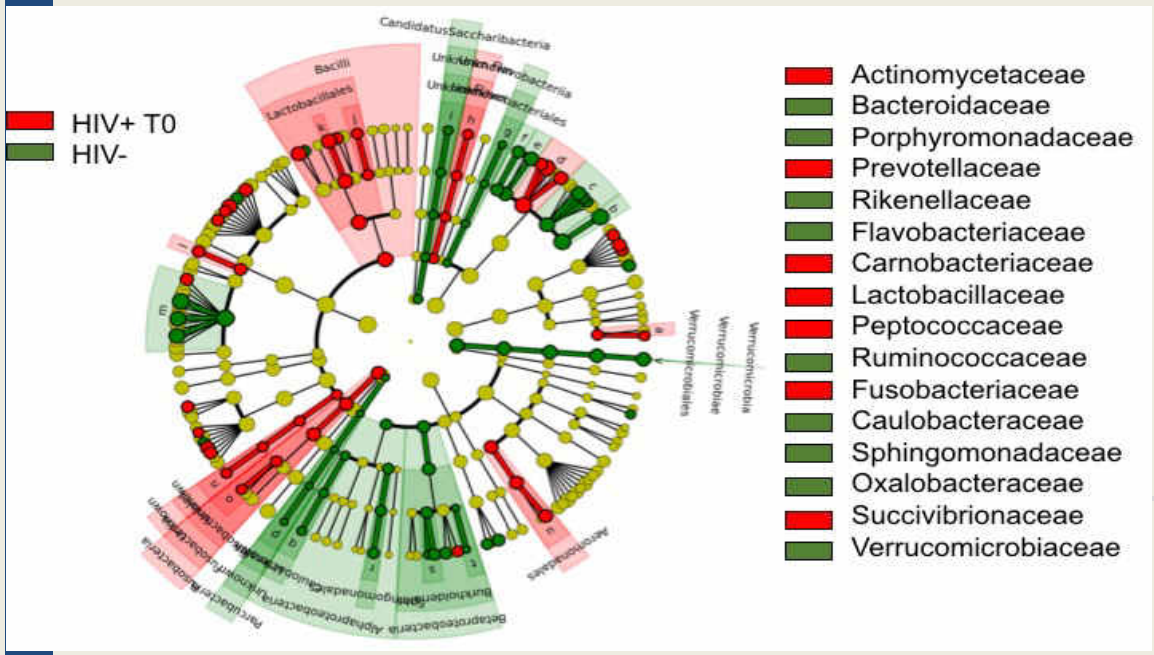


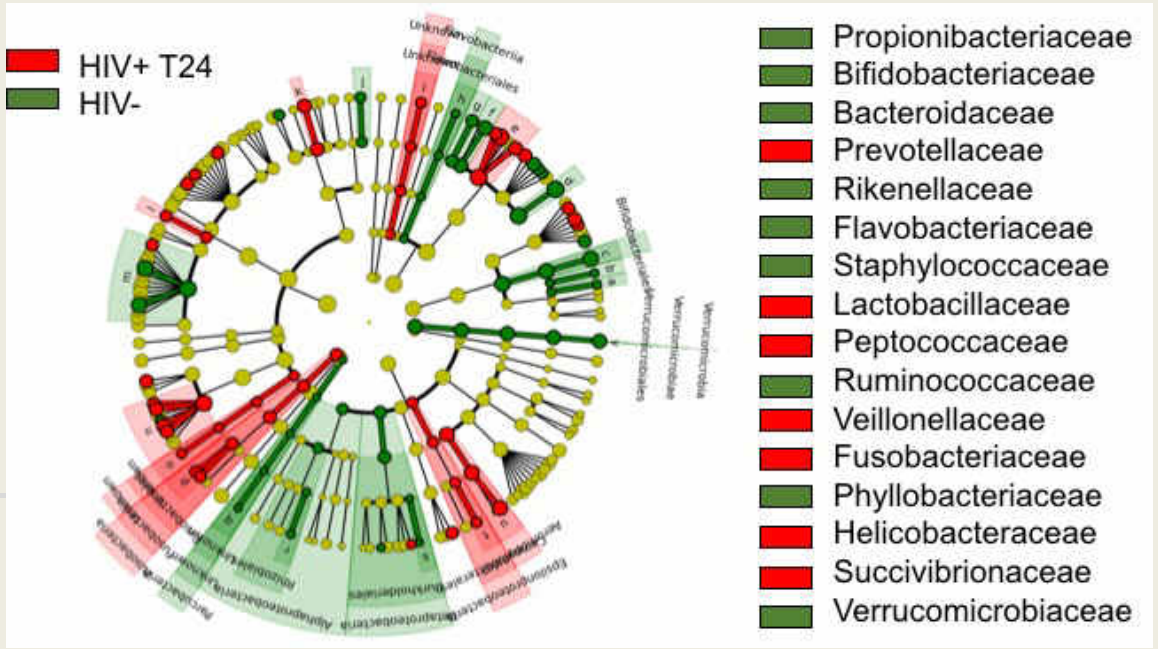
Harris et al. JID 2017



Dillon et al., Mucosal Immunol 2014

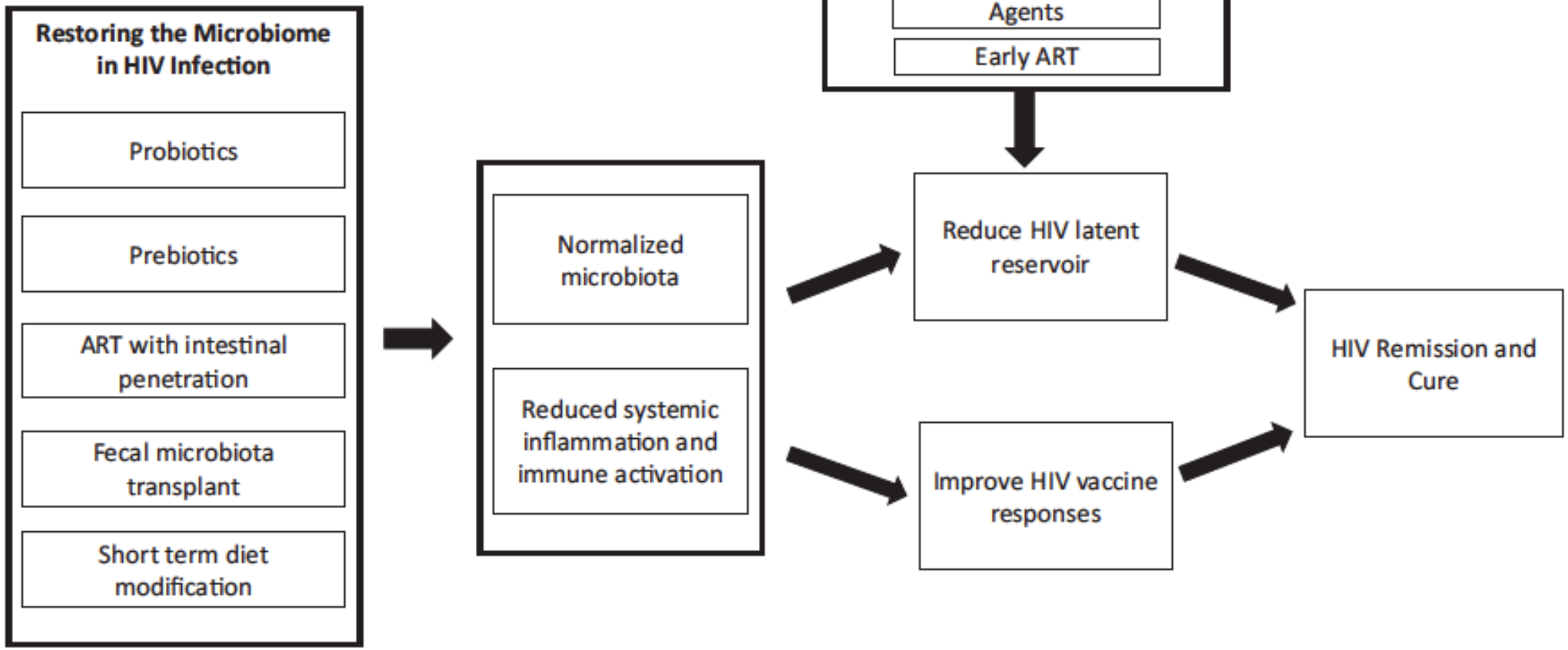
41 HIV+ patients before and at 1 year and 2-3 years of cART





Ancona G et al. CROI 2017 #215

Targeting the microbiome for HIV cure?



Wei Li et al. Curr Opin HIV AIDS 2018

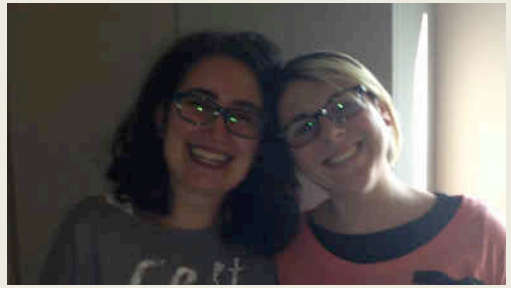
“He who is best prepared can best serve his moment of inspiration”

Samuel Taylor Coleridge (1772-1834)

HIV (functional) cure: not quite there, yet almost there .....

*Dept of Health Sciences- Clinic of Infectious Diseases - Univ of Milan, San Paolo H

Esther Merlini
Camilla Tincati
Elvira S Cannizzo
Giuseppe Ancona
Giusi M Bellistrì
Francesca Bai
Antonella d'Arminio Monforte
***all the patients and staff



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