XX. TÜRK KLİNİK MİKROBİYOLOJİ VE İNFEKSİYON HASTALIKLARI KONGRESİ

HIVÇG

KÜR ÇALIŞMALARINDA SON DURUM

Simpozyum 10
HIV İnfeksiyonu Yönetiminde Yenilikler

DOÇ. DR. ULUHAN SİLİ

MARMARA ÜNİVERSİTESİ TIP FAKÜLTESİ

İNFEKSİYON HASTALIKLARI VE KLİNİK MİKROBİYOLOJİ AD

15 MART 2019, 8:30 – 9:00

MARMARA ÜNİVERSİTESİ 1883

Tıp Fakültesi

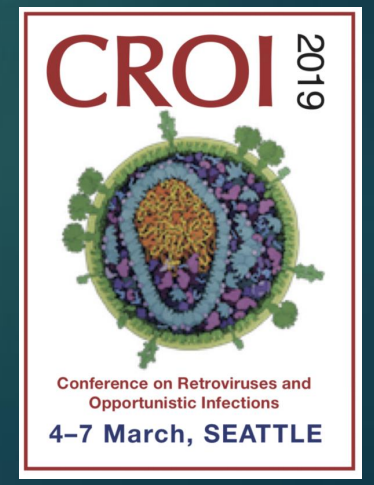
HIV Kürü

- Tanım
- Gereksinim
- Engel
- Umut
- Stratejiler

HIV Kür Çalışmalarında Son Durum

- 2018 International AIDS Society (IAS) Conference
  - HIV Cure Research with the Community Workshop
  - Strategies for cure: Pitfalls, possibilities and promise
  - Durable Control of HIV Infection in the Absence of Antiretroviral Therapy: Opportunities and Obstacles
  - Eliminating HIV latency: Shock and kill or block and lock?

- 2019 Conference on Retroviruses and Opportunistic Infections (CROI)
  - Update on HIV Cure
  - Strategies for HIV Cure



2018 Research-For-Cure Academy

31 October – 2 November 2018

TOWARDS AN HIV CURE

PEOPLE FOCUSED
SCIENCE DRIVEN

Wits Rural Facility, South Africa

International AIDS Society global scientific strategy: towards an HIV cure 2016

Steven G Deeks[1,20], Sharon R Lewin[2,3,20], Anna Laura Ross[4], Jintanat Ananworanich[5,6], Monsef Benkirane[7], Paula Cannon[8], Nicolas Chomont[9], Daniel Douek[10], Jeffrey D Lifson[11], Ying-Ru Lo[12], Daniel Kuritzkes[13], David Margolis[14], John Mellors[15], Deborah Persaud[16], Joseph D Tucker[17], Françoise Barre-Sinoussi[18] & International AIDS Society Towards a Cure Working Group[19]

NATURE MEDICINE VOLUME 22 | NUMBER 8 | AUGUST 2016

International AIDS Society global scientific strategy: towards an HIV cure 2016

- Tanımı netleştirmek araştırmacılar, klinisyenler ve HIV ile yaşayan bireyler için önemli
- **Optimal**: tüm çoğalabilen (replication competent) HIV'in kökünün kazınması
  - "sterilizing cure"
  - Başarması zor, göstermesi de zor
- **Yapılabilir**: uzun dönemli remisyon
  - "functional cure"
  - ART olmadan uzun dönemli saptanamaz viremi
  - Çoğalabilen HIV rezervinin uzun dönemli kontrolü

Box 1 Defining cure in HIV disease

The definition of cure is important to clarify for researchers, clinicians and people who are living with HIV. The optimal outcome would be the complete eradication within an individual of all replication-competent HIV. Such a sterilizing cure will be challenging to achieve and impossible to prove with current technologies[111]. A more feasible outcome will be the achievement of long-term remission. Remission is likely to be a necessary precursor for the development of an HIV cure, and is increasingly utilized in the field to indicate the goal of long-term undetectable viremia for an as-yet-undefined period (probably of several years) in the absence of ART[112]. The concept of disease remission denotes improvement, albeit with some uncertainty, and is already well entrenched in medical settings[113].

HIV kürü
-kamuoyu tartışması-

AIDS 2018

- Kamuoyunun kür ile ilgili görüşü nedir?
- Hastalar kür istiyorlar mı?
  - Kür denemelerine katılmaya istekliler mi?
  - Kür denemelerinin riskleri nelerdir?
- Hastaların beklentisi ne?
  - ART'yi kesebilmek yeter mi?
  - Anti-HIV negatifliği?
- Kür denemesi demek eninde sonunda ART'yi kesip nüks var mı diye beklemek demek? "**A**nalytical **T**reatment **I**nterruption (**ATI**)"
  - Nüksün hastaya zararı var mı?
  - Nüks ettiğinde bulaş olur mu?
    - Eşlerin durumu
- Güvenli, güvenli, güvenli!!!

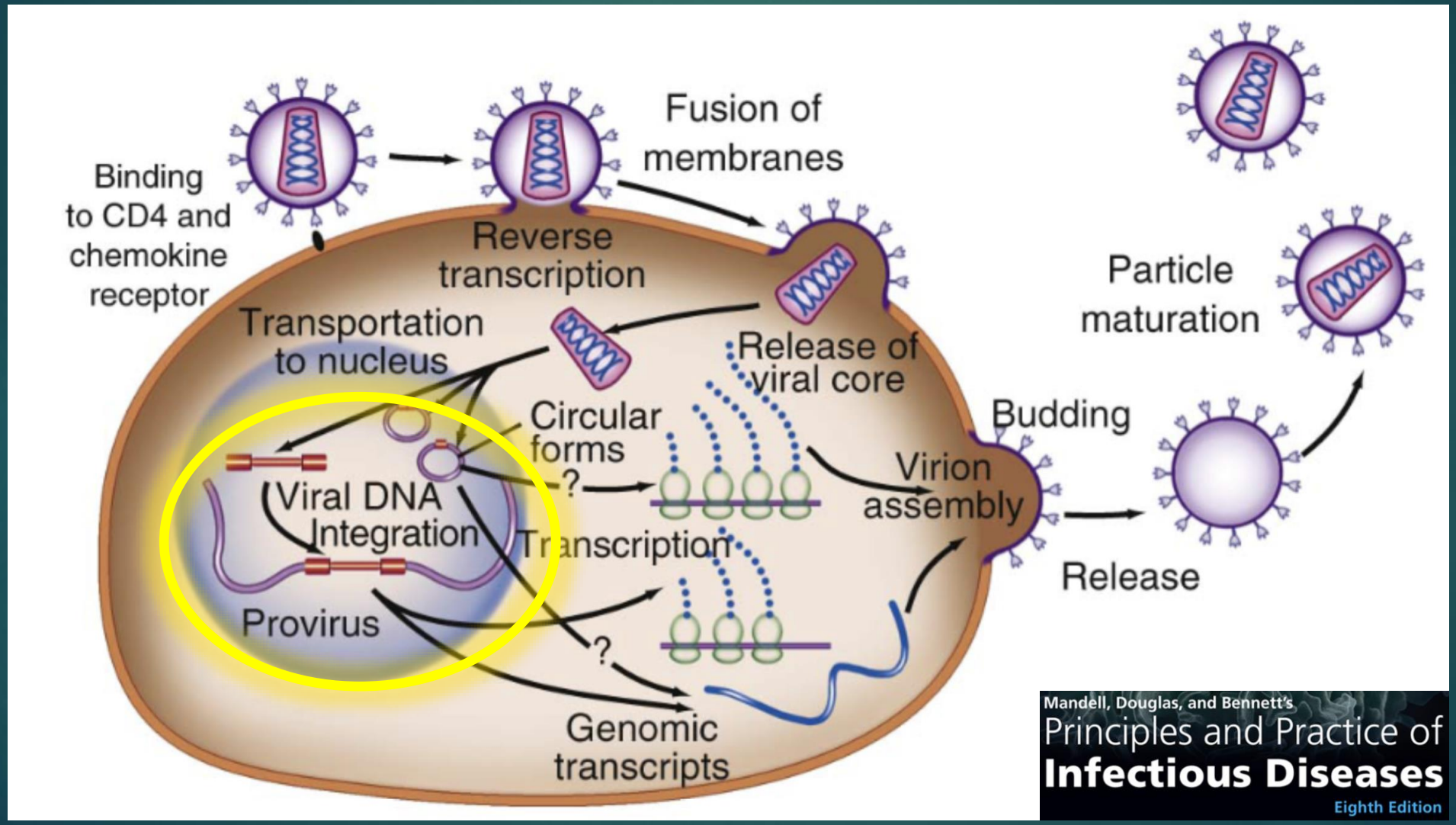
HIV kürüne gereksinim var mı?

- Etkin tedavi ve korunma metotları varken küre gereksinim var mı?
  - 90-90-90 hedefi ve PrEP/PEP uygulamaları
  - Tek tablet + uyum = normale yakın yaşam süresi (yönetilebilir müzmin hastalık)

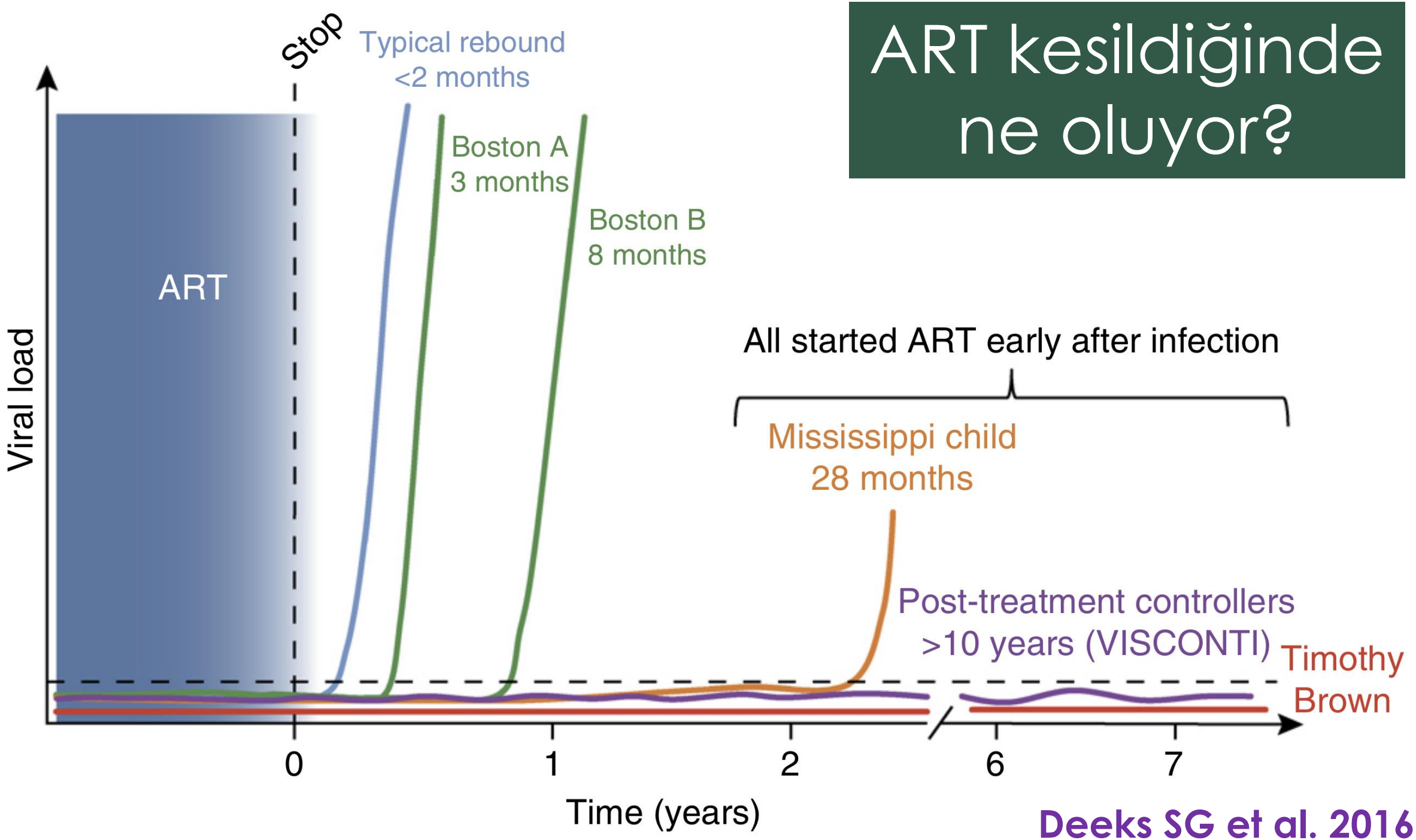
- UNAIDS: Global HIV istatistiği 2018
  - 2017'de 1.8 milyon yeni infeksiyon
  - 2017 itibariyle küresel ölçekte 36.9 milyon HIV ile infekte birey
    - 21.7 milyon (%58.9) HIV ile infekte birey ART almakta

- Klinik takipte tutabilme (retention): %76 - %88 (Colasanti J et al. 2016)

HIV replikasyon döngüsü



ART kesildiğinde ne oluyor?



Deeks SG et al. 2016

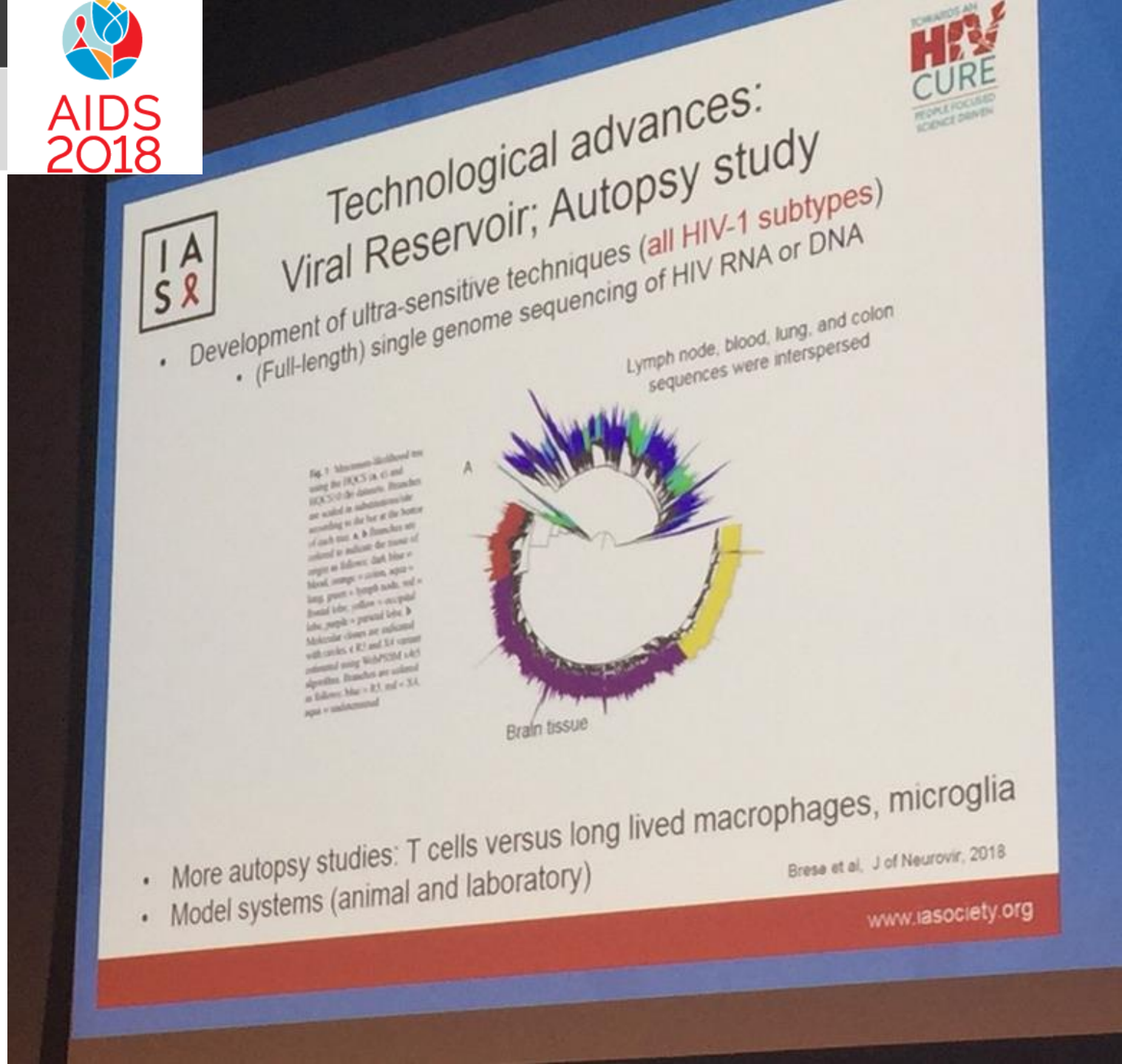
Where is the Reservoir?

Cellular reservoirs

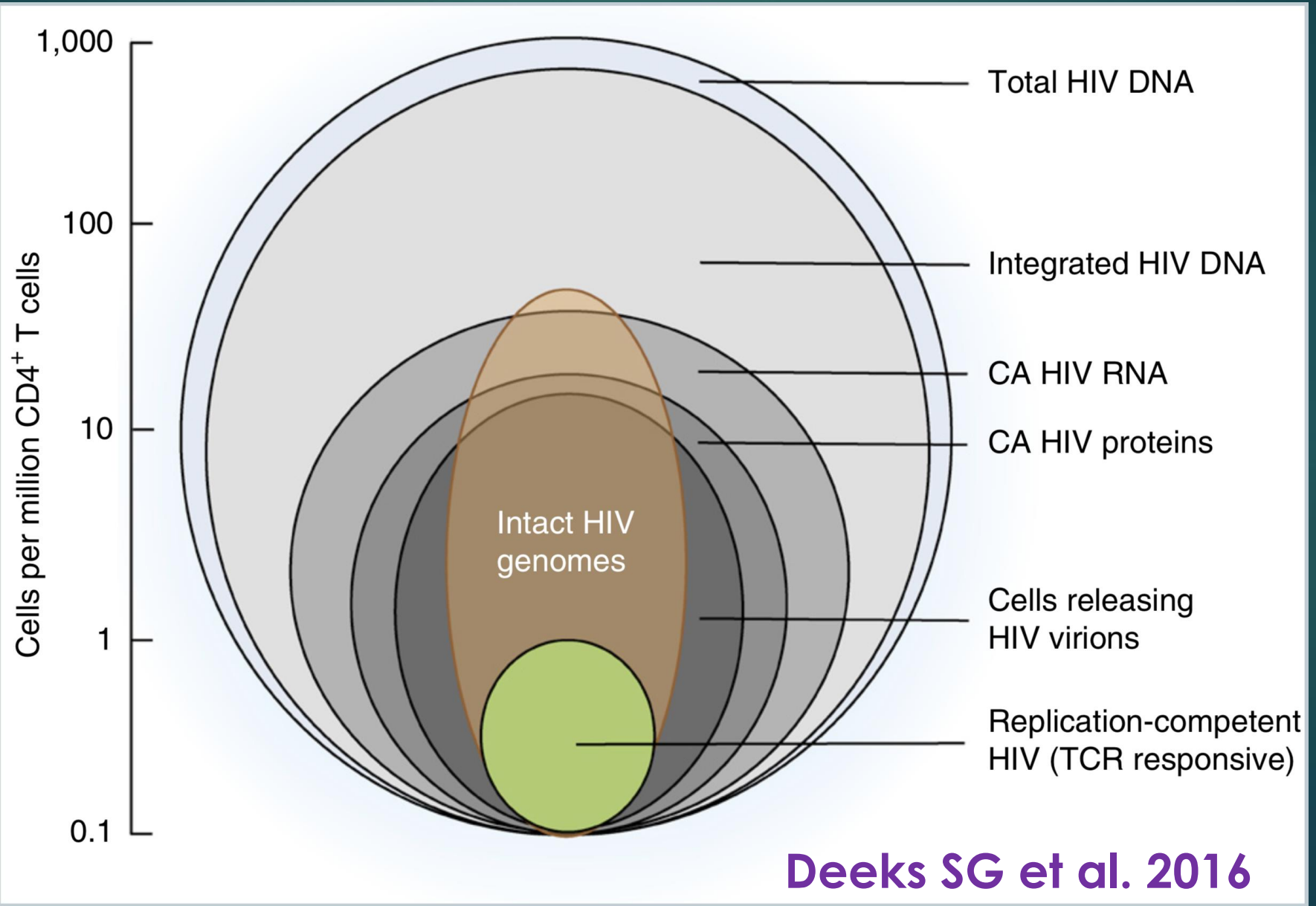
- T cells: all CD4+ T cells
  - varying contribution of subsets
  - Memory: Central > Transitional
    - Effector Memory cells
    - Stem Memory cells, small reservoir, but persist
    - Follicular T helper cells (Tfh) in lymph nodes
  - Naïve: smaller contribution
- these cells are **resting** not activated
- Monocytes/macrophages & DC

Tissue reservoirs

- Brain: Microglia, Astrocytes
- Gut/Genitourinary tracts



Suprese hastada rezerv ölçümü



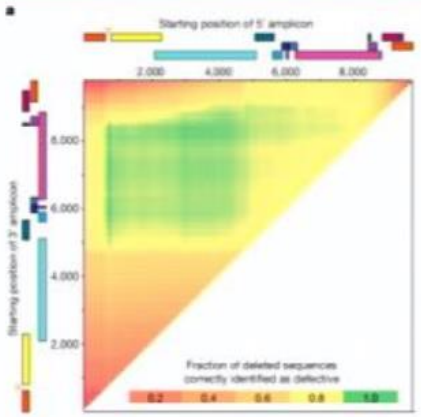
Deeks SG et al. 2016

UPDATE ON HIV CURE

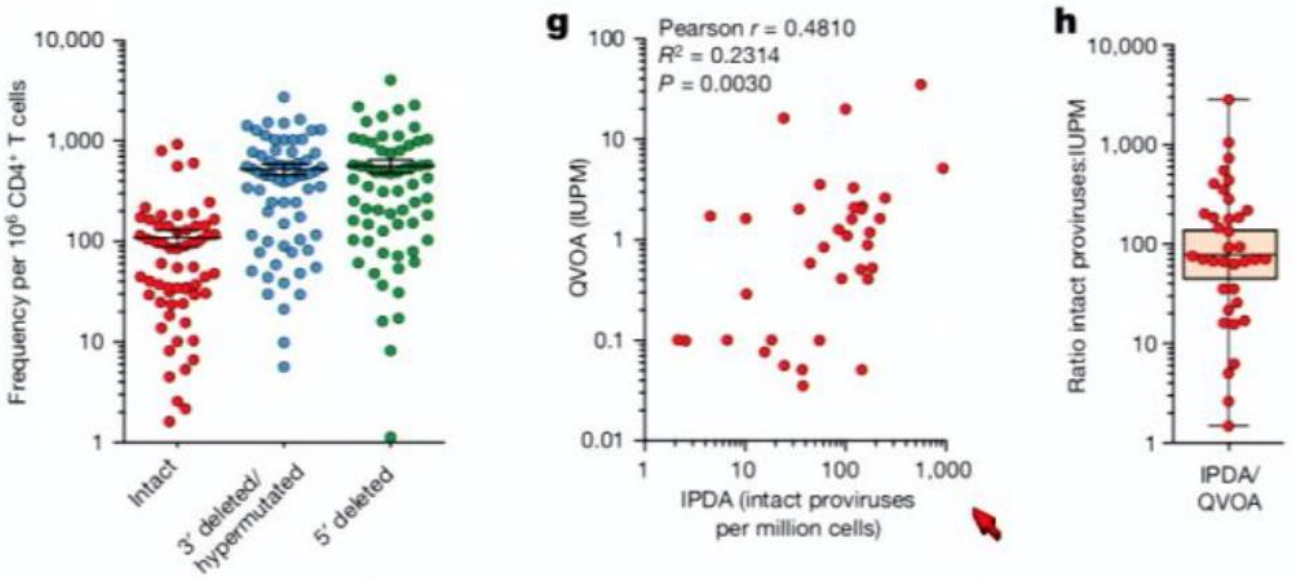
Katharine J. Bar
University of Pennsylvania
Philadelphia, PA, USA

CROI 2019

IPDA: Intact Proviral DNA

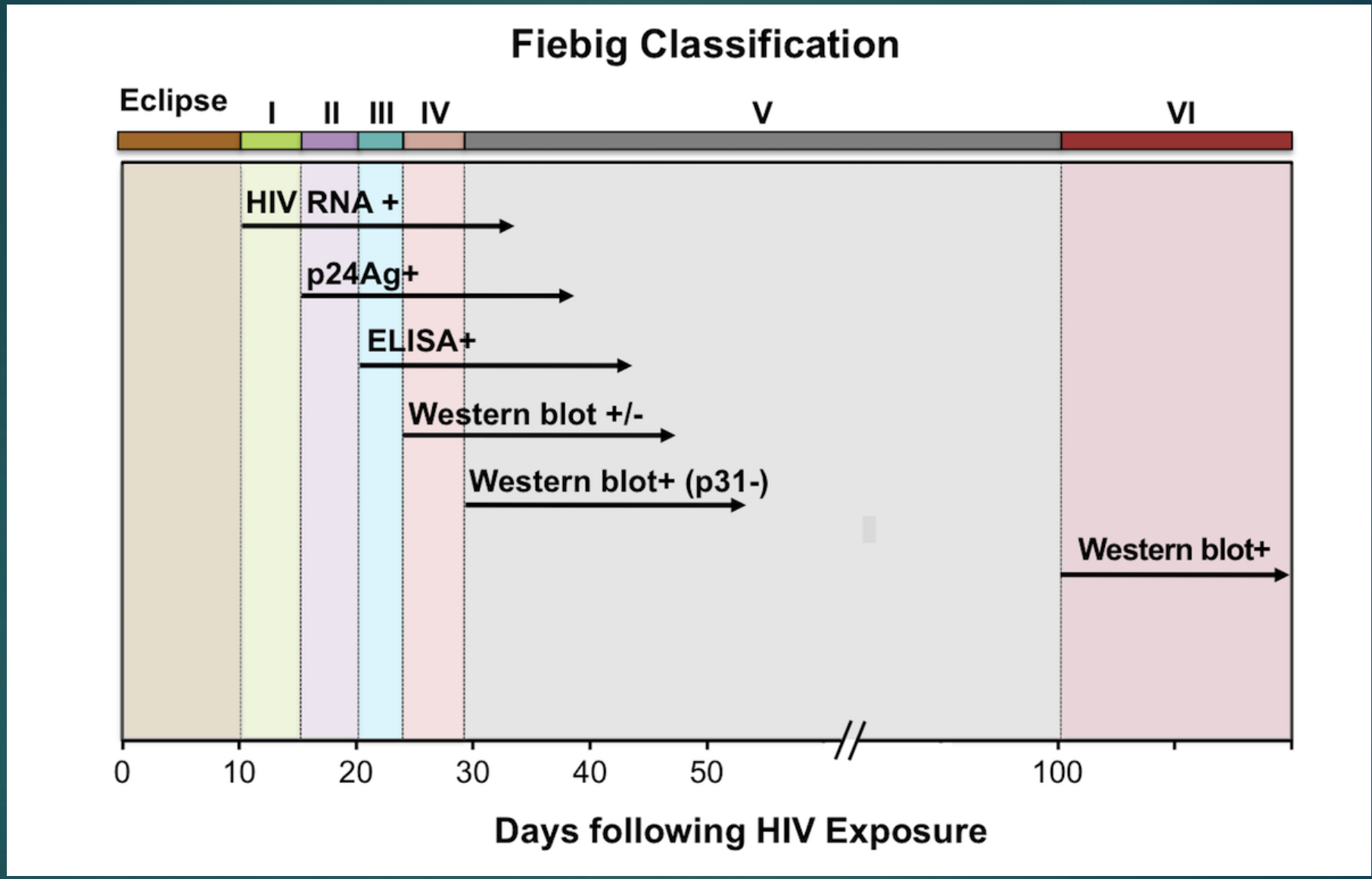


Probes placed to identify intact viruses without (i) large 3' or 5' deletions or (ii) hypermutation



- Excludes 97% defective viruses (by NFL sequencing); 70% of "intact" IPDA viruses are intact by NFL sequencing
- Strong correlation with QVOA (r=0.48; p=0.003), ~100X higher
- Can measure & track intact and defective viruses over time

Bruner et al., Nature 2019



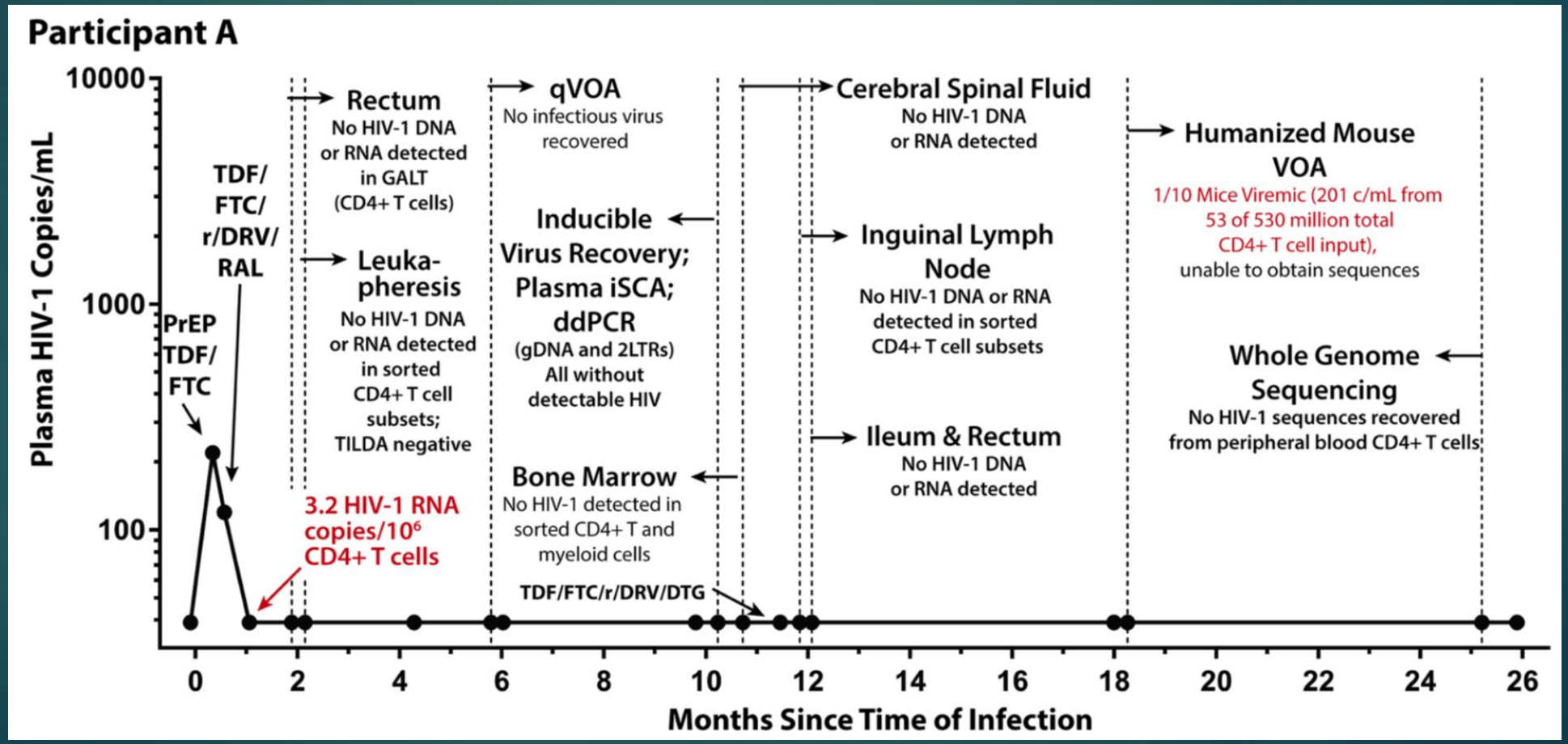
Fiebig EW *et al.* AIDS 2003, 17:1871-1879

HIV-1 persistence following extremely early initiation of antiretroviral therapy (ART) during acute HIV-1 infection: An observational study

PLOS Medicine

November 7, 2017

Timothy J. Henrich[1]*, Hiroyu Hatano[2], Oliver Bacon[2,3], Louise E. Hogan[1], Rachel Rutishauser[1,2], Alison Hill[4], Mary F. Kearney[5], Elizabeth M. Anderson[5], Susan P. Buchbinder[2,3], Stephanie E. Cohen[2,3], Mohamed Abdel-Mohsen[2,6], Christopher W. Pohlmeyer[7], Remi Fromentin[8], Rebecca Hoh[2], Albert Y. Liu[2,3], Joseph M. McCune[1], Jonathan Spindler[5], Kelly Metcalf-Pate[7], Kristen S. Hobbs[1], Cassandra Thanh[1], Erica A. Gibson[1], Daniel R. Kuritzkes[9,10], Robert F. Siliciano[11,12], Richard W. Price[13], Douglas D. Richman[14,15], Nicolas Chomont[8], Janet D. Siliciano[10], John W. Mellors[16], Steven A. Yuki[17,18], Joel N. Blankson[7], Teri Liegler[2], Steven G. Deeks[2]



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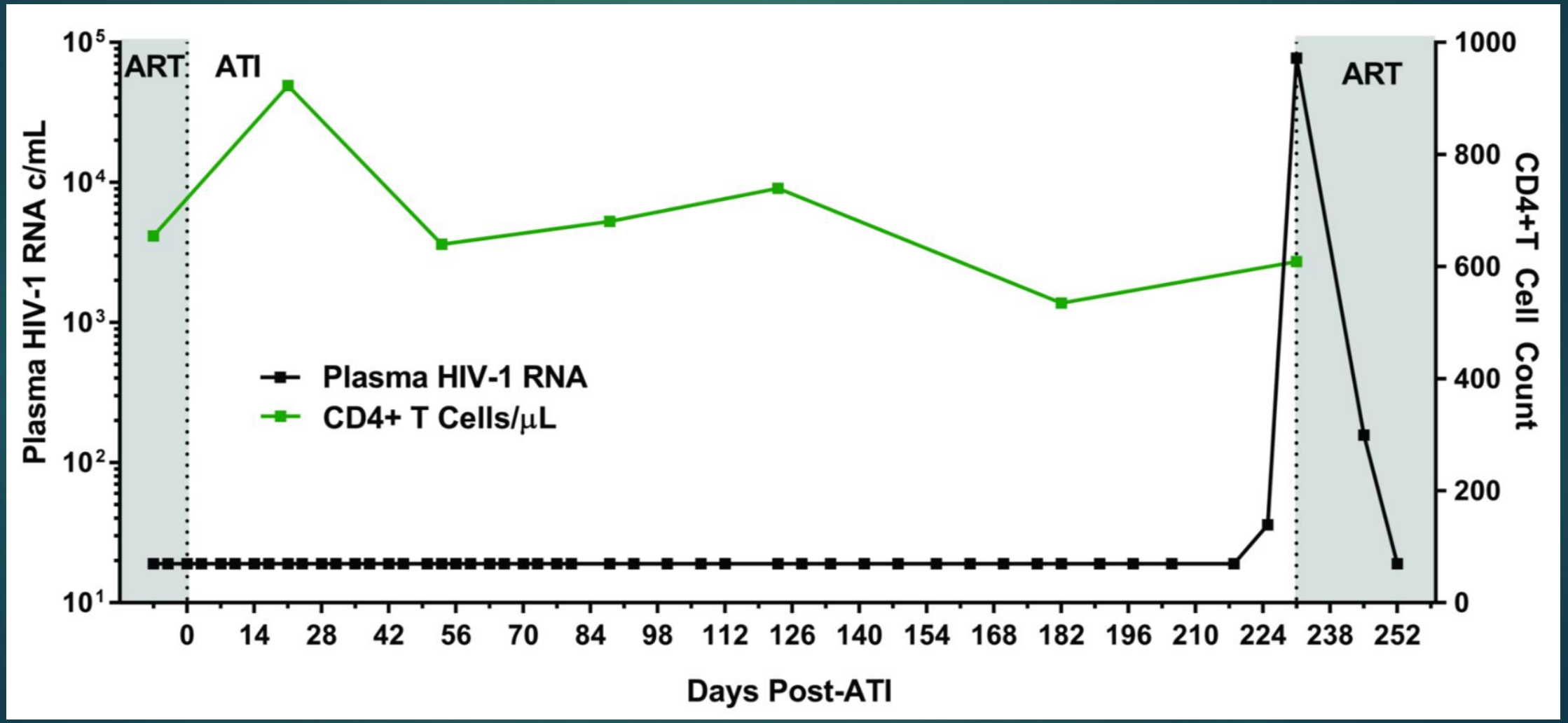
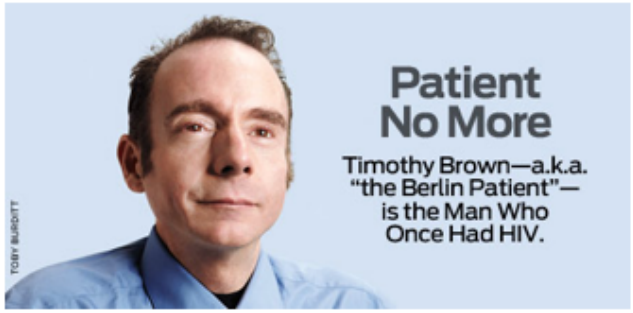


Which factors contributed to the cure?



- CCR5Δ32Δ32 donor cells[1]
- Absence of viruses able to use other co-receptors (i.e. CXCR4 tropic-virus)[2]
- Immune suppressive treatment (i.e. ATG levels)
- Total body irradiation
- Graft Versus Host Disease
- Patient's own CCR5 heterozygous state (smaller HIV-DNA reservoir?)

[1]Hutter et al, NEJM, 2008; [2]Symons et al, CID, 2014

Dominant HIV DNA populations present in different T-cell subsets before stem cell transplantation persist in tissues early after transplantation with CCR5Δ32 stem cells

A. M.J. Wensing , K. Bosman , A. Bruns , P. Ellerbroek , T. de Jong , K. Tesselaar , A. Stam , M. Salgado , G. Hutter , L. Brosens , M. Kwon , J. Diez Martin , J. Boelens , J. Martinez-Picado , J. Kuball and M. Nijhuis on behalf of the IciStem consortium

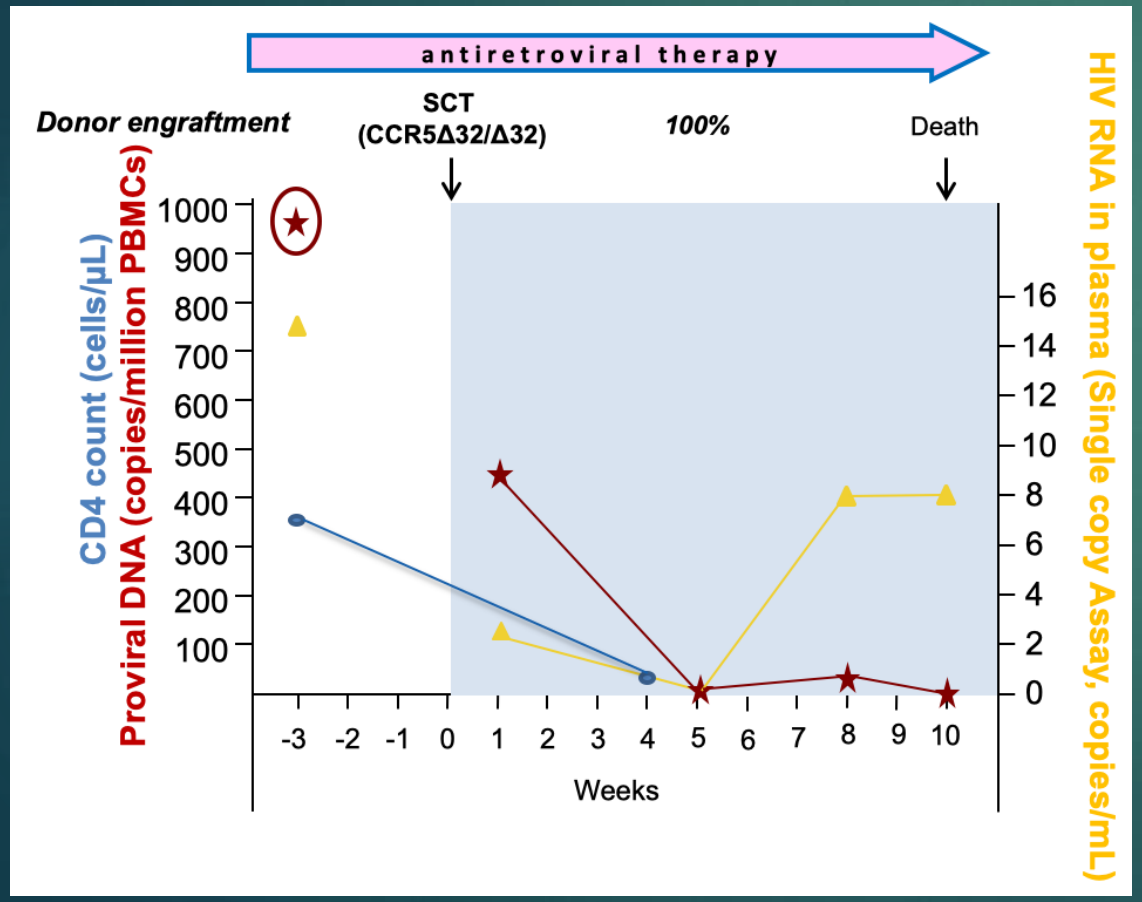
AIDS2018

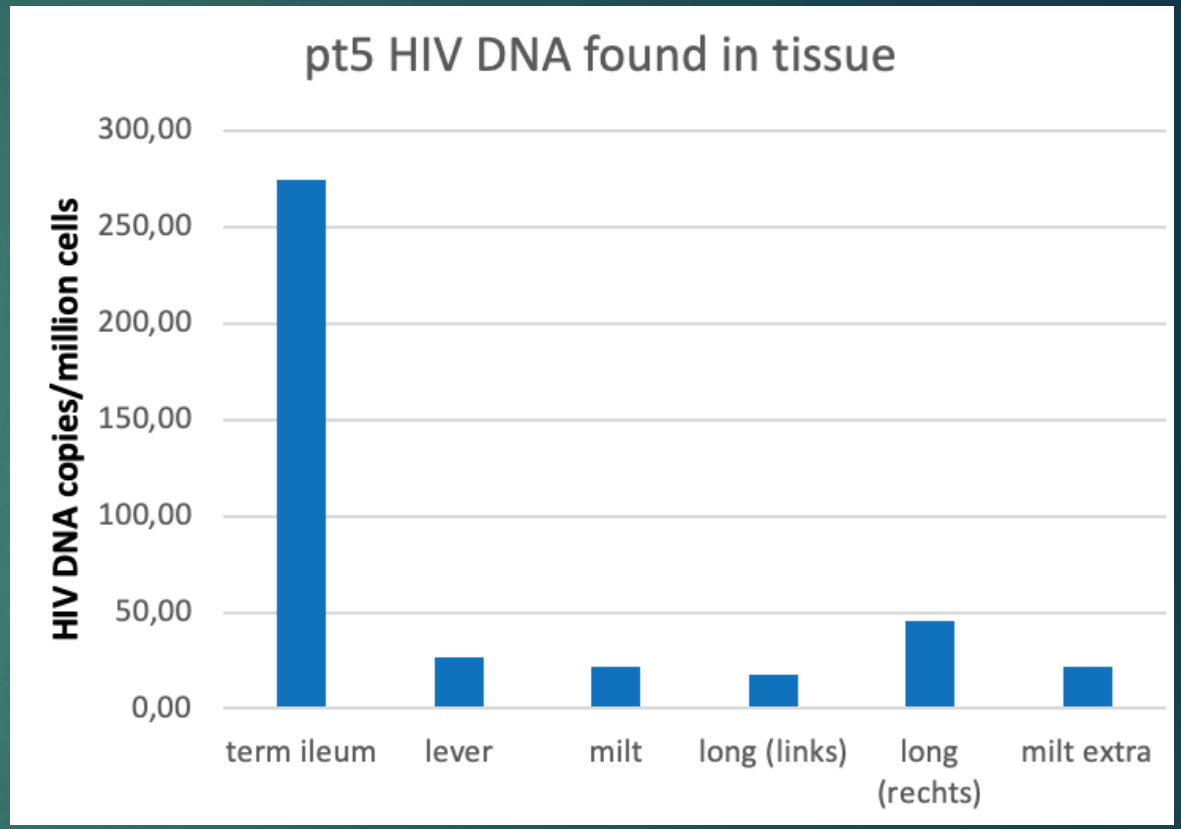
Overview of registration

- 37 patients registered from 9 different countries
- 30 patients transplanted
- Mean follow-up: 887 days
  12 patients deceased after SCT (Δ32/Δ32)
  12 patients beyond 2nd year post-SCT

	CCR5WT/WT	CCR5Δ32/Δ32			alive
Adult Donor	20*	7	27	→	17
Umbilical Cord	1	2	3	→	1
	21	9			
	↓	↓	*3 CCR5 Δ32/WT		
alive	13	5			
	%62	%56			

Patient	HIV Diagnosis	Start of ART	Indication of SCT	Date of trans plant	Stem cell therapy	CCR5 genotype stem cells	cART cessation
#5 Utrecht	1998	1998	Myelodysplastic syndrome (MDS)	May 2012	Cord blood transplant+3rd party donor	**CCR5 Δ32/Δ 32**	No





Future directions

ICISTEM

IciStem Patient	HSCT	Year of transplant	Single copy assay (HIV-RNA cp/ml)	Total DNA (cp/10^6 CD4)	qVOA in CD4 (IUPM)	Ileum, CSF, LN
1	CCR5WT	2012	5	25	0.034	-
3	CCR5WT	2013	undetectable	undetectable	undetectable	undetectable
6	CCR5WT	2014	undetectable	undetectable	undetectable	undetectable
17	CCR5WT	2010	undetectable	undetectable	undetectable	undetectable
19	CCR5Δ32	2013	-	undetectable	undetectable	Trace/undetectable
27	CCR5WT	2009	undetectable	undetectable	undetectable	undetectable
28	CCR5WT	2013	undetectable	undetectable	undetectable	undetectable

SUSTAINED HIV-1 REMISSION FOLLOWING HOMOZYGOUS CCR5 DELTA32 ALLOGENIC HSCT

Ravindra K. Gupta
University College London
London, United Kingdom

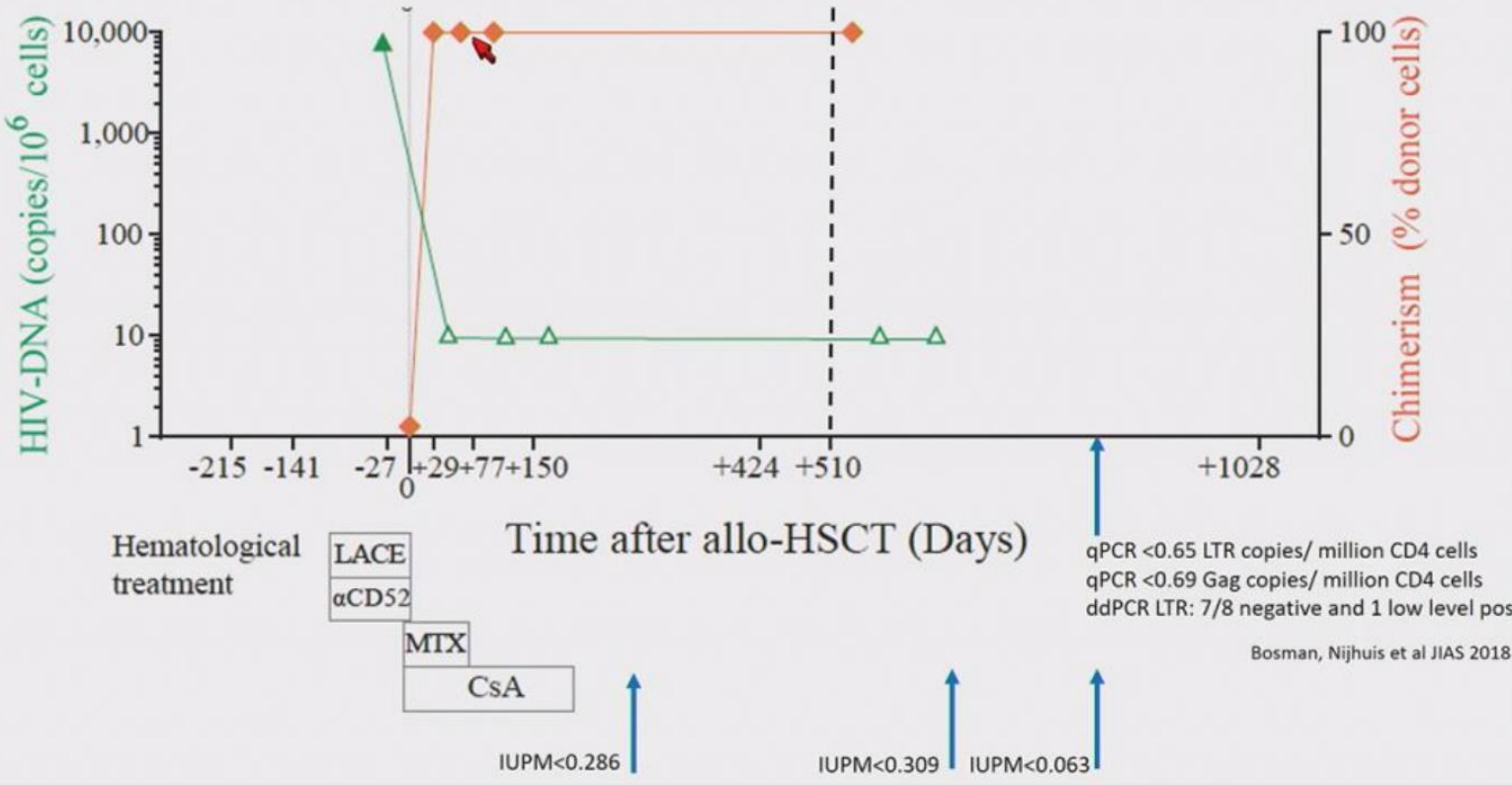
CROI 2019
Conference on Retroviruses and Opportunistic Infections
4–7 March, SEATTLE

Case History

- **HIV-1 Diagnosis 2003**
- **2013:** Stage IVb Hodgkin lymphoma
  Atripla initiated. Viral suppression achieved
  Switch to TDF/FTC/Raltegravir (ABVD chemo)

- Failed multiple lines of chemotherapy and mobilisation for auto SCT
- Donor registry search for allo HSCT
  - Unrelated 9/10 HLA high-resolution match.
  - Donor homozoygous CCR5-d32 mutation

Cellular HIV-1 DNA Reservoir Measurements



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'The London Patient'	*Timothy Brown*
• Homozygous for wild type CCR5	• Heterozygous for △32
• Infection with R5 using virus	• Infection with R5 using virus
• Hodgkin Lymphoma	• Acute Myelogenous Leukemia
• Single HSCT	• Two HSCT
• No irradiation	• Total Body Irradiation
• Reduced intensity conditioning	• Full intensity conditioning
• T cell depletion with aCD52	• T cell depletion with ATG
• Mild GVH	• Mild GVH
• 100% T cell donor chimerism	• 100% T cell donor chimerism

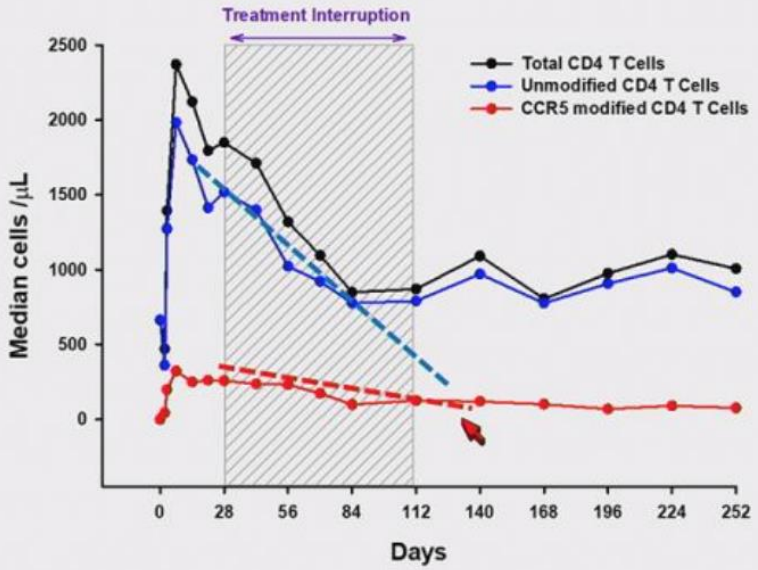
DELAYED VIRAL REBOUND DURING ATI AFTER INFUSION OF CCR5 ZFN-TREATED CD4 T CELLS

Pablo Tebas

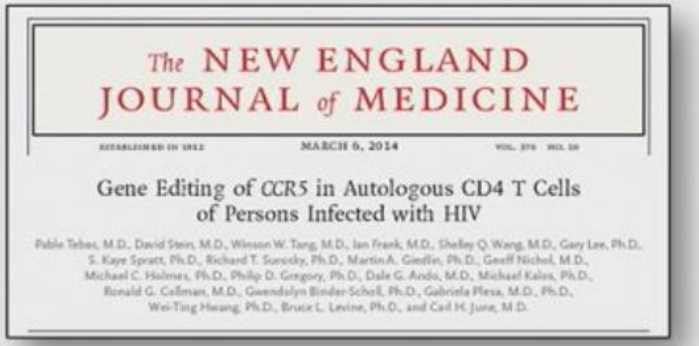
University of Pennsylvania
Philadelphia, PA, USA

CROI 2019
Conference on Retroviruses and Opportunistic Infections
4–7 March, SEATTLE

The modified cells had a survival advantage in the presence of HIV



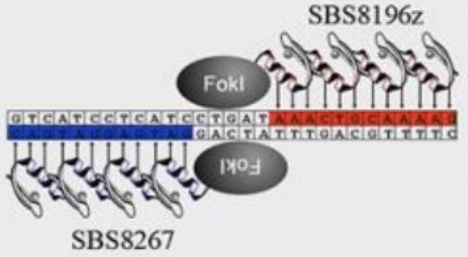
Autologous CCR5 Modified CD4+ T-cells

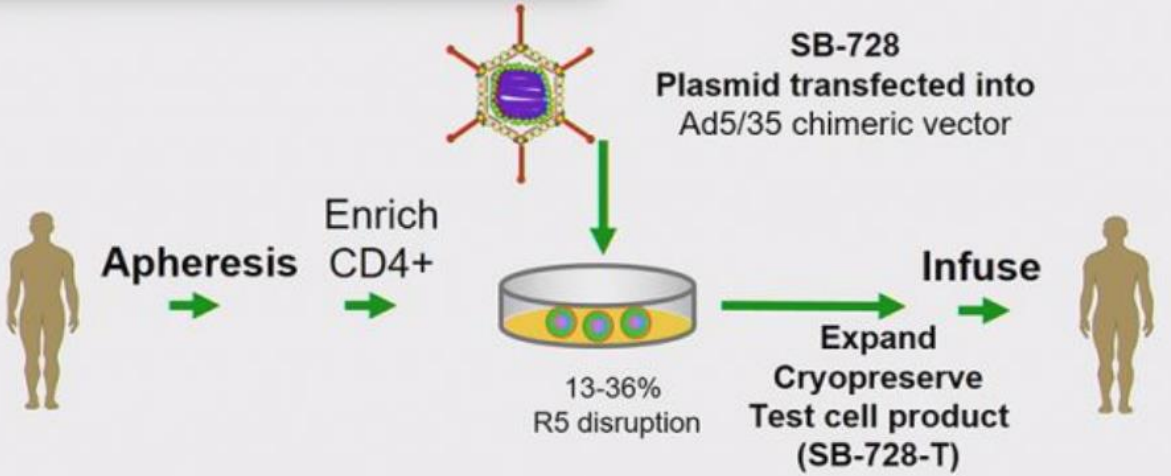

The NEW ENGLAND JOURNAL of MEDICINE

MARCH 6, 2014

Gene Editing of CCR5 in Autologous CD4 T Cells of Persons Infected with HIV

Pablo Tebas, M.D., David Stein, M.D., Winson W. Tang, M.D., Ian Frank, M.D., Shelley Q. Wang, M.D., Gary Lee, Ph.D., S. Kaye Spratt, Ph.D., Richard T. Surosky, Ph.D., Martin A. Giedlin, Ph.D., Geoff Nichol, M.D., Michael C. Holmes, Ph.D., Philip D. Gregory, Ph.D., Dale G. Ando, M.D., Michael Kalos, Ph.D., Ronald G. Collman, M.D., Gwendolyn Binder-Scholl, Ph.D., Gabriela Plesa, M.D., Ph.D., Wei-Ting Hwang, Ph.D., Bruce L. Levine, Ph.D., and Carl H. June, M.D.





Penn Medicine

Tebas et al. NEJM 2014; 370: 901-10

DELAYED VIRAL REBOUND DURING ATI AFTER INFUSION OF CCR5 ZFN-TREATED CD4 T CELLS

Pablo Tebas

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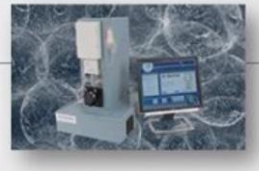
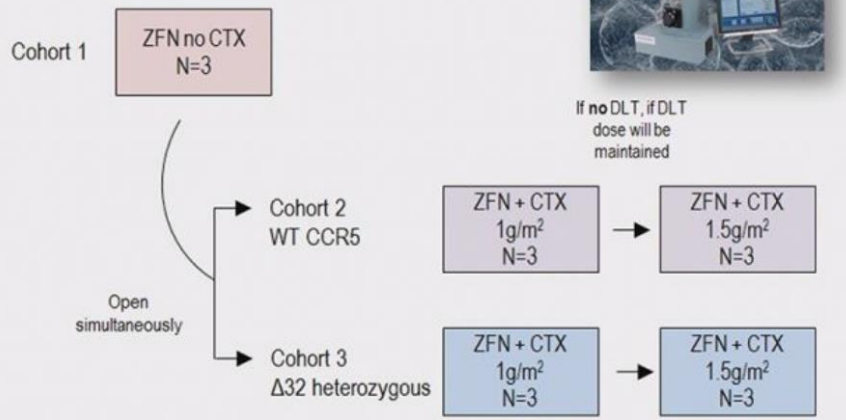
Design

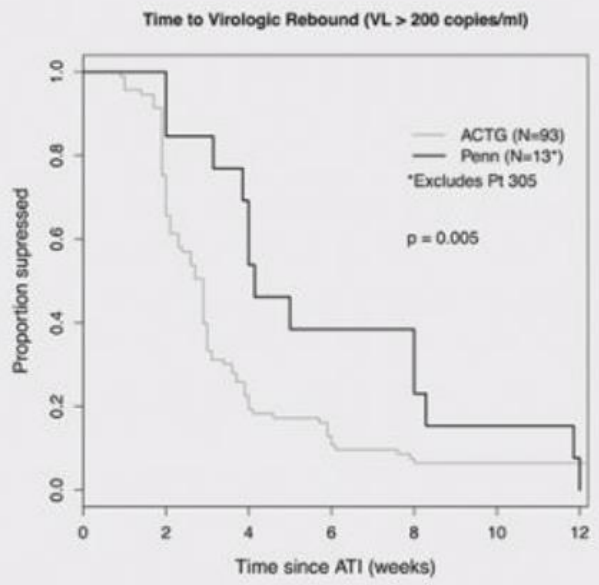


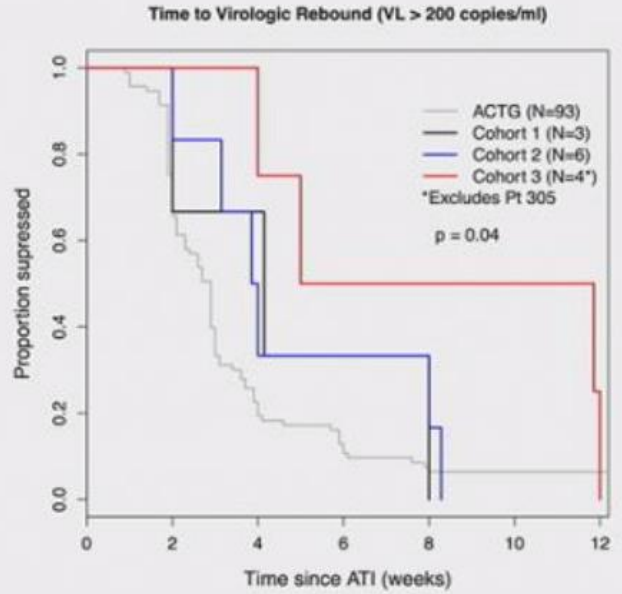


- 3-arm open-label pilot study
- Well controlled HIV+ individuals in which some were CCR5 Δ32 heterozygotes
- Single infusion of autologous CD4 T cells modified at the CCR5 gene by RNA encoding ZFN SB-728
- With or without the prior administration of two different doses of CTX

Results. Time to virological rebound > 200 copies/mL

- Modest delay in viral rebound compared to historical ACTG controls.





Getting the "Kill" into "Shock and Kill": Strategies to Eliminate Latent HIV

Youry Kim,[1,2] Jenny L. Anderson,[2] and Sharon R. Lewin[2,3,*]

Cell Host & Microbe *23*, January 10, 2018

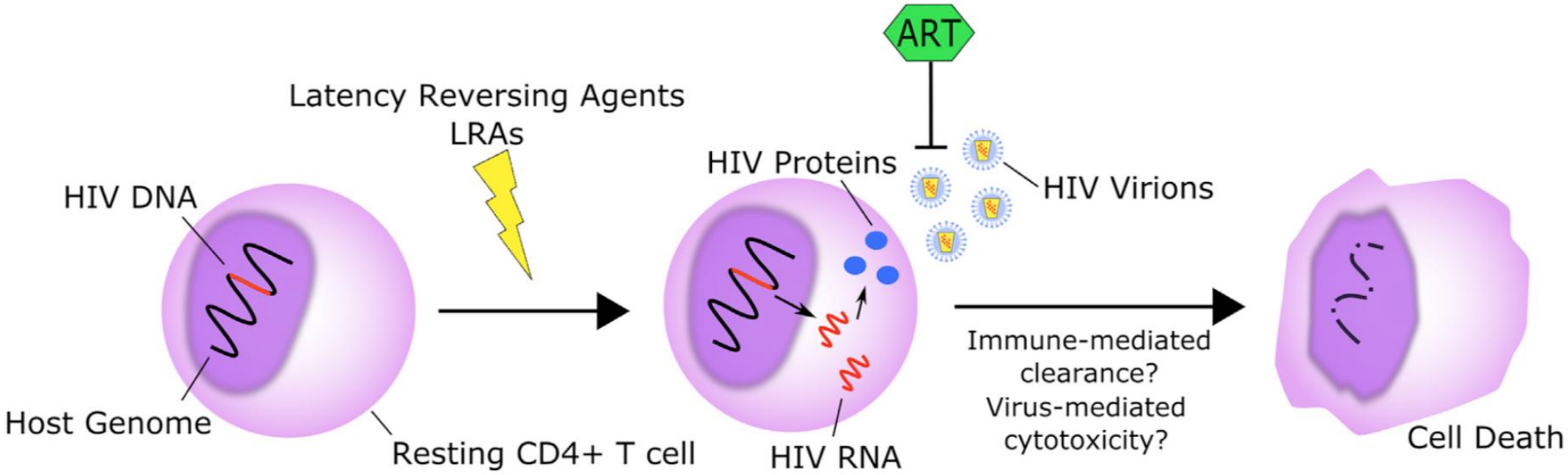


Figure 1. Shock and Kill Strategy to Eliminate HIV Latently Infected Cells

The "shock and kill" strategy uses LRAs to increase HIV transcription, protein expression, and virion production. The cell may potentially die through virus-mediated cytopathic events or immune-mediated clearance. LRAs, latency reversing agents; ART, antiretroviral therapy.

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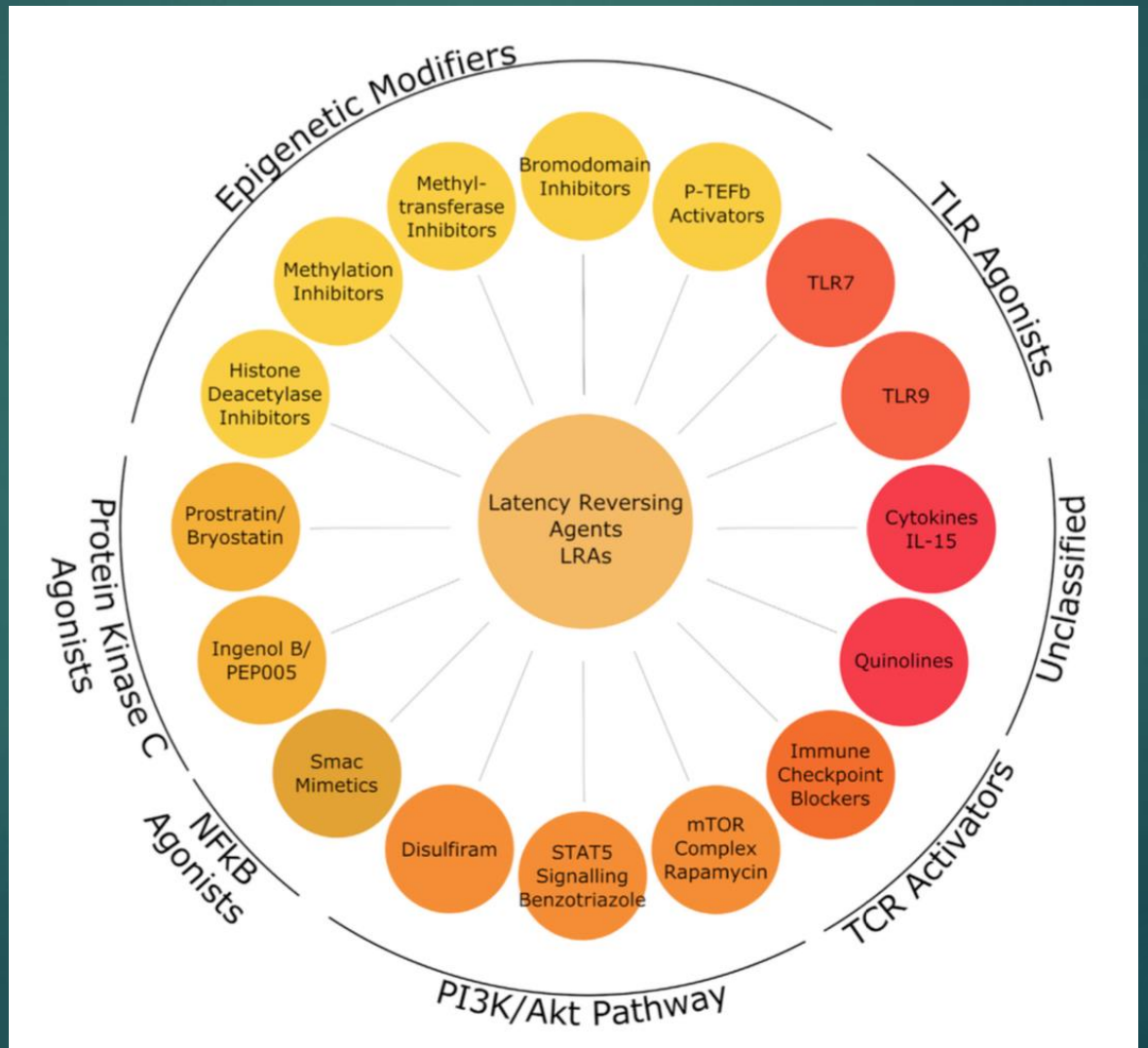


A-899-0059-12977

RIVER

Research In Viral Eradication of HIV Reservoirs

A two-arm (proof of concept) randomised phase II trial Vorinostat plus a prime boost Vaccine

Presented by Professor Sarah Fidler

on behalf of the RIVER study team and investigators

NHS National Institute for Health Research

CHERUB

Imperial College London

MRC Medical Research Council

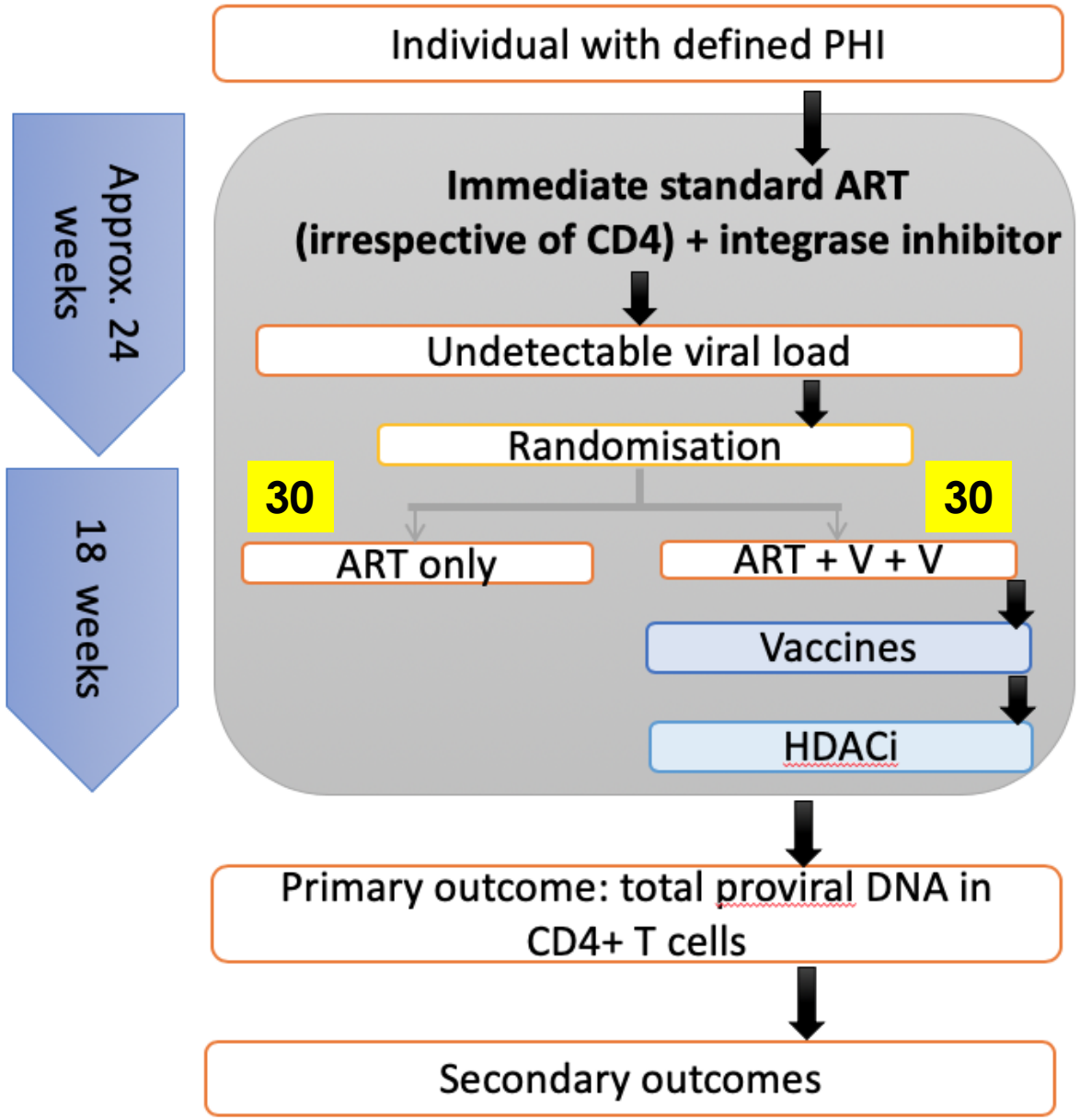
UNIVERSITY OF CAMBRIDGE

MRC Clinical Trials Unit

UCL

UNIVERSITY OF OXFORD

Study design

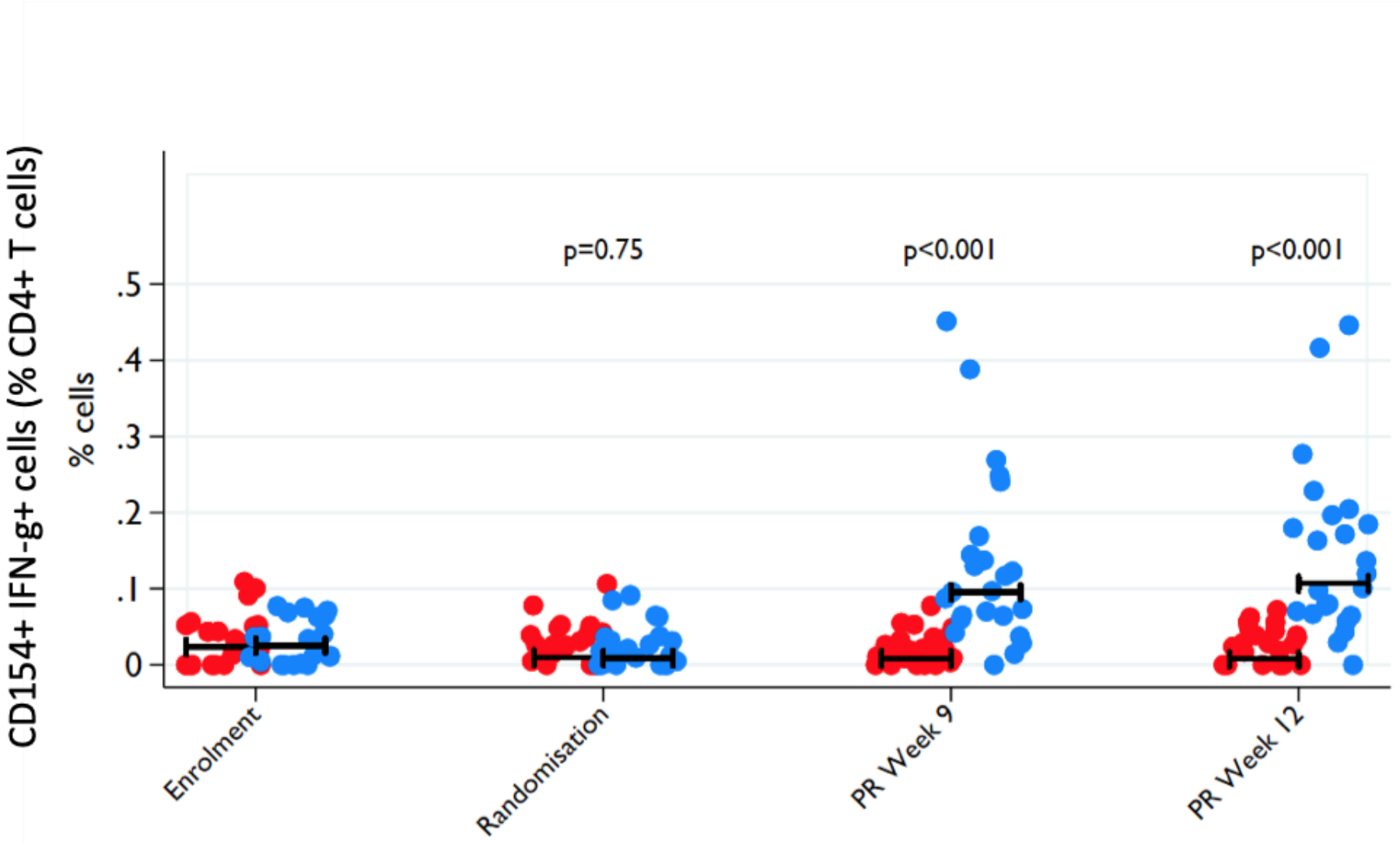


Vaccination:
Prime ChAdV63.HIVconsv at randomisation
Boost MVA.HIVconsv week 8 post-randomisation

Vorinostat
400mg od every 72 hours*
total 10 doses

*Archin et al J Clin Invest 2017 Aug 1;127(8):3126-3135.

ART + V + V boosts functional HIV-specific CD4+ T cells

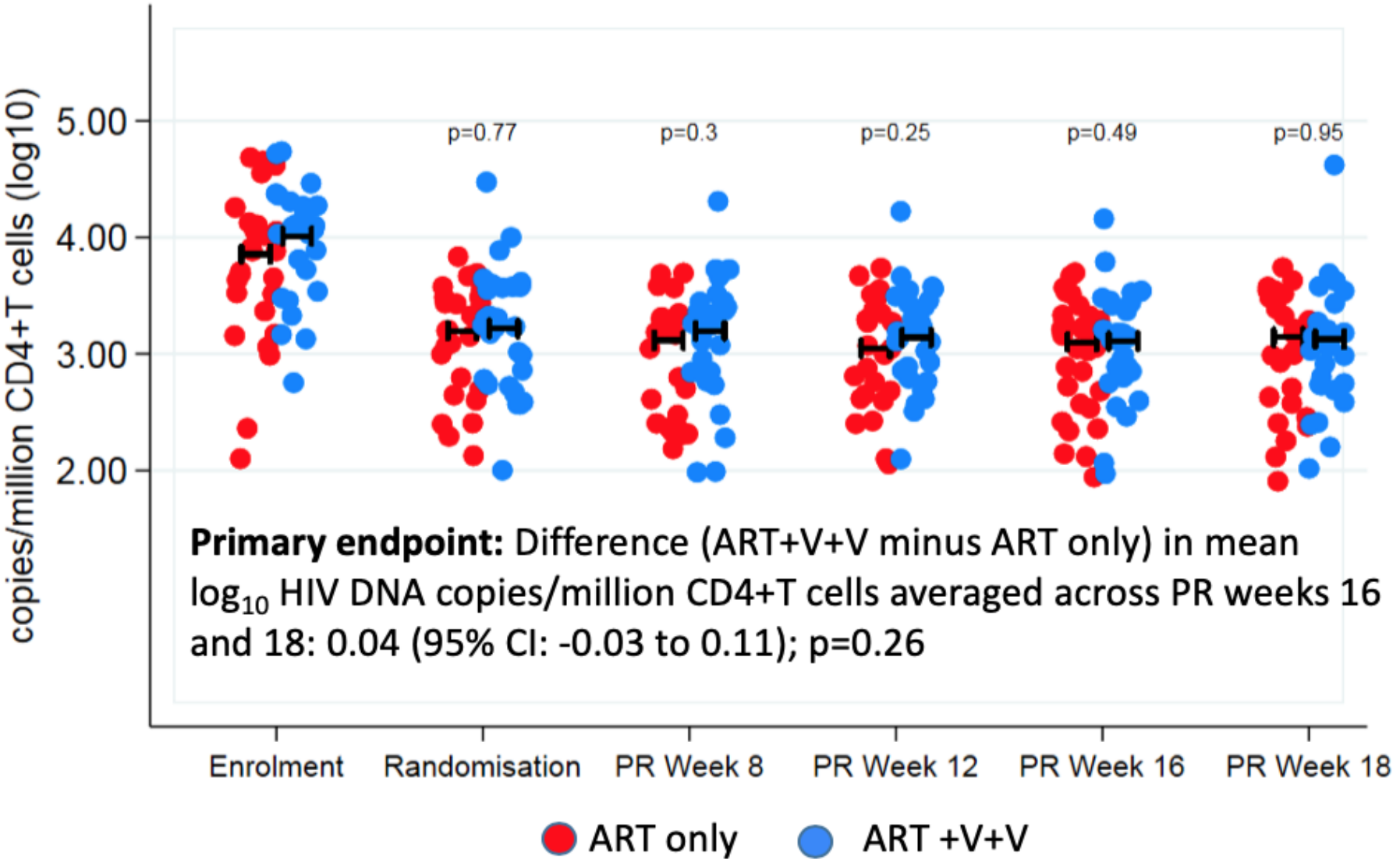


p-values: rank tests for difference between groups per time-point

ART only

ART +V+V

Total HIV DNA over time, by arm



Primary endpoint: Difference (ART+V+V minus ART only) in mean $\log_{10}$ HIV DNA copies/million CD4+T cells averaged across PR weeks 16 and 18: 0.04 (95% CI: -0.03 to 0.11); p=0.26

Tartışma
Analitik Tedavi Kesimi Yapılmalı mı?

Summary of findings

- The interventions used in this trial did no harm
- No significant difference in measures of HIV DNA at weeks 16 & 18 post randomisation between arms.
- Outstanding commitment from participants
  - No loss to follow-up
  - 97% adherence to intervention.
- Vorinostat significantly increased histone deacetylation.
- ART + V + V significantly stimulated HIV-specific CD4 and CD8 T-cell responses compared with controls.
- Study highlights importance of a control arm. The result is definitive, but disappointing

Discussion

This approach to “kick and kill” did not confer any significant reduction to the HIV reservoir over ART alone, as measured by total HIV DNA, 1 year after PHI, however, this does not mean the approach is wrong;

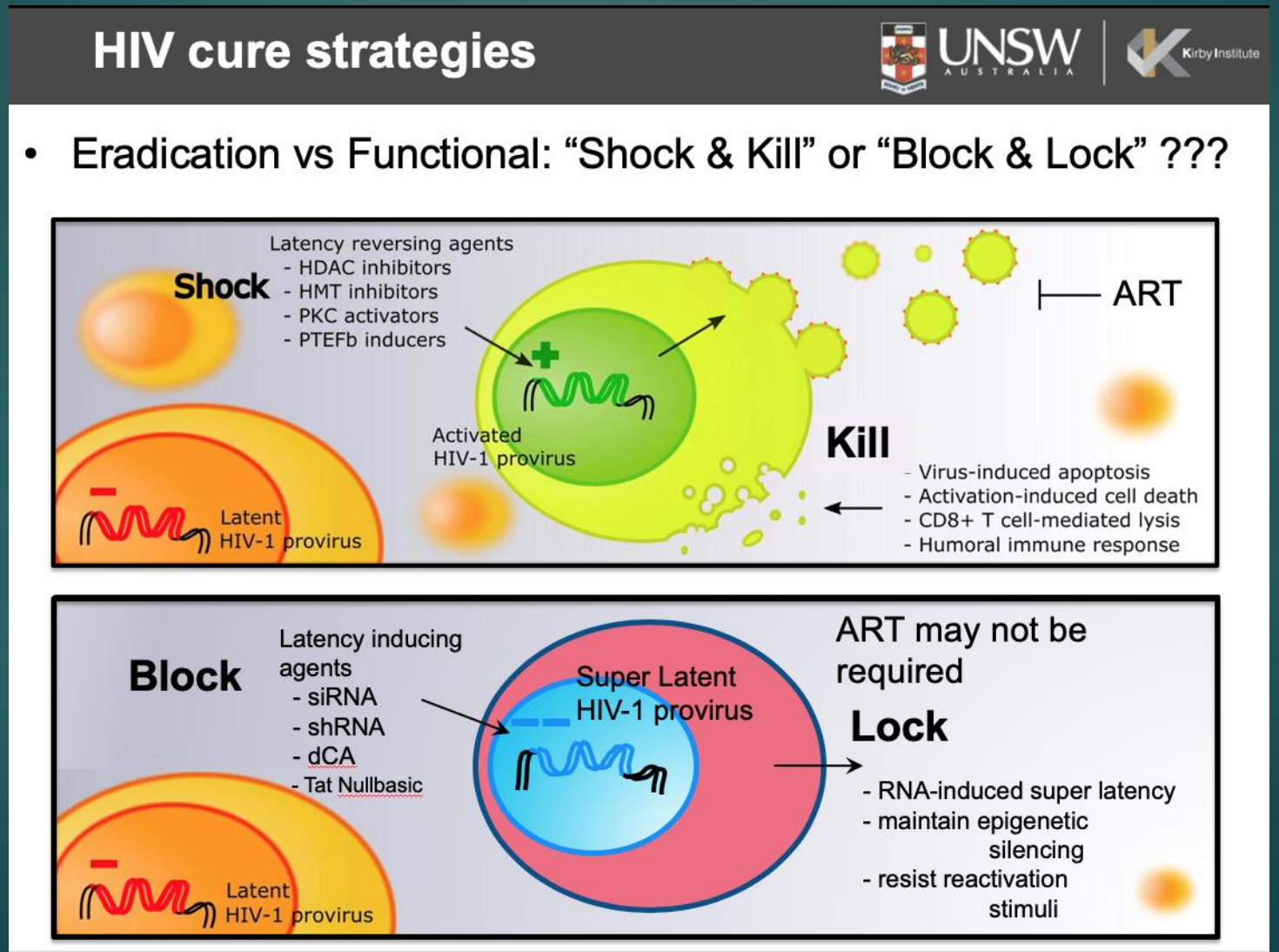
It may be the latency reversing agent used here is not potent enough, there are many new agents under study.

It may be the epitopes included in the vaccine constructs were not the correct ones to recognize latently infected cells.

More detailed laboratory research needs to be done to better understand the results.

Block-and-Lock using gene silencing

Tony Kelleher, Kirby Institute

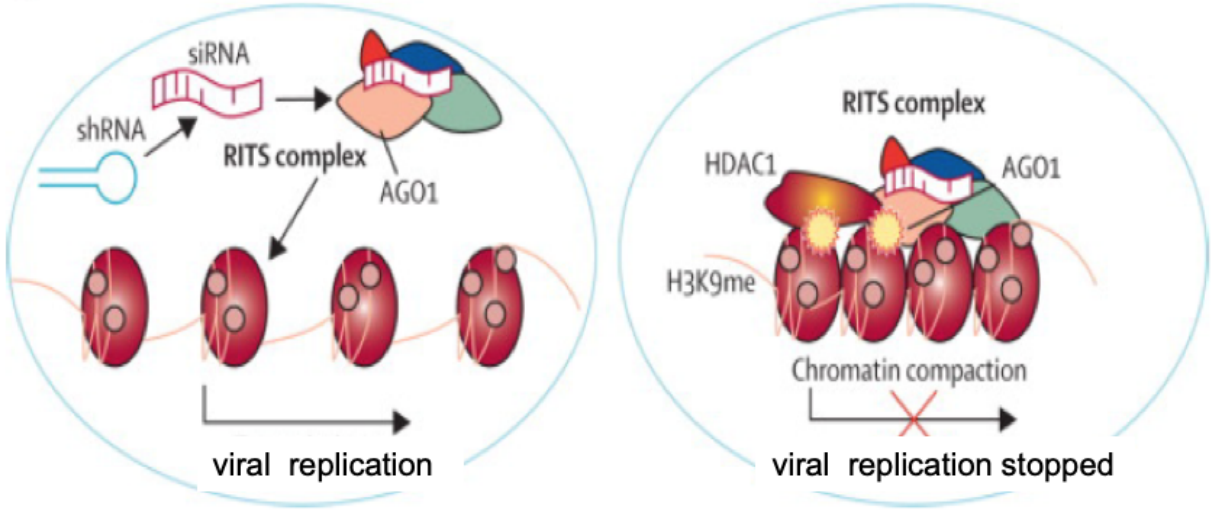


Gene therapy for drug free remission of HIV

HIV Functional cure: enforcing viral latency

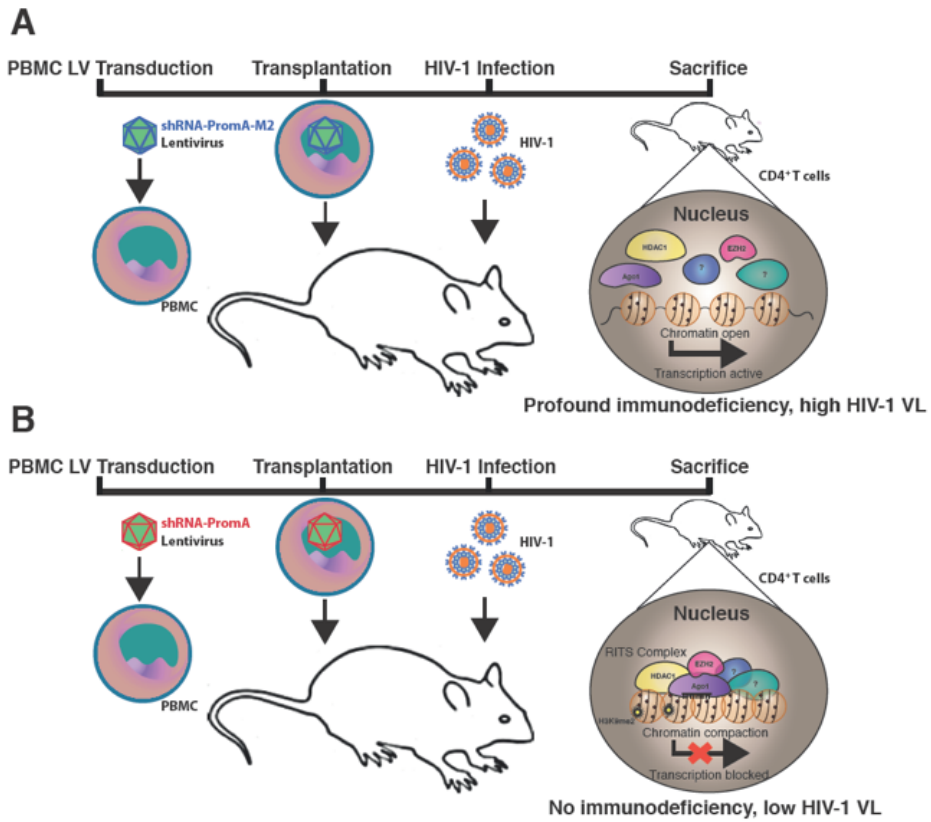
"BIND and GAG" or "BLOCK and LOCK"

- Gene therapy: si/shRNA which target sequences within HIV promoter
- Induces **long term lock down of virus in latent form,** by inducing change in histone tails and nucleosome architecture, resistant to a range of reactivation stimuli



Ahlenstiel et al, 2016

Preclinical mouse data in humanised acute HIV mouse model



Susceptible to HIV

Protected against HIV

Reconstitution of SCID-humanised mice with **shPromA-transduced PBMC or CD34 stem cells** suppresses acute HIV-1 infection

Suzuki et al., MTNA 2013; Ahlenstiel *et al.*, Frontiers in Immunology Review 2015

SORUN

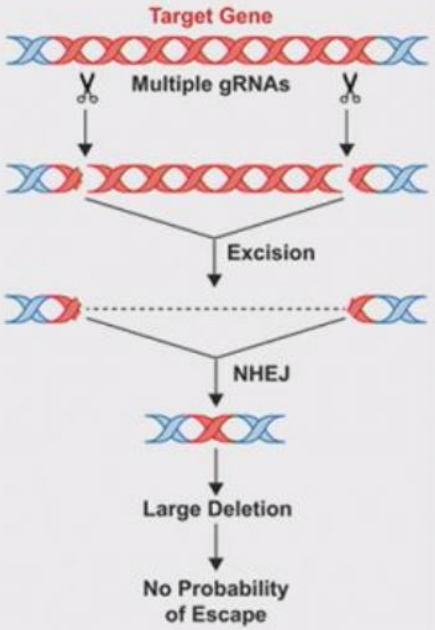
rezervin olduğu hücrelere bu kilitleyici nükleotid dizilerini aktarabilmek

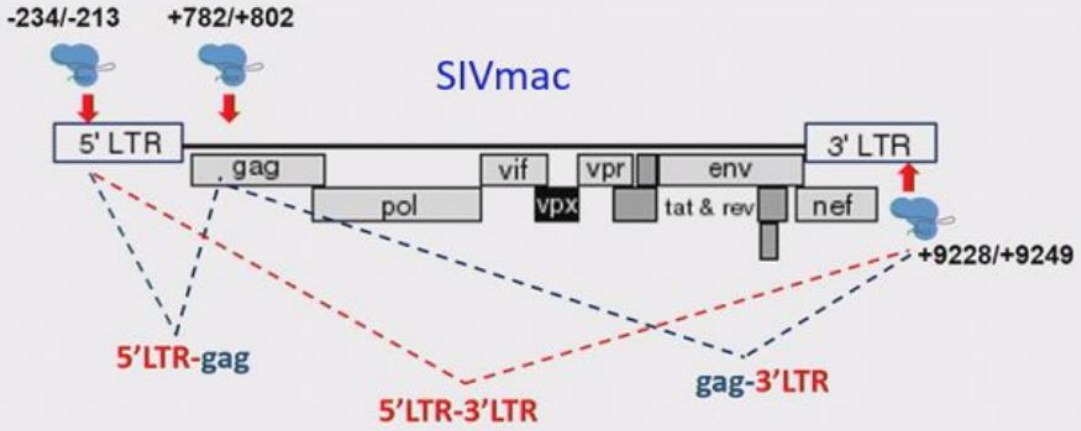
EX VIVO AND IN VIVO EDITING OF THE SIV GENOME IN NONHUMAN PRIMATES BY CRISPR-CAS9

Tricia H. Burdo
Temple University School of Medicine
Philadelphia, PA, USA

CROI 2019
Conference on Retroviruses and Opportunistic Infections
4–7 March, SEATTLE

Targeting LTRs and gag of the SIV genome with CRISPR/Cas9 multiplex gRNAs

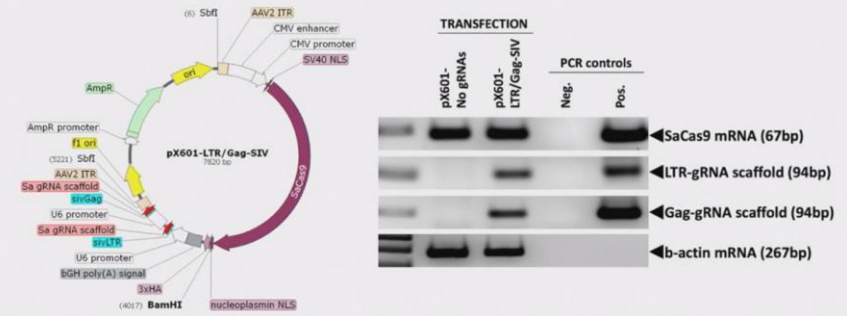




LTR gRNA/PAM- AGGCATATGTTAGATACCCAGAAGAGT

Gag gRNA/PAM- GCGTCATCTGGTGCATTCACGCAGAAG

All-in-one AAV delivery vector



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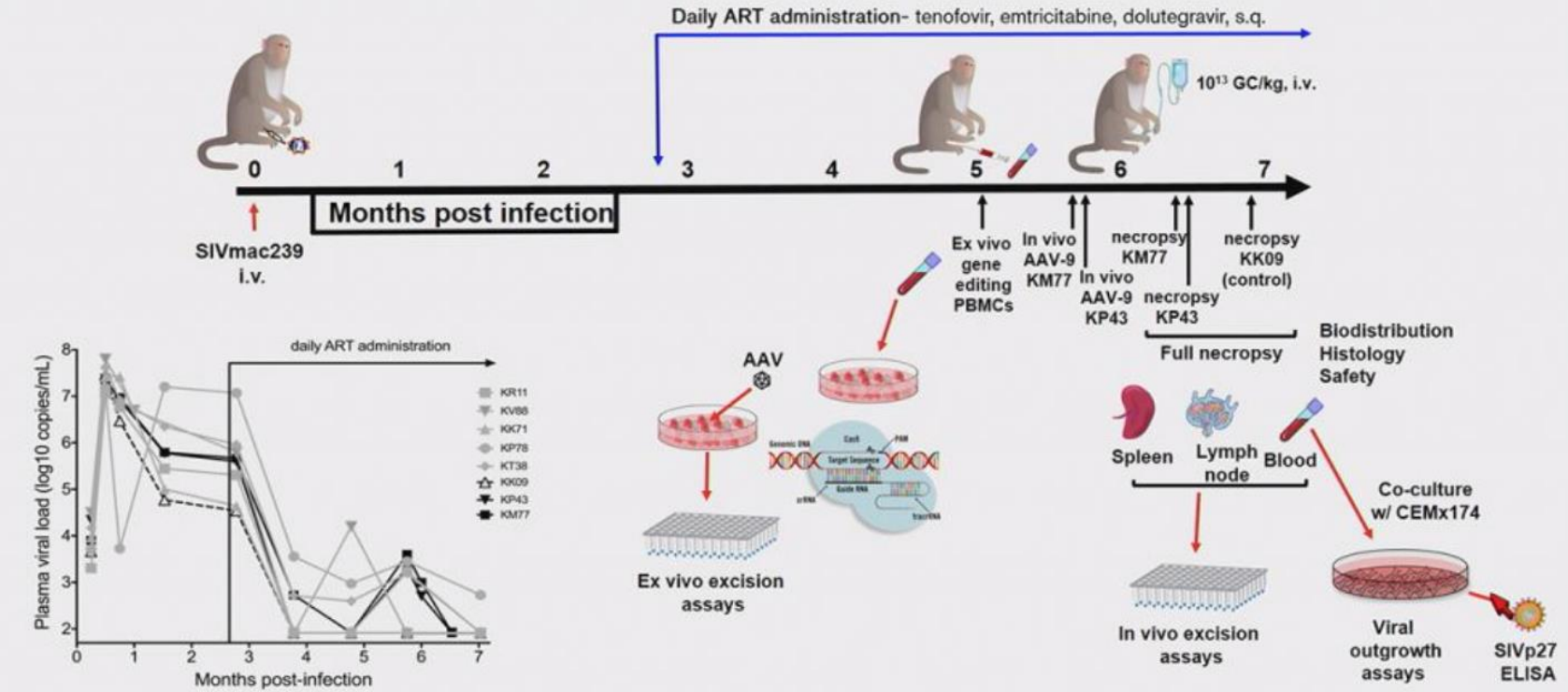
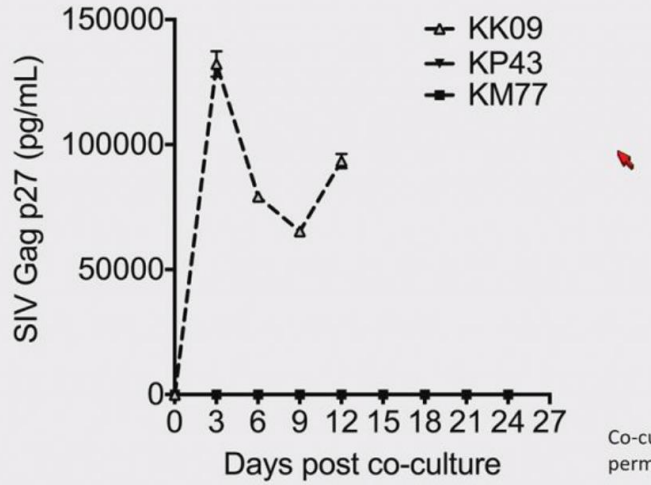
Non-human primate experimental design



No viral outgrowth from PBMCs from NHP after *in vivo* CRISPR-Cas9



Co-culture with permissive CEM

HIV kürü için immunoterapi

- Şimdiye kadar başarısız oldu
- İmmünojenliğin zayıf oluşu
  - Varolan immün baskın yanıt
  - Sitotoksik T lenfositlerden kaçış
- İnflamasyon ve ters yönde çalışan regulatuvar immünsupresyon
- Dokularda immün kontrolden saklanılan bölgeler

AIDS 2018 22nd INTERNATIONAL AIDS CONFERENCE
AMSTERDAM, NETHERLANDS
23-27 JULY 2018
BREAKING BARRIERS • BUILDING BRIDGES

Durable Control of HIV Infection in the Absence of Antiretroviral Therapy: Opportunities and Obstacles

Anthony S. Fauci, M.D.
Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health

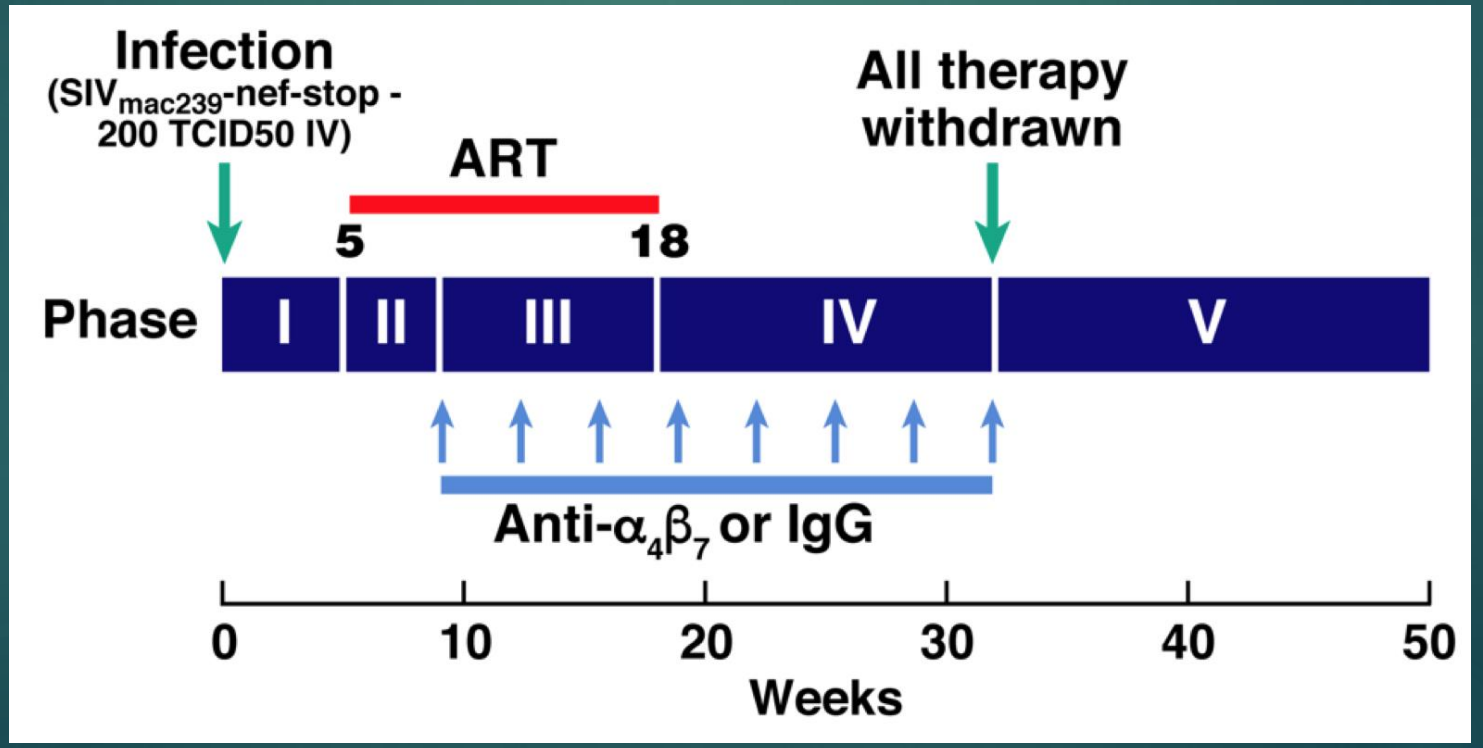
July 25, 2018

NIH National Institute of Allergy and Infectious Diseases

Thank you very much, Pedro. A

Evaluation of an antibody to Alpha4Beta7 in the control of SIV infection

Michele Di Mascio, Jeffrey D. Lifson, Sharat Srinivasula, Paula DeGrange, Brandon Keele, Yuge Wang, Paolo Lusso, Michael Proschan, H. Clifford Lane, Anthony S. Fauci

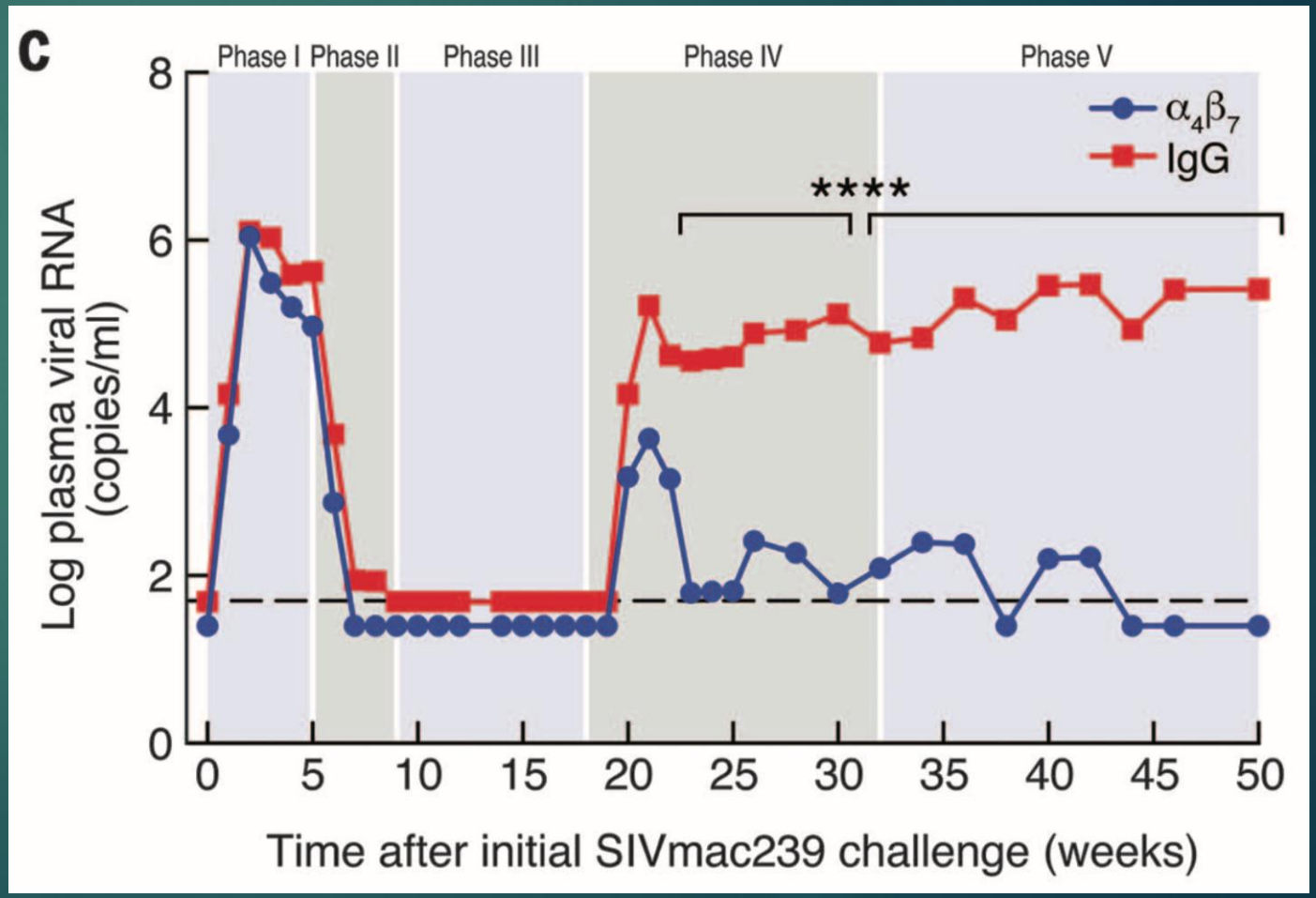


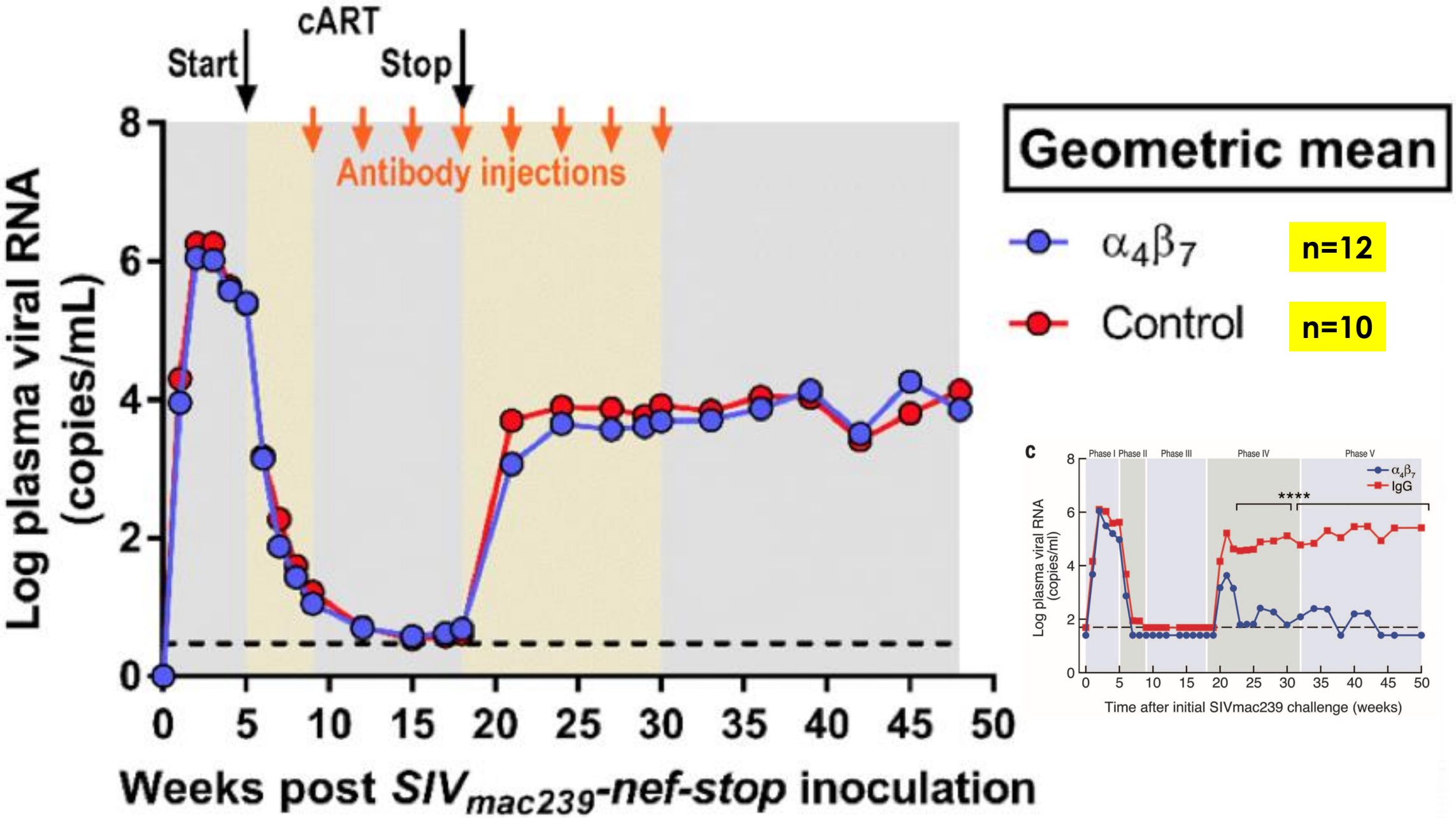
Sustained virologic control in SIV$^+$ macaques after antiretroviral and $\alpha_4\beta_7$ antibody therapy

Siddappa N. Byrareddy,[1*†] James Arthos,[2*] Claudia Cicala,[2*] Francois Villinger,[1,3‡] Kristina T. Ortiz,[1] Dawn Little,[1] Neil Sidell,[4] Maureen A. Kane,[5] Jianshi Yu,[5] Jace W. Jones,[5] Philip J. Santangelo,[6] Chiara Zurla,[6] Lyle R. McKinnon,[7§] Kelly B. Arnold,[8] Caroline E. Woody,[8] Lutz Walter,[9] Christian Roos,[9] Angela Noll,[9] Donald Van Ryk,[2] Katija Jelicic,[2] Raffaello Cimbro,[10] Sanjeev Gumber,[3] Michelle D. Reid,[1] Volkan Adsay,[1] Praveen K. Amancha,[3] Ann E. Mayne,[1] Tristram G. Parslow,[1] Anthony S. Fauci,[2] Aftab A. Ansari[1||]

SCIENCE

14 OCTOBER 2016 • VOL 354 ISSUE 6309



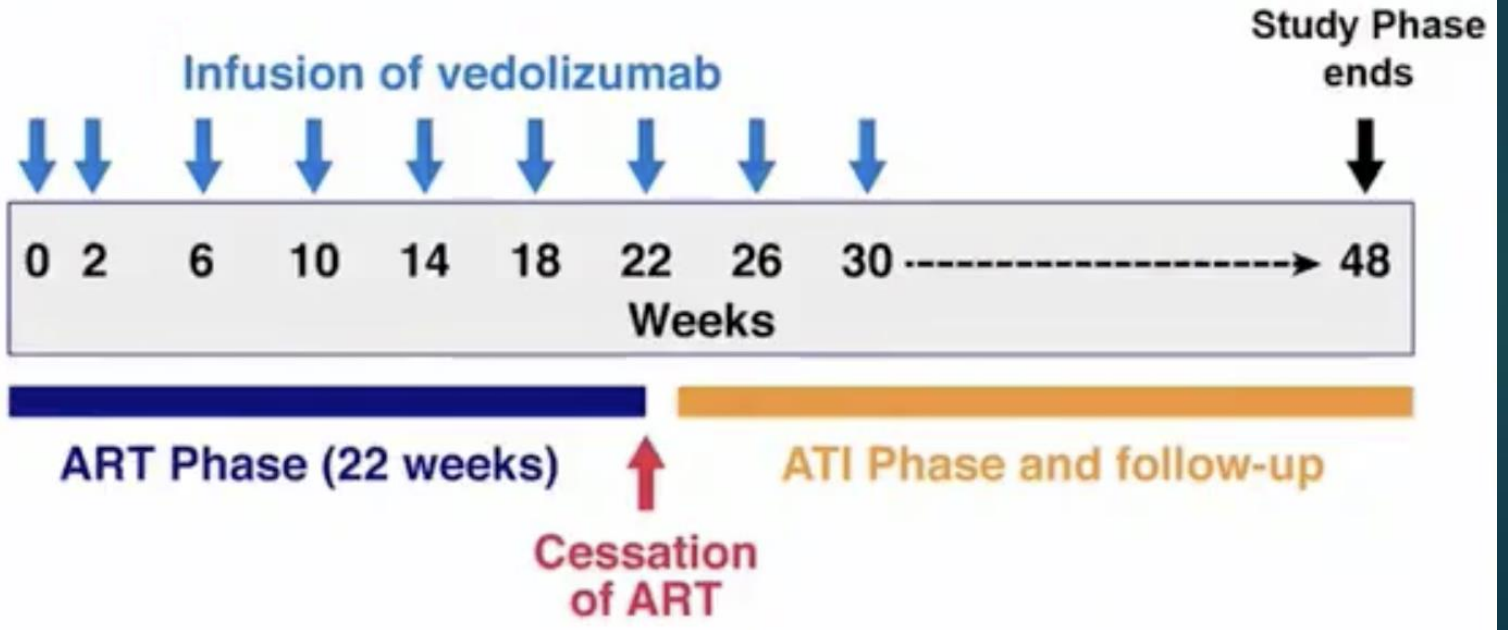

cART
Start
Stop
Antibody injections
Log plasma viral RNA (copies/mL)
Weeks post SIVmac239-nef-stop inoculation
Geometric mean
α4β7
n=12
Control
n=10
c
Phase I
Phase II
Phase III
Phase IV
Phase V
α4β7
IgG
****
Log plasma viral RNA (copies/ml)
Time after initial SIVmac239 challenge (weeks)

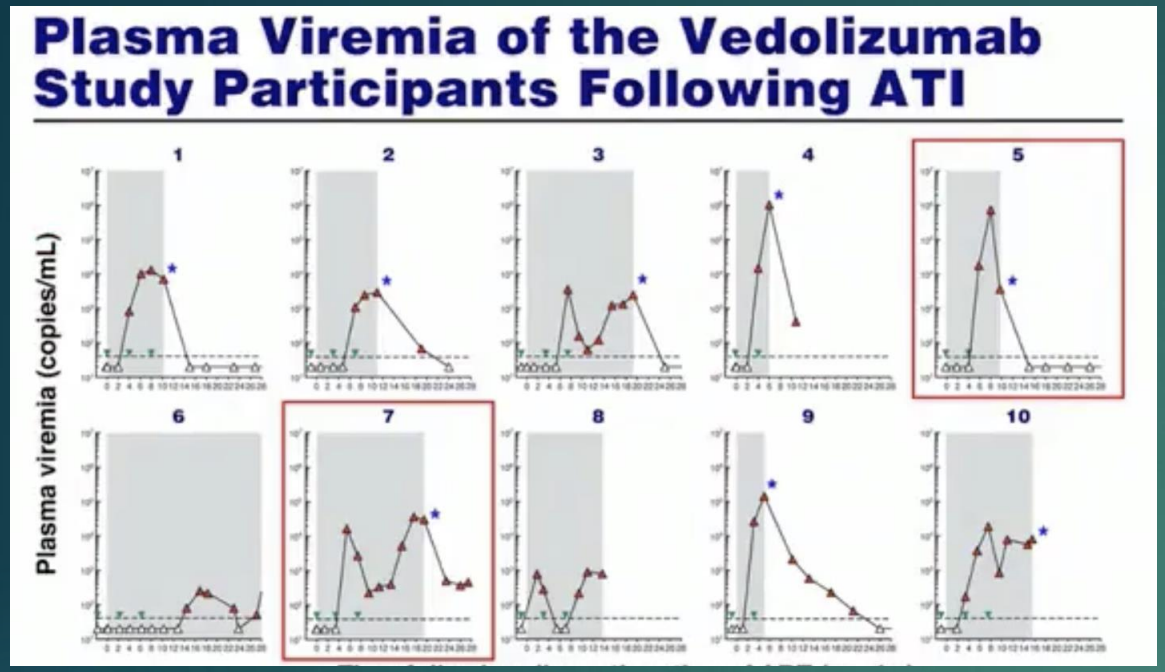
An Exploratory Open-Label Study of Vedolizumab (anti-$\alpha_4\beta_7$ Monoclonal Antibody) in Subjects with HIV Infection Undergoing Analytical Treatment Interruption

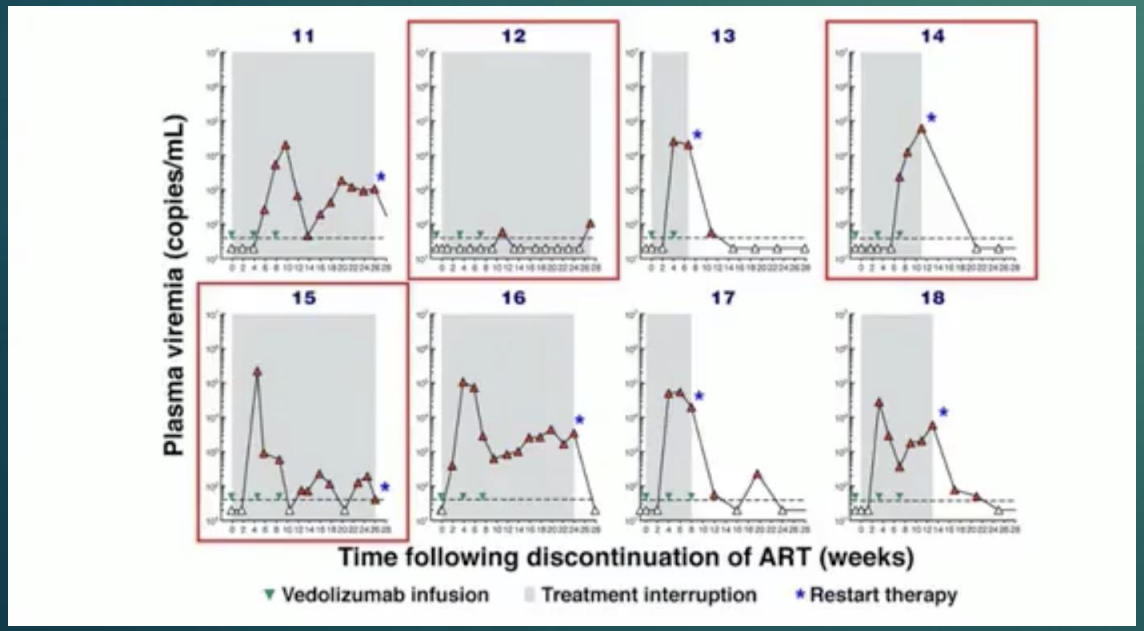
Principal Investigator: Michael C. Sneller, M.D.
Associate investigators: Anthony S. Fauci, M.D., Tae-Wook Chun, Ph.D., Susan Moir, Ph.D., Katherine Clarridge, M.D., Avi Nath, M.D., Bryan Smith, M.D.

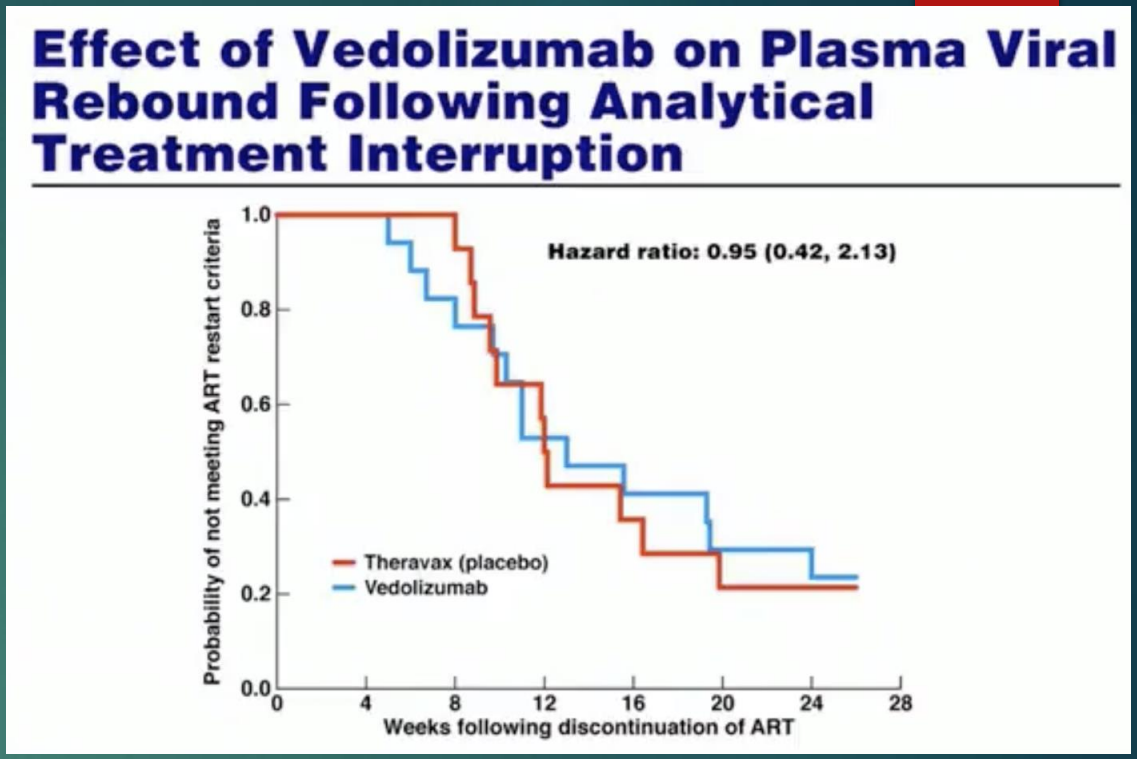
- **ClinicalTrials.gov Identifier:** NCT02788175
- 18 volunteers enrolled

- Age 18-65 years
- Good general health
- $CD4^+$ T cell count >450/μL
- Documented suppressed viremia for ≥2 years on cART
- Absence of chronic HBV or HCV







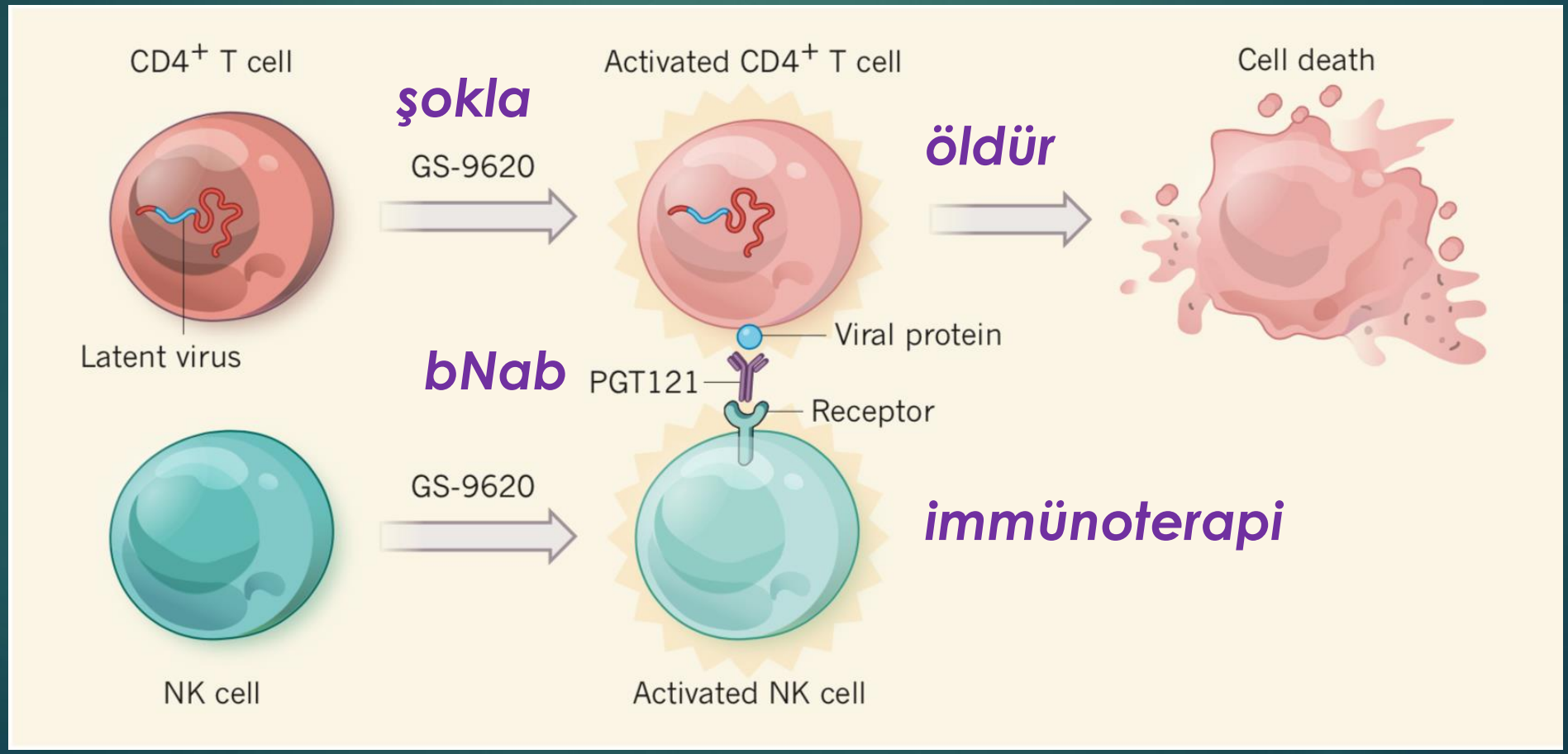


- Anti-$\alpha_4\beta_7$ çalışmalarında primat model ile insan arasındaki farklar?
  - antikorlardaki farklılık_Fc kısımları
  - çalışma tasarım farkları_ART tekrar başlama kriterleri
  - konak farklılıkları

Antibody and TLR7 agonist delay viral rebound in SHIV-infected monkeys

Erica N. Borducchi[1,6], Jinyan Liu[1,6], Joseph P. Nkolola[1,6], Anthony M. Cadena[1,6], Wen-Han Yu[2], Stephanie Fischinger[2], Thomas Broge[2], Peter Abbink[1], Noe B. Mercado[1], Abishek Chandrashekar[1], David Jetton[1], Lauren Peter[1], Katherine McMahan[1], Edward T. Moseley[1], Elena Bekerman[3], Joseph Hesselgesser[3], Wenjun Li[4], Mark G. Lewis[5], Galit Alter[2], Romas Geleziunas[3] & Dan H. Barouch[1,2]*

| NATURE | VOL 563 | 15 NOVEMBER 2018



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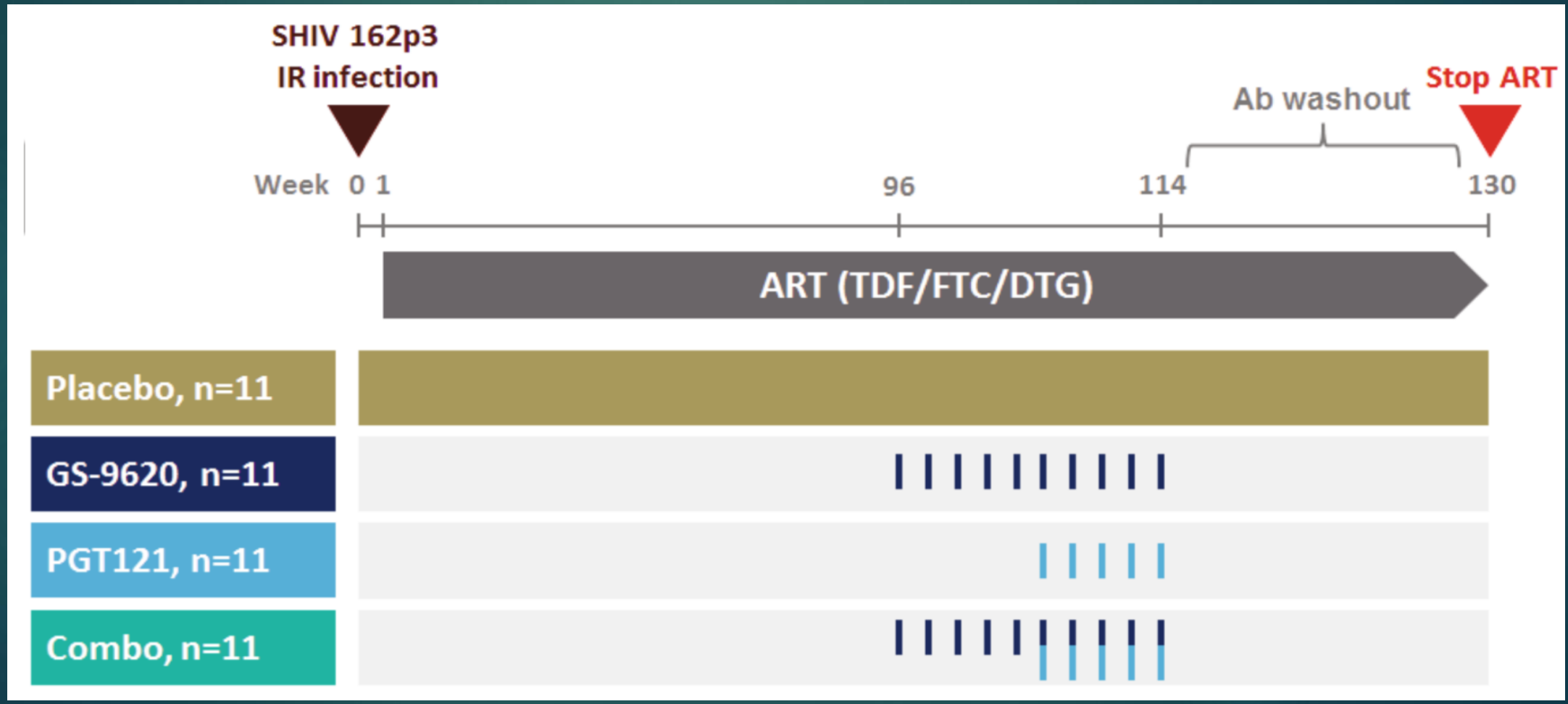

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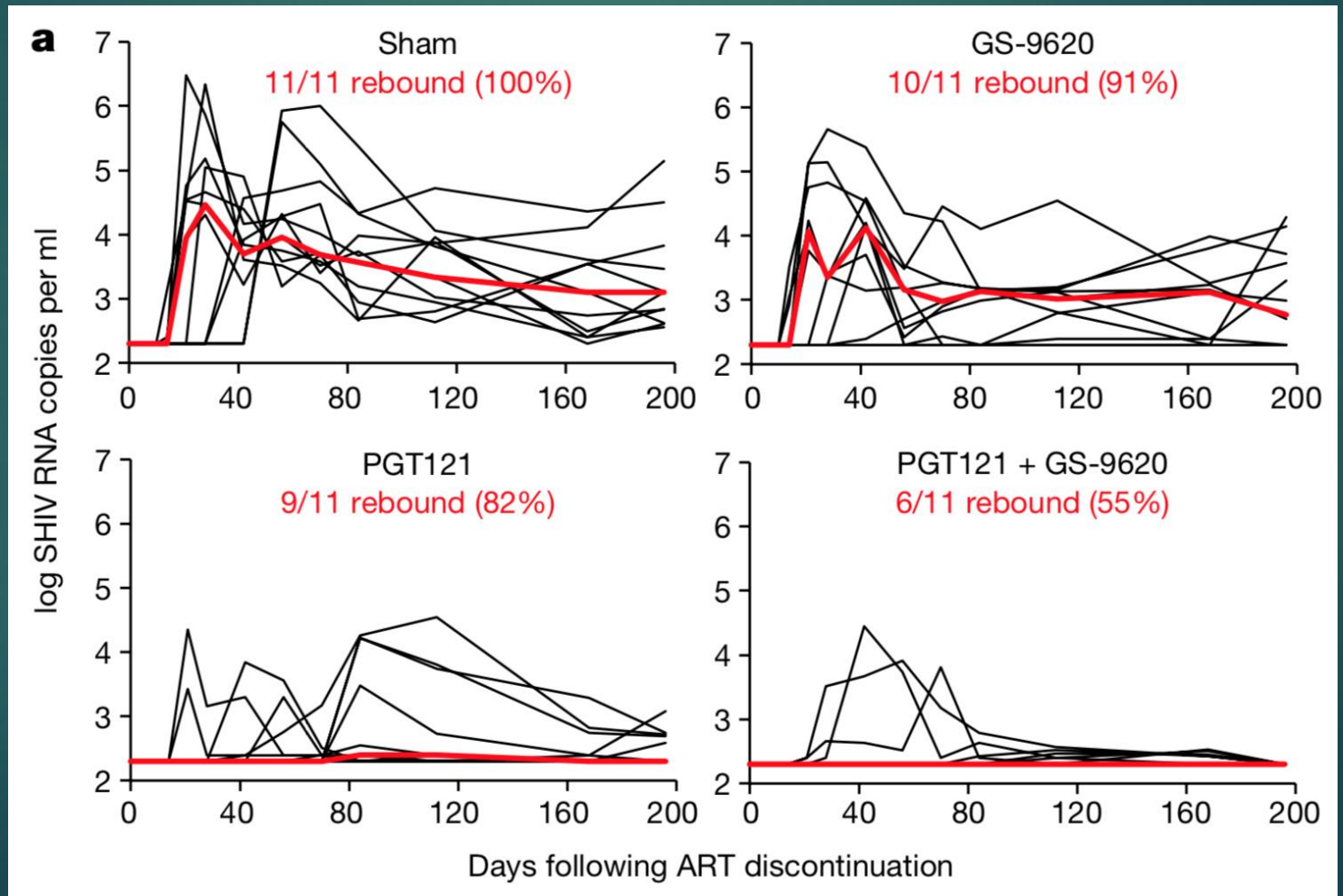
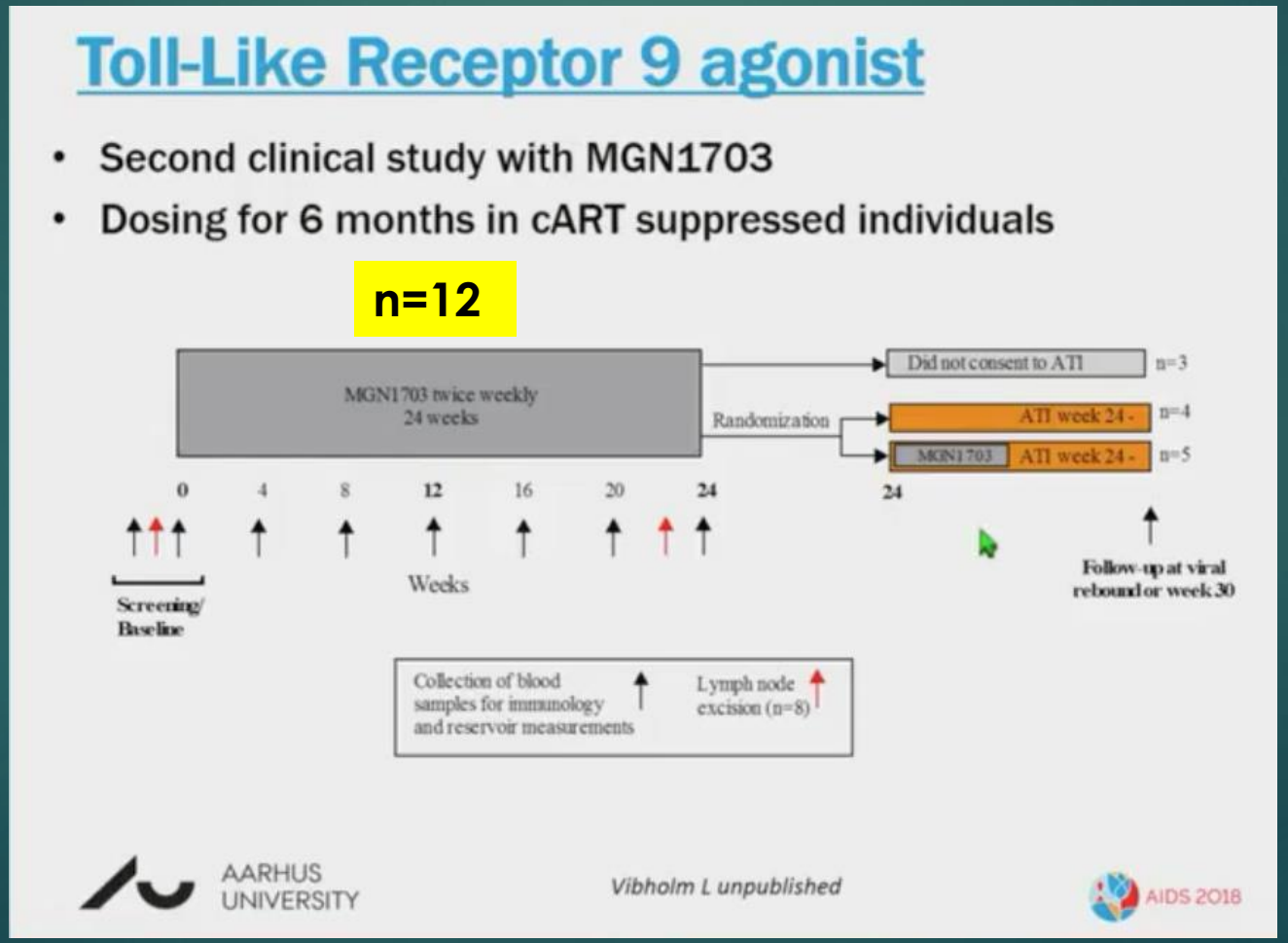


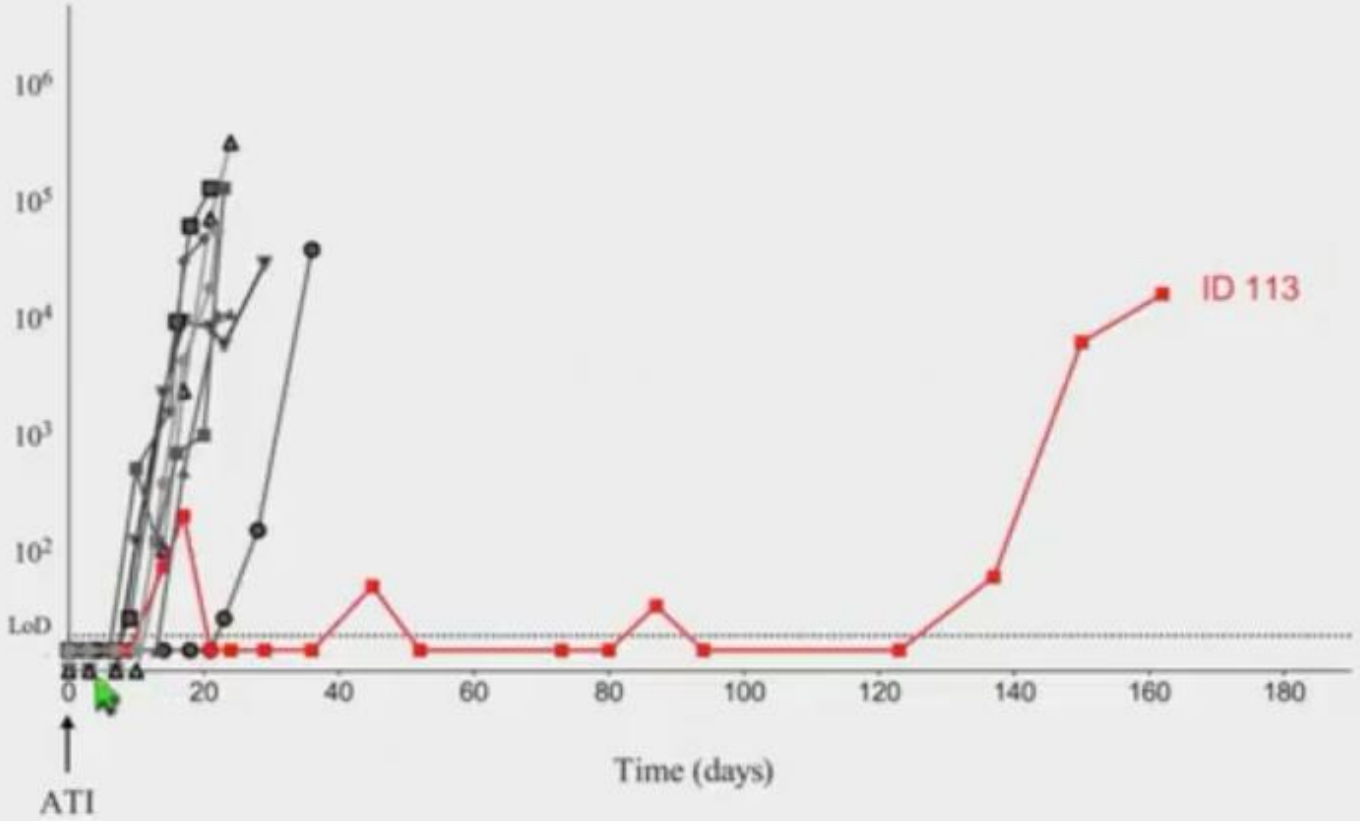
TLR agonists and latency reversal: can they both shock and kill?

Martin Tolstrup, Aarhus University



Analytical Treatment Interuption

n=9



- **Patient 113 was capable of prolonged immune control of HIV-1 infection for more than 24 weeks during cART interruption (ATI).**

AARHUS UNIVERSITY

Vibholm L unpublished

AIDS 2018

Toll-Like Receptor 9 agonist

- **Shock:**
  - No clear induction of HIV transcription in peripheral CD4+
  - Clear impact on plasma viral load
  - Opposing effects from latency reversal and IFN-stimulated antiviral responses
- **Kill:**
  - Powerfull systemic activation of immune effector cells
  - Enhancement of HIV-specific CD4 and CD8 T cell responses
  - No reduction in any reservoir measures
  - One participant controlled virus for 24 weeks in absence of cART despite a relative large reservoir

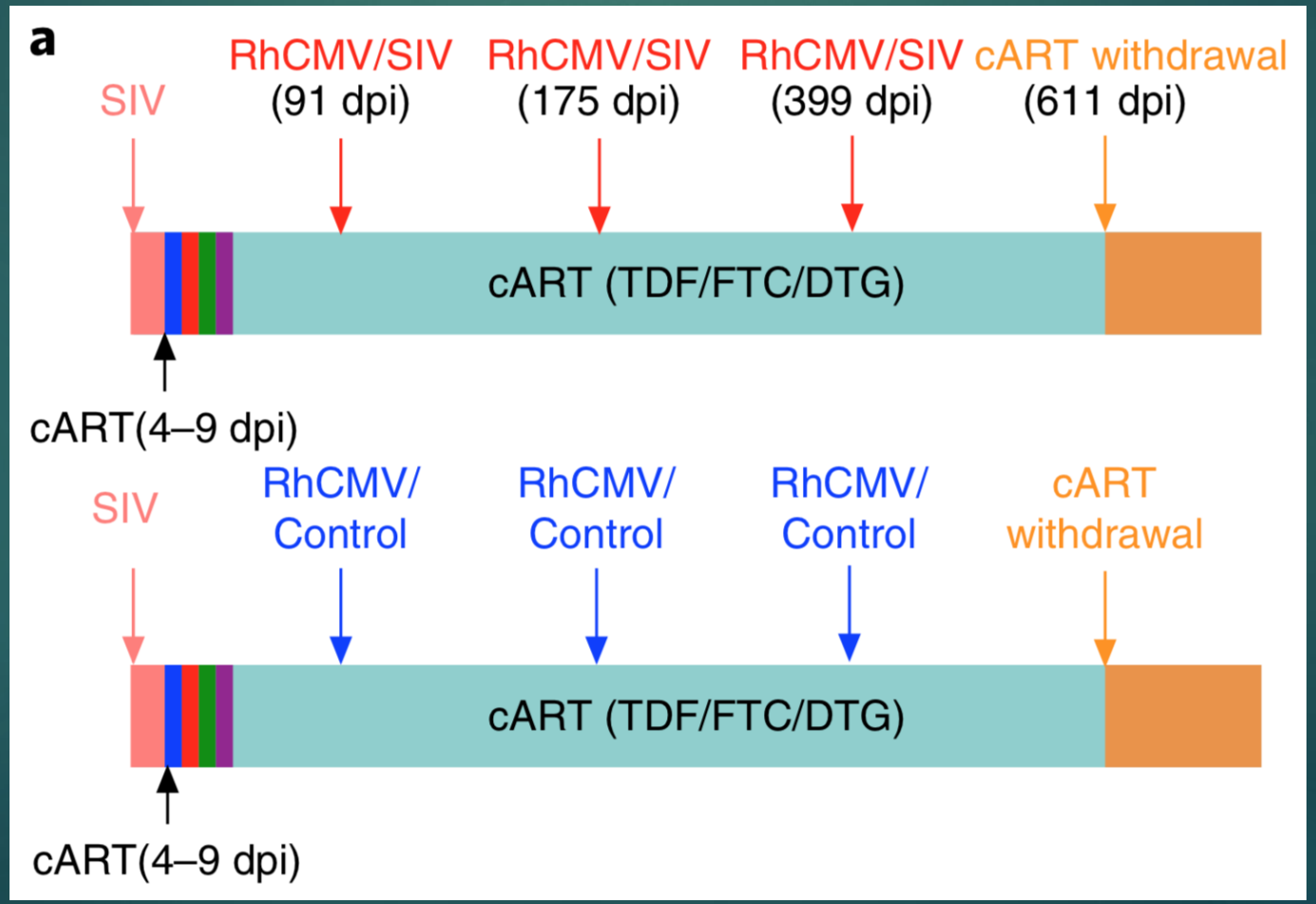
AARHUS UNIVERSITY

AIDS 2018

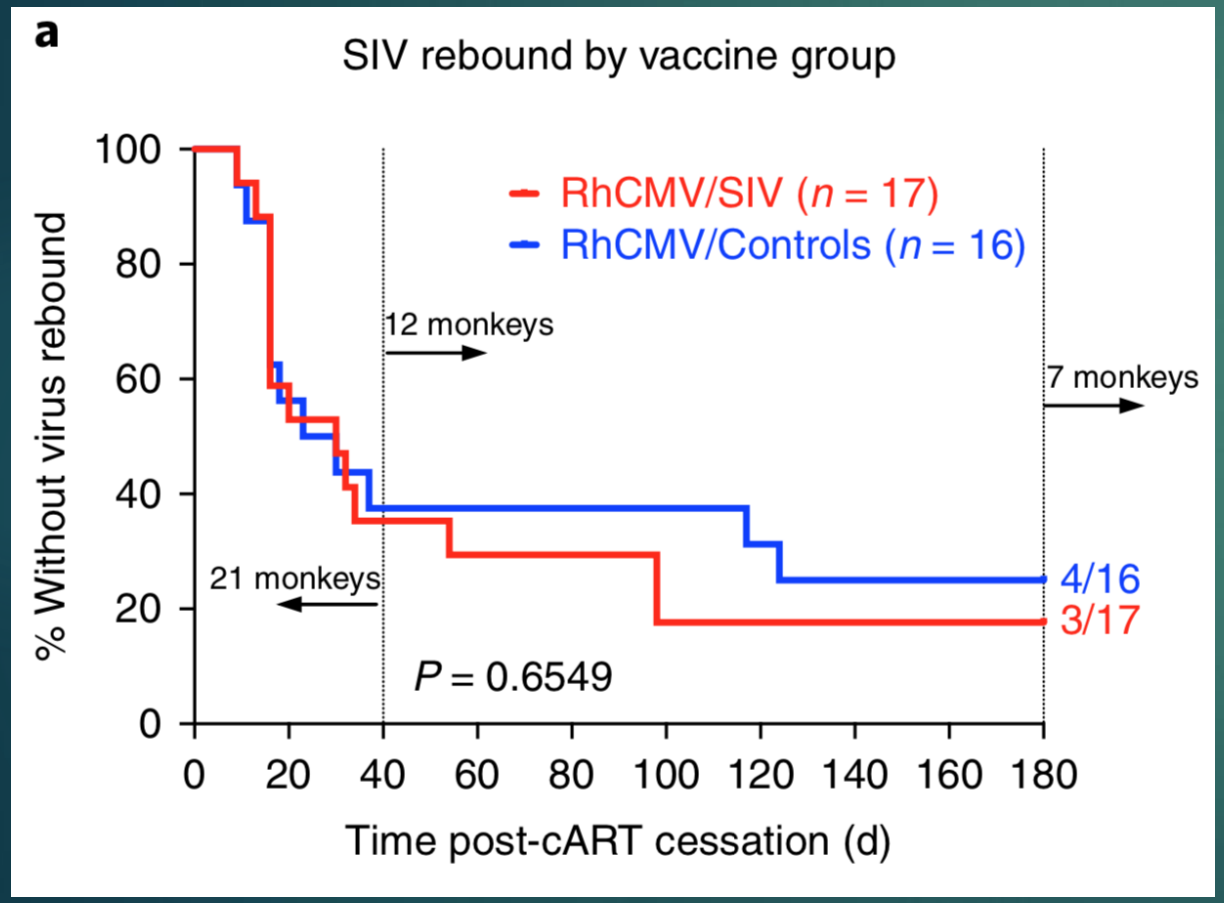
Early antiretroviral therapy limits SIV reservoir establishment to delay or prevent post-treatment viral rebound

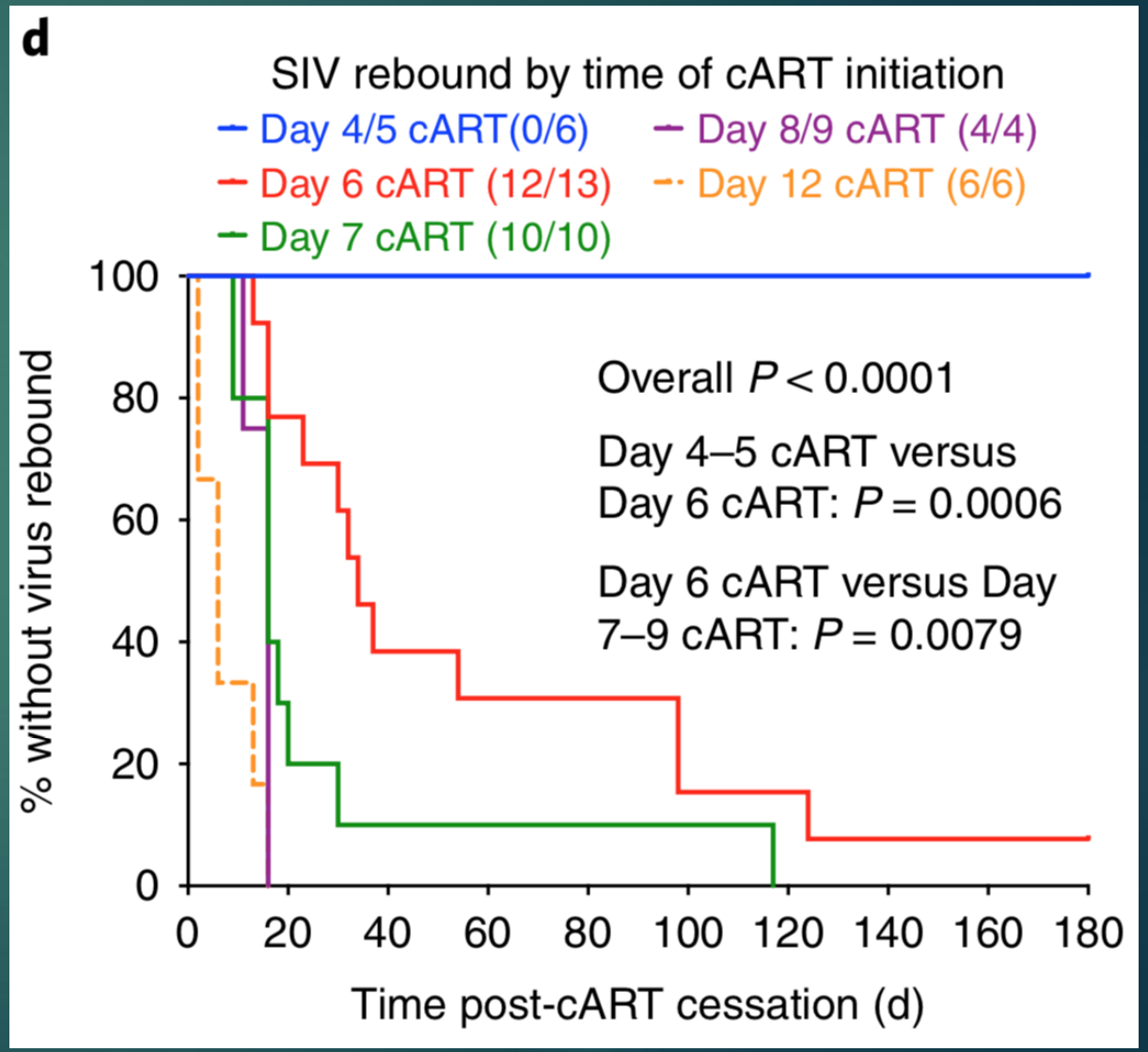
Afam A. Okoye[1], Scott G. Hansen[1], Mukta Vaidya[1], Yoshinori Fukazawa[1], Haesun Park[1], Derick M. Duell[1], Richard Lum[1], Colette M. Hughes[1], Abigail B. Ventura[1], Emily Ainslie[1], Julia C. Ford[1], David Morrow[1], Roxanne M. Gilbride[1], Alfred W. Legasse[1], Joseph Hesselgesser[2], Romas Geleziunas[2], Yuan Li[3], Kelli Oswald[3], Rebecca Shoemaker[3], Randy Fast[3], William J. Bosche[3], Bhavesh R. Borate[4], Paul T. Edlefsen[4], Michael K. Axthelm[1], Louis J. Picker[1]* and Jeffrey D. Lifson[3]*

NATURE MEDICINE | VOL 24 | SEPTEMBER 2018 | 1430–1440 |



Early antiretroviral therapy limits SIV reservoir establishment to delay or prevent post-treatment viral rebound





Research-for-Cure Academy

Krista Dong

Nationality: South Africa
Institution: FRESH Clinical Cohort / UKZN / MGH / Ragon Institute
Country of work: South Africa

TOWARDS AN HIV CURE
PEOPLE FOCUSED
SCIENCE DRIVEN

What is your current area of research?

In 2012 I helped design the FRESH Cohort to enable study of the earliest immunological events following HIV infection. Located in hyper-endemic KwaZulu-Natal, South Africa (>50% antenatal prevalence), FRESH has enrolled over 1,400 at risk, HIV-negative young women and identified 74 hyperacute infections, for an incidence rate of 8.2%. The majority are detected during Fiebig stage 1, a median of 4-days after their last negative HIV RNA and started on immediate ART. We are currently preparing to implement a clinical trial aimed at cure, with a combination of broadly neutralizing antibodies (bNAbs) and a latency reversal agent.

CAR T cells for infection, autoimmunity and allotransplantation

*Colby R. Maldini[1,2], Gavin I. Ellis[1,2] and James L. Riley[1]**

NATURE REVIEWS | IMMUNOLOGY

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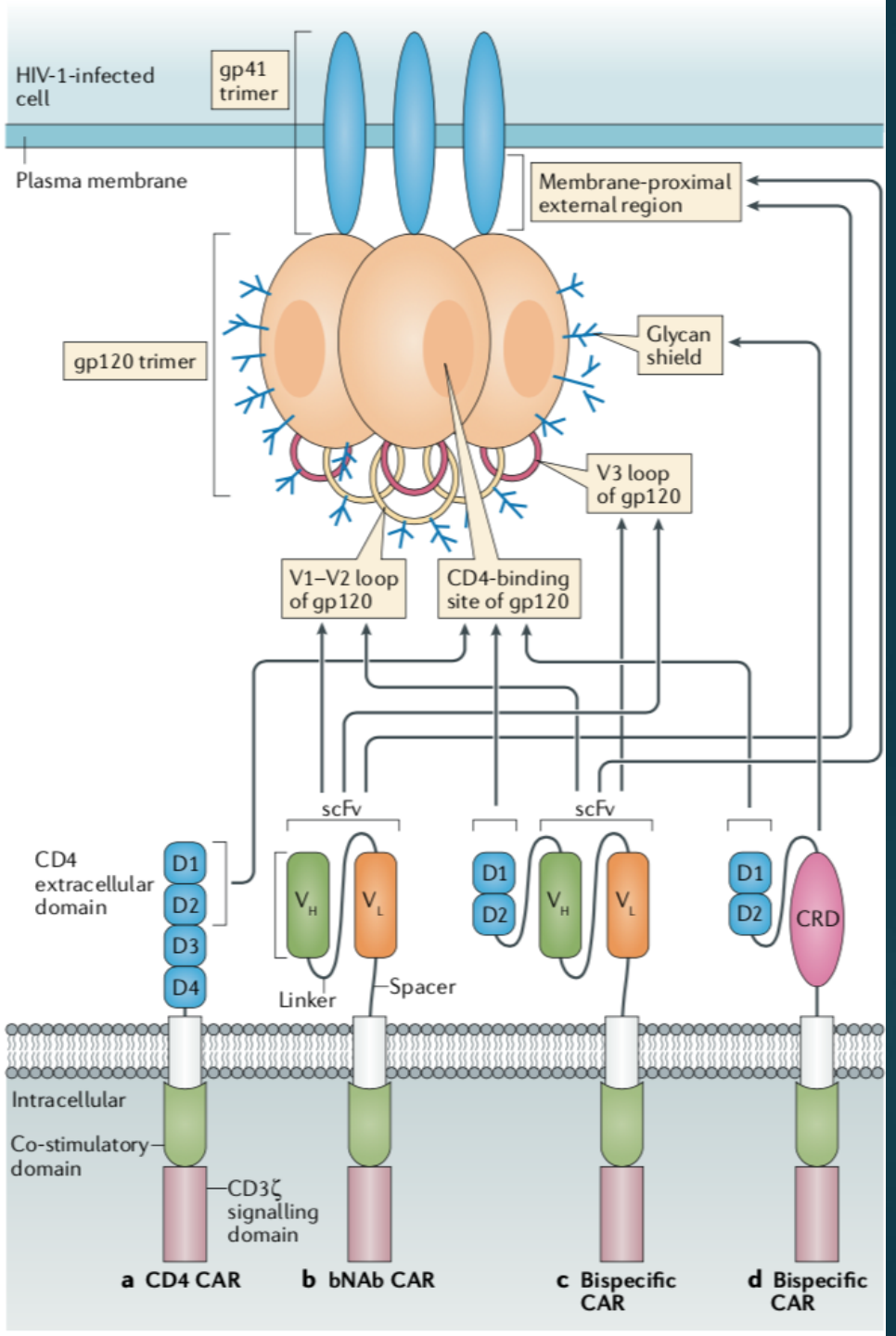
CD4-based CARs for HIV-1



Therapeutic vaccines

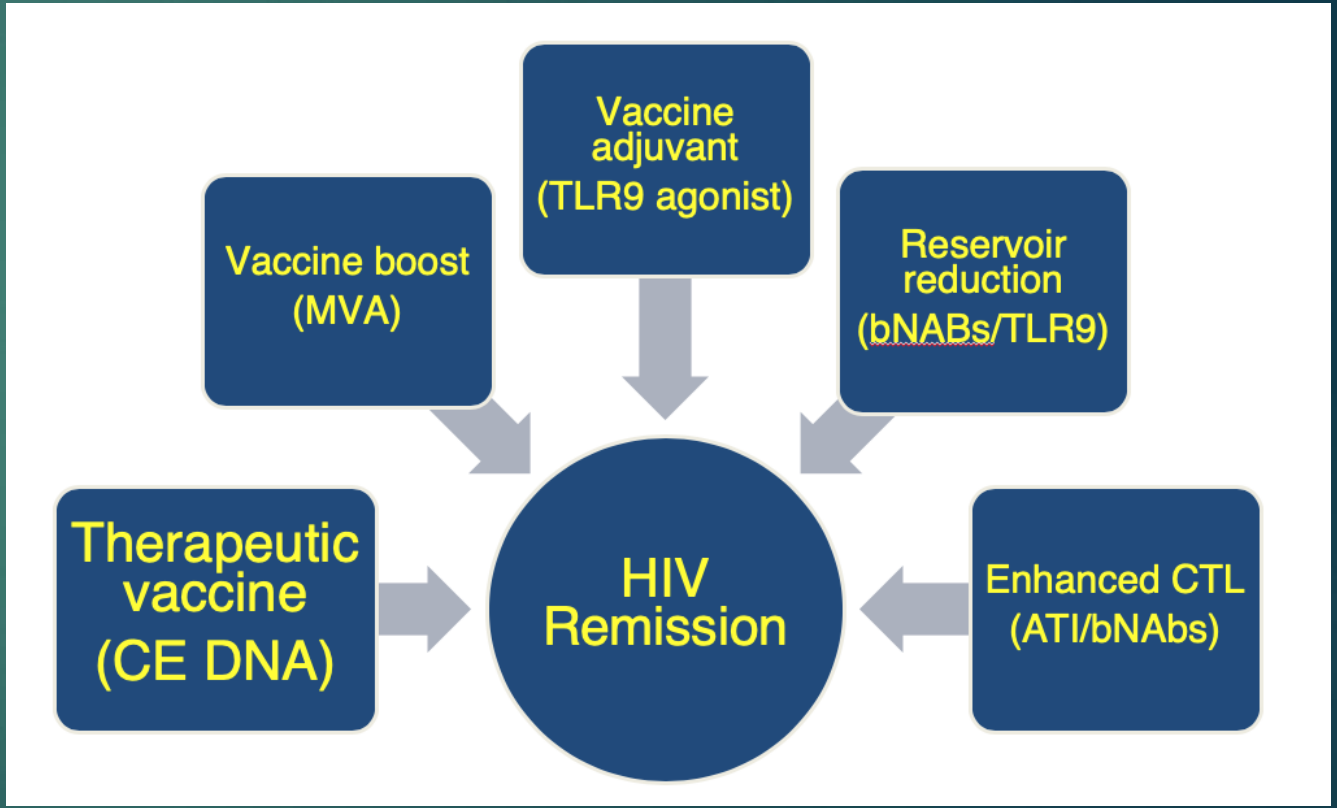
Harnessing the Immune System to Control HIV

Steven Deeks, MD
Professor of Medicine
University of California, San Francisco

UCSF University of California San Francisco · ACTG AIDS CLINICAL TRIALS GROUP · Delaney AIDS Research Enterprise DARE to find a cure · amfAR Institute FOR HIV CURE RESEARCH

AIDS 2018

All models of durable SIV/HIV control suggest the need for (1) a low disease burden, (2) low inflammation and (3) sustained host responses that are primed, reside in tissues, and target susceptible epitopes



HIV Kürü

- Hedef remisyon
  - ART olmadan uzun dönemli saptanamaz viremi
- Rezerv en önemli engel
  - çok erken oluşuyor, iyi dağılıyor, yok etmesi zor
- Denemelerde güvenlik ön planda olmalı
  - Kontrol göstergesi olarak analitik tedavi kesimi kaçınılmaz
  - Analitik tedavi kesiminin standardizasyonu
- *İmmunoterapiyi de içeren kombine bir müdahale rezervi azaltma ve kontrol etmede en umut veren yaklaşım*

XX. TÜRK KLİNİK MİKROBİYOLOJİ VE İNFEKSİYON HASTALIKLARI KONGRESİ

HIVÇG

KÜR ÇALIŞMALARINDA SON DURUM

İLGİNİZ İÇİN TEŞEKKÜRLER!

DOÇ. DR. ULUHAN SİLİ

uluhan@hotmail.com

MARMARA ÜNİVERSİTESİ 1883

Tıp Fakültesi

UK patient likely to be the second person cured of HIV: two further cases at CROI 2019 of HIV remission after allogenic stem cell transplants

Simon Collins, HIV i-Base

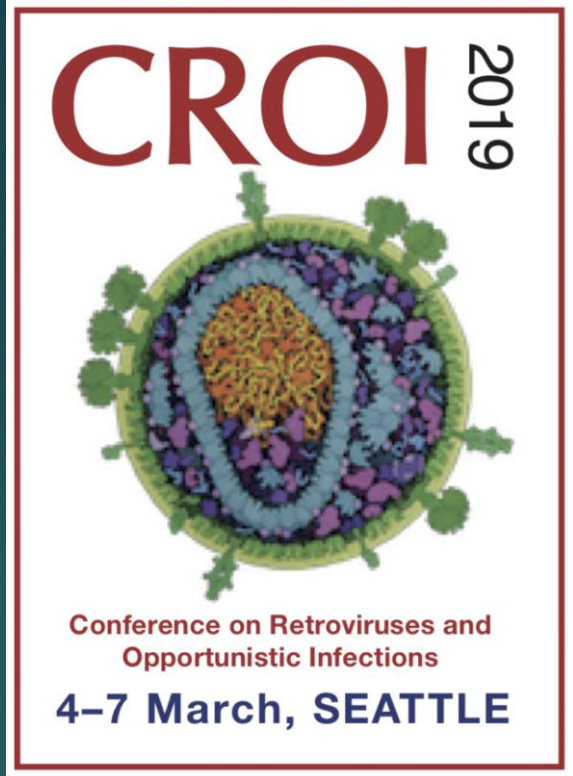


Table 1: Summary regimens of UK, Dusseldorf and Berlin patients

	UK patient	Dusseldorf patient	Berlin patient
Underlying condition	HL	AML	AML
ASCT, donor CCR5-d32/d32	Once	Once	Twice
Conditioning	reduced intensity: anti–CD52 (alemtuzumab)	reduced intensity: fludarabine/ treosulfan	Total body irradiation (twice)
GvH disease	Grade 1	Grade 1	Grade 1
ART post-transplant	16 months	66 months	None
Time with HIV remission	18 months	3 months	> 10 years

HIV Immunotherapy: Decades of experimental research have largely failed to identify any promising interventions

Trial	Regimen	Comment	Author/Paper
ACTG 5068	ALVAC (vCP1452)	Intermitting interruptions but not vaccine associated with reduced VL	Jacobson, JID 2006
ACTG 5024	ALVAC (vCP1452) + IL-1	0.5 log VL reduction during ATI	Kilby, JID 2006
ACTG 5097	Ad5	0.24 log10	Schooley, JID 2010
MANON-02	ALVAC-HIV	No VL effect; activated CD4 cells may have induced early failure	Papagno, AIDS 2011
Bionor	p24 peptide mixture (Vacc-4x)	ATI: no VL effect at primary endpoint, mild benefit at later time points	Pollard, Lancet HIV 2014
ERAMUNE 02	DNA prime/MVA boost	No effect (HIV DNA)	Achenbach, Lancet HIV 2015
GeneCure	Replication-defective HIV with VZV fusion protein (HIVAX)	Reduced VL set-point (compared to historical data)	Tung, Vaccine 2016
GeoVax	DNA prime/MVA boost (virus-like particles)	No apparent effect during ATI (uncontrolled)	Thompson, PLoS ONE 16
ACTG 5281	Gag/Pol, Nef/Tat/Vif/Env and IL-12 plasmids (Profectus)	Minimal CD4 effects, no CD8 effects, low dose IL-12 better than high dose IL-12	Jacobson, JAIDS 2016
BCN 02	ChAdV63.HIVconsv + MVA.HIVconsv	5/13 controlled (ATI)	Mothe, CROI 17

Slide courtesy of Steven Deeks

HIV "Cure": Target Product Profile

The Journal of Infectious Diseases

MAJOR ARTICLE

Identifying Key Drivers of the Impact of an HIV Cure Intervention in Sub-Saharan Africa

Andrew N. Phillips,[1] Valentina Cambiano,[1] Paul Revill,[3] Fumiyo Nakagawa,[1] Jens D. Lundgren,[4] Loveleen Bansi-Matharu,[1] Travor Mabugu,[5] Mark Sculpher,[3] Geoff Garnett,[7] Silvija Staprans,[7] Stephen Becker,[11] Joseph Murungu,[6] Sharon R. Lewin,[9,10] Steven G. Deeks,[8] and Timothy B. Hallett[2]

Efficacy: aviremia in absence of therapy > 2 years; early failure is tolerable, late failures must be rare

Product: administered for limited period of time (e.g., 6 months); specialized (tertiary) care not required

Target Population: effective ART initiated at any stage and in all populations

Long-term safety: comparable to ART, transmission risk negligible

Cost: < $1400 (RLS)

BILL & MELINDA GATES foundation

Slide courtesy of Steven Deeks

Duration of Treatment Interruption in Study Subjects