HIV Cure: Are we making any progress?

ZUCKERBERG SAN FRANCISCO GENERAL
Hospital and Trauma Center

Steven Deeks, MD
Professor of Medicine
Division of HIV, Infectious Diseases, and Global Medicine
Zuckerberg San Francisco General
University of California, San Francisco

Delaney AIDS Research Enterprise DARE to find a cure
CIRM CALIFORNIA'S STEM CELL AGENCY
BILL & MELINDA GATES foundation
ACTG AIDS CLINICAL TRIALS GROUP
amfAR Institute FOR HIV CURE RESEARCH

It is not likely economically nor logistically feasible to deliver daily antiretroviral therapy (ART) to > 38 million people with HIV for their entire lives

Tony Fauci

HIV Cure: Background

- Only ~1% of genomes are intact and only a subset of these are inducible (the “replication-competent reservoir”)
  - Assays to measure relevant reservoir in development (IPDA, imaging) but treatment interruptions remain most informative
- Reservoir primarily maintained by clonal proliferation
  - Antigen (CMV), cytokines (IL-7), integration events
- SIV/SHIV remission (durable control) and even cure (eradication) achieved in many monkey experiments; progress in people limited

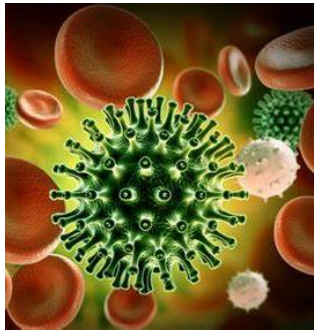
How will HIV be cured?

HIV cure strategies

Most approaches involve combination of reservoir reduction and immune enhancement ("reduce and control"), with growing interest in gene therapy and eventually "one shot" cures

Early ART

Latency reversal
Latency silencing

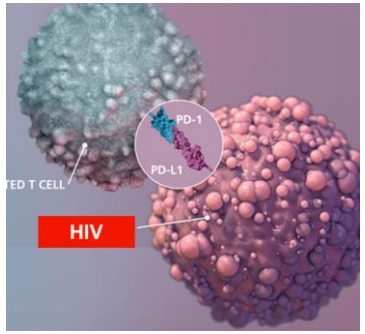


Gene therapy

Reservoir reduction and elimination

Vaccines
Antibodies

Immunotherapy

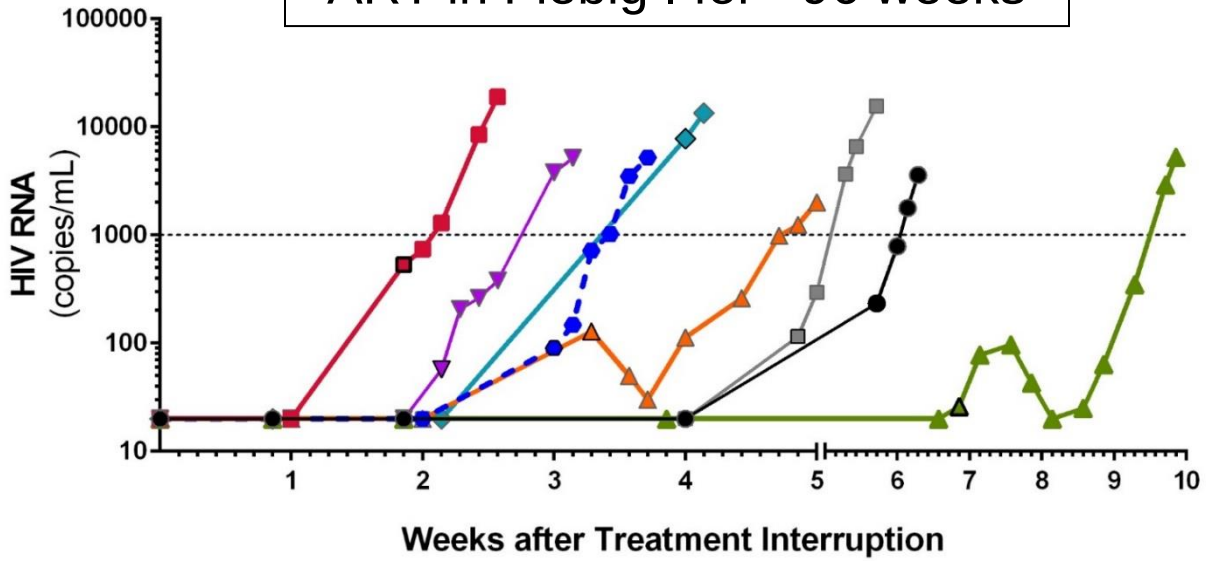


Immune enhancement

Early ART

Very early ART (including “Fiebig 0”) is not curative

ART in Fiebig I for >96 weeks

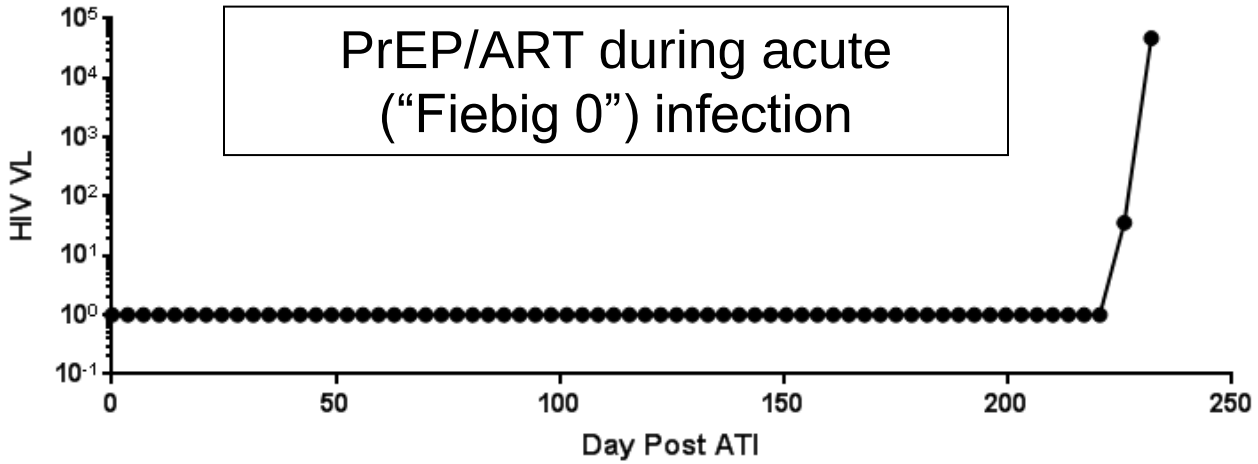


nature medicine

Rapid HIV RNA rebound after antiretroviral treatment interruption in persons durably suppressed in Fiebig I acute HIV infection

Donn J. Colby[1], Lydie Trautmann[2,3], Suteeraporn Pinyakorn[2,3], Louise Leyre[4], Amélie Pagliuzza[4], Eugène Kroon[1], Morgane Rolland[2,3], Hiroshi Takata[2,3], Supranee Buranapraditkun[2,3,5,6], Jintana Intasan[1], Nitiya Chomchey[1], Roshell Muir[7], Elias K. Haddad[7], Sodsai Tovanabutra[2,3], Sasiwimol Ubolyam[8], Diane L. Bolton[2,3], Brandie A. Fullmer[9], Robert J. Gorelick[9], Lawrence Fox[10], Trevor A. Crowell[2,3], Rapee Trichavaroj[11], Robert O'Connell[11], Nicolas Chomont[4], Jerome H. Kim[2,13], Nelson L. Michael[2], Merlin L. Robb[2,3], Nittaya Phanuphak[1], Jintanat Ananworanich[1,2,3,12*]
and The RV411 study group

PrEP/ART during acute (“Fiebig 0”) infection



PLOS | MEDICINE

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

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. Yukl[17,18], Joel N. Blankson[7], Teri Liegler[2], Steven G. Deeks[2]

The Journal of Infectious Diseases

The Control of HIV After Antiretroviral Medication Pause (CHAMP) Study: Posttreatment Controllers Identified From 14 Clinical Studies

Golnaz Namazi,[1,a] Jesse M. Fajnzylber,[1,a] Evgenia Aga,[2] Ronald J. Bosch,[2] Edward P. Acosta,[3] Radwa Sharaf,[1] Wendy Hartogensis,[4] Jeffrey M. Jacobson,[5] Elizabeth Connick,[6] Paul Volberding,[4] Daniel Skiest,[7] David Margolis,[8] Michael C. Sneller,[9] Susan J. Little,[10] Sara Gianella,[10] Davey M. Smith,[10] Daniel R. Kuritzkes,[1] Roy M. Gulick,[11] John W. Mellors,[12] Vikram Mehraj,[13] Rajesh T. Gandhi,[14] Ronald Mitsuyasu,[15] Robert T. Schooley,[10] Keith Henry,[16] Pablo Tebas,[17] Steven G. Deeks,[4] Tae-Wook Chun,[9] Ann C. Collier,[18] Jean-Pierre Routy,[13] Frederick M. Hecht,[4] Bruce D. Walker,[19] and Jonathan Z. Li[1,©]

PLOS | PATHOGENS

Post-Treatment HIV-1 Controllers with a Long-Term Virological Remission after the Interruption of Early Initiated Antiretroviral Therapy ANRS VISCONTI Study

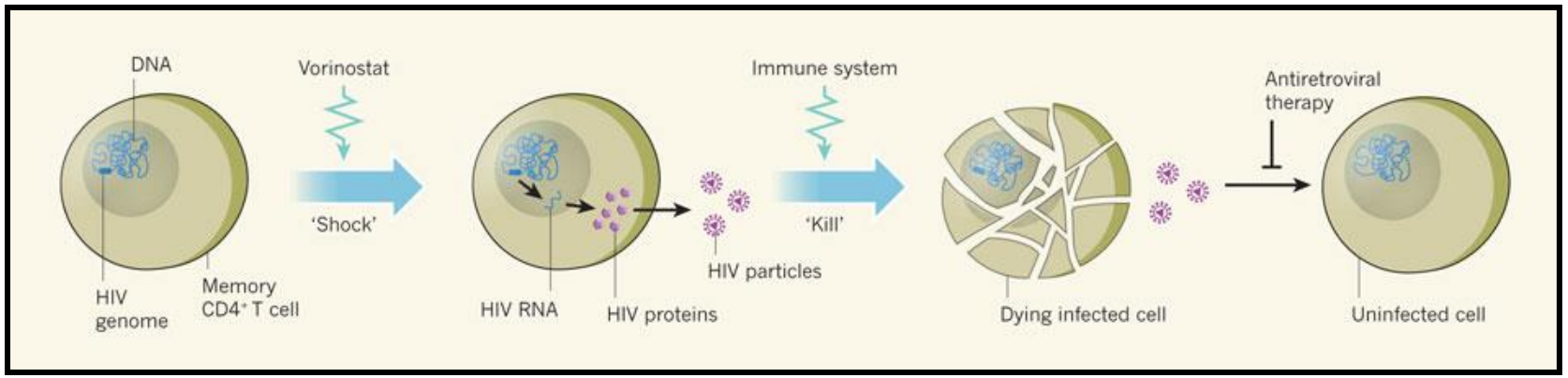
Asier Sáez-Cirión[1*], Charline Bacchus[2], Laurent Hocqueloux[3], Véronique Avettand-Fenoel[4,5], Isabelle Girault[6], Camille Lecuroux[6], Valerie Potard[7,8], Pierre Versmisse[1], Adeline Melard[4], Thierry Prazuck[3], Benjamin Descours[2], Julien Guergnon[2], Jean-Paul Viard[5,9], Faroudy Boufassa[10], Olivier Lambotte[6,11], Cécile Goujard[10,11], Laurence Meyer[10,12], Dominique Costagliola[7,8,13], Alain Venet[6], Gianfranco Pancino[1], Brigitte Autran[2], Christine Rouzioux[4,5*], the ANRS VISCONTI Study Group[¶]

- Some (~10%) of people who start therapy early (but not too early) and remain on therapy for years exhibit at least partial control after ART is interrupted
  - May occur in chronic infection (rare)
- No biomarker available
- Mechanism unknown
  - Elite controllers: Adaptive immunity (CD8+ T cells)
  - PTCs: Innate immunity (NK cells)

Latency reversal (shock and kill)

Shock and kill

Force virus out of hiding (latency) and hope the cell dies



- Multiple latency reversing agents tested: effect in humans is modest at best, and not associated with reservoir reduction
- Basic discovery aimed at identifying novel pathways or combinations

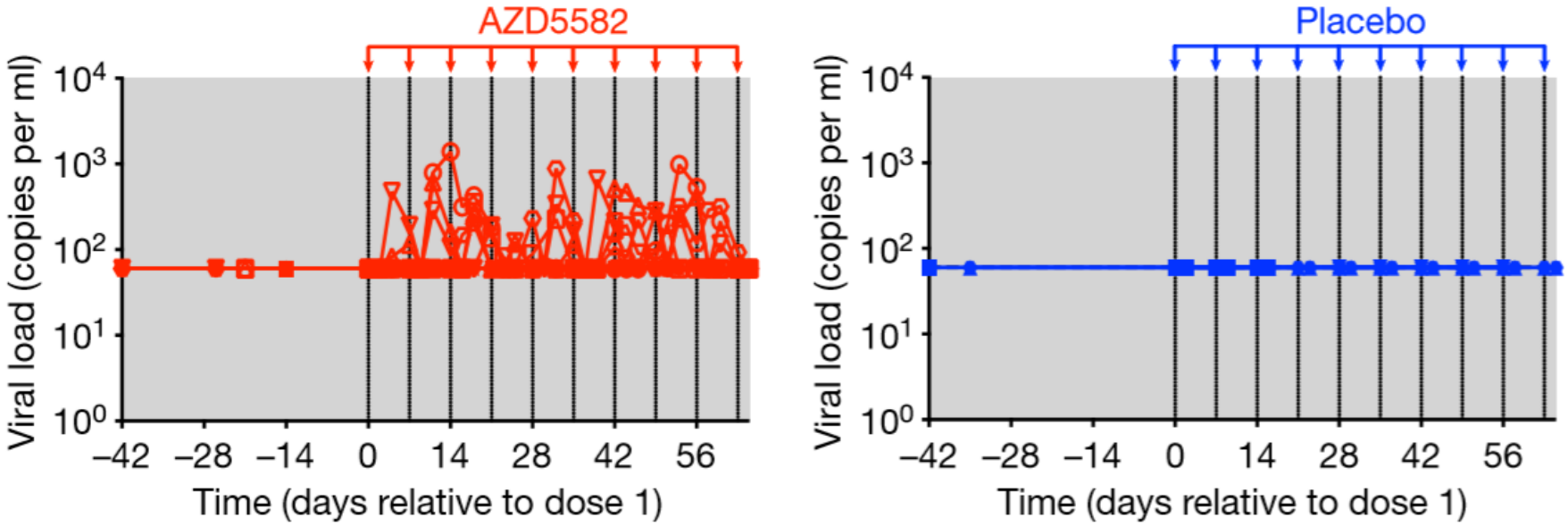
SMAC-mimetics routinely induce latency reversal in animal models

nature

Systemic HIV and SIV latency reversal via non-canonical NF-κB signalling in vivo

https://doi.org/10.1038/s41586-020-1951-3
Received: 12 April 2019
Accepted: 16 December 2019
Published online: 22 January 2020

Christopher C. Nixon[1,2,3,20], Maud Mavigner[4,20], Gavin C. Sampey[2,3,5,6], Alyssa D. Brooks[4], Rae Ann Spagnuolo[1,2,3], David M. Irlbeck[6,7], Cameron Mattingly[4], Phong T. Ho[1,2,3], Nils Schoof[4], Corinne G. Cammon[1,2,3], Greg K. Tharp[8], Matthew Kanke[9,10], Zhang Wang[11], Rachel A. Cleary[1,2,3], Amit A. Upadhyay[8], Chandrav De[1,2,3], Saintedym R. Wills[2,3,5,6], Shane D. Falcinelli[2,3,5,12], Cristin Galardi[6,7], Hasse Walum[8], Nathaniel J. Schramm[1,2,3], Jennifer Deutsch[11], Jeffrey D. Lifson[13], Christine M. Fennessey[13], Brandon F. Keele[13], Sherrie Jean[8], Sean Maguire[11], Baolin Liao[1,2,3,14], Edward P. Browne[2,3,5], Robert G. Ferris[6,7], Jessica H. Brehm[6,7], David Favre[6,11], Thomas H. Vanderford[8], Steven E. Bosinger[9,15], Corbin D. Jones[9,10], Jean-Pierre Routy[16,17], Nancie M. Archin[2,3,5], David M. Margolis[2,3,5,6,12,18], Angela Wahl[1,2,3], Richard M. Dunham[2,3,5,6,7,21]*, Guido Silvestri[9,15], Ann Chahroudi[4,8,19,21]* & J. Victor Garcia[1,2,3,21]*



- No change in reservoir or delay in rebound
  - Why do productive, virus-producing cells persist?
- Toxicity may prevent rapid clinical development

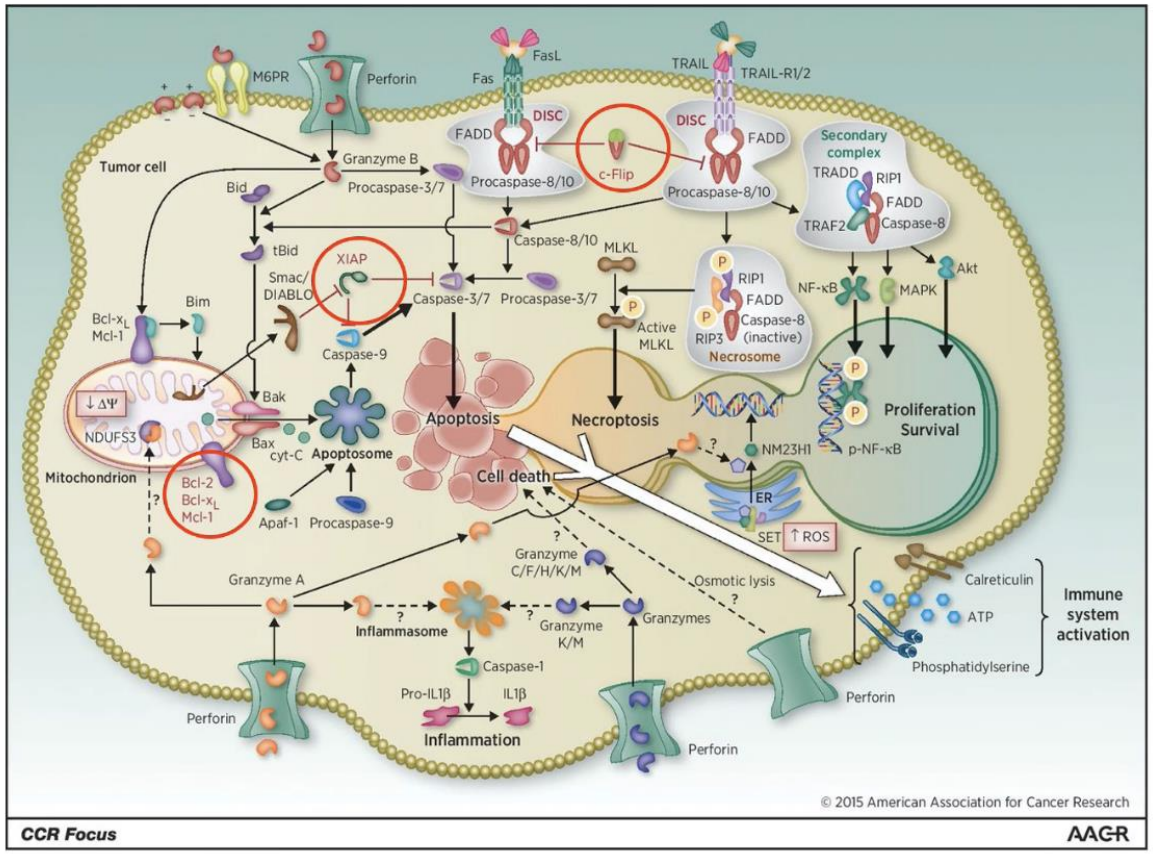
Intrinsic resistance of reservoir cells to immune killing

Many cellular factors associated with cell survival are enhanced (Bcl-2, others) in infected cells

"Target Cells"
Are active and self-regulating partners in 'killing'

○ Examples of known inhibitors of killing

- HIV persistence on ART is tied to the properties of reservoir-harboring cells
- Do cells that over-express CTL resistance factors preferentially survive to form the reservoir? Undergo clonal expansion?



Luis Martinez-Lostao et al. *Clin Cancer Res*, **2015.**

Latency silencing (block and lock)

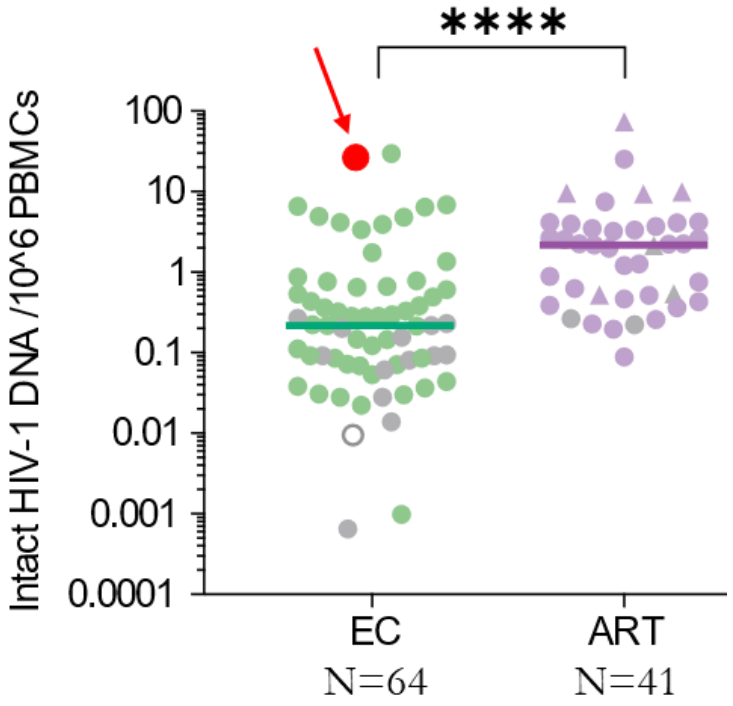
Natural cures and exceptional control

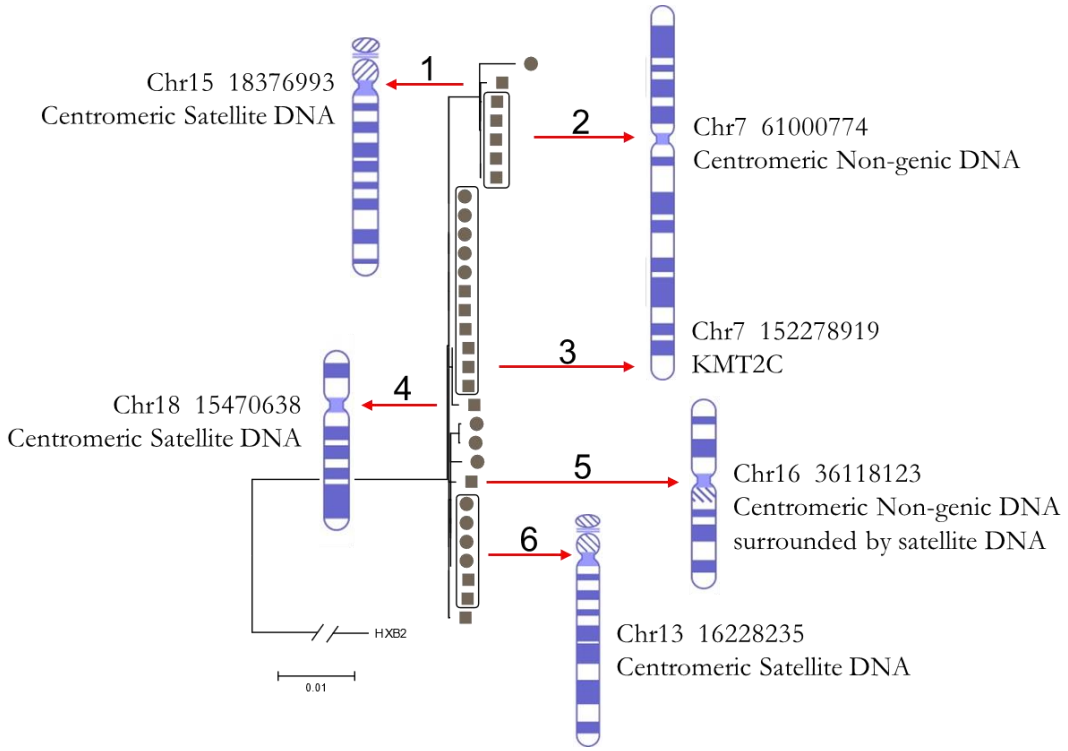
Intact proviral genomes accumulate in “gene deserts”, which is associated with deep and possibly irreversible latency

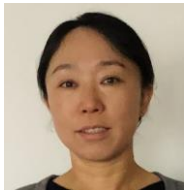
nature

Distinct viral reservoirs in individuals with spontaneous control of HIV-1

Chenyang Jiang[1,2,15], Xiaodong Lian[1,2,15], Ce Gao[1,15], Xiaoming Sun[1], Kevin B. Einkauf[1,2], Joshua M. Chevalier[1,2], Samantha M. Y. Chen[1], Stephane Hua[1], Ben Rhee[1,2], Kaylee Chang[1], Jane E. Blackmer[1], Matthew Osborn[1], Michael J. Peluso[3], Rebecca Hoh[3], Ma Somsouk[3], Jeffrey Milush[3], Lynn N. Bertagnolli[4], Sarah E. Sweet[4], Joseph A. Varriale[4], Peter D. Burbelo[5], Tae-Wook Chun[6], Gregory M. Laird[7], Erik Serrao[8,9], Alan N. Engelman[8,9], Mary Carrington[1,10], Robert F. Siliciano[4,11], Janet M. Siliciano[4,11], Steven G. Deeks[3], Bruce D. Walker[1,11,12,13], Mathias Lichterfeld[1,2,14] & Xu G. Yu[1,2]✉

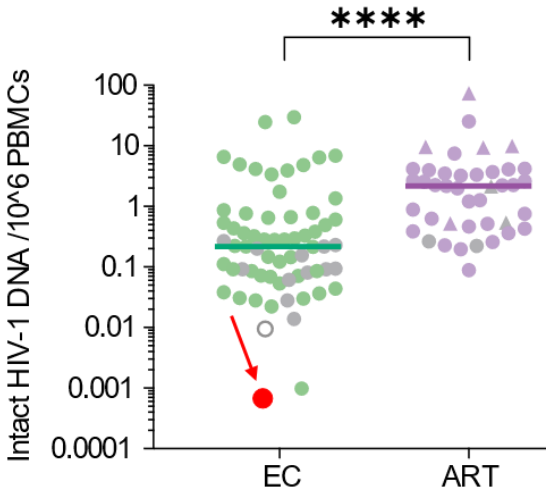




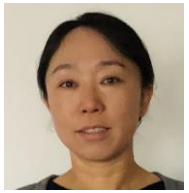


Natural Cures

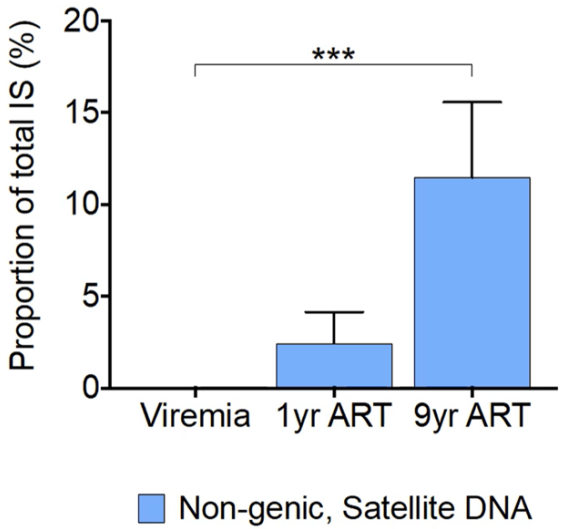
HIV diagnosed in 1992, no ART, undetectable virus 24 years (39 viral loads; one blip), no intact HIV DNA, low and declining HIV antibody levels; lowest level of HIV ever recorded; second case reported at CROI 2021

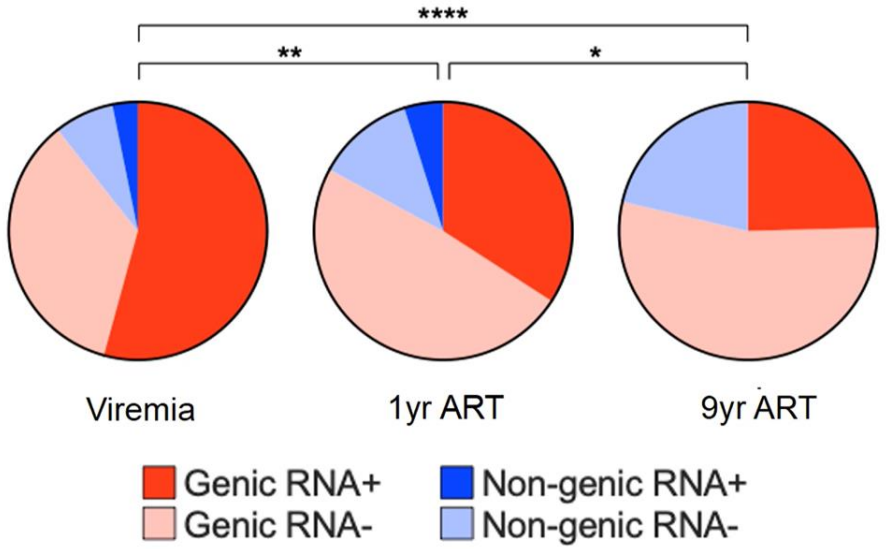


Test	Cell number	Cell type
Sequencing	>1.5b	PBMC
Intact DNA (PCR)	14m	Resting CD4
Viral outgrowth	340m	Resting CD4

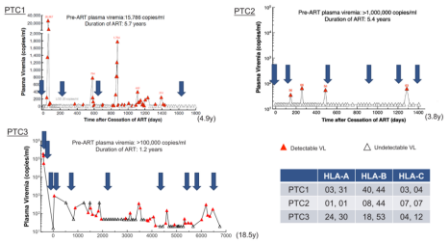


Post-treatment control: Block and lock





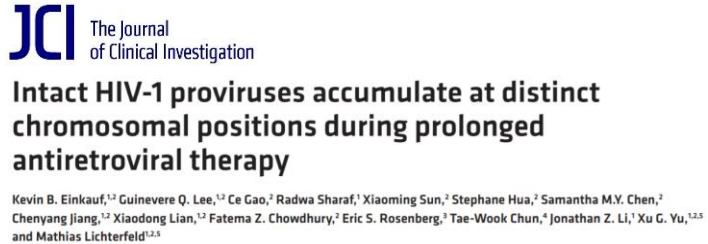
- Provirus population increasingly enriched in “gene deserts”
- Intact genomes in ex-genic regions are clonal; those in genic regions are less clonal (singlets)
- Data suggests potent elimination of any expressed proviruses



Lian/Lichterfeld., CROI 2021

Exceptional Controllers and “Block and Lock”

- Rare clinical phenotype
- Mechanism unknown
- Similar trends reported in PTCs (CROI 2021)
- Are we treating too many elite controllers?
- Can we recapitulate this phenotype therapeutically?
  - Lock-and-block strategies: mTOR inhibitors
  - Long-term ART



Gene therapy

Gene editing for an HIV Cure: Proof of concept

The NEW ENGLAND JOURNAL of MEDICINE

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

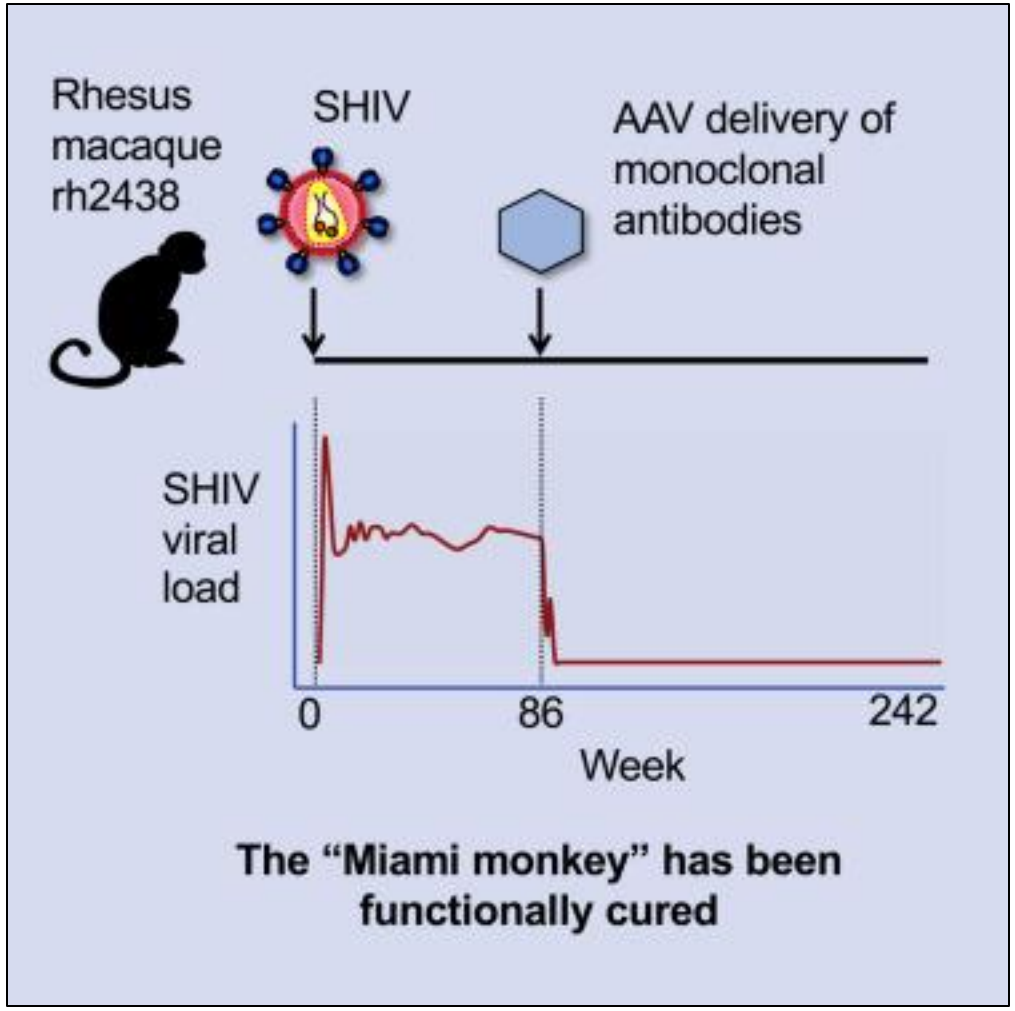
Gero Hütter, M.D., Daniel Nowak, M.D., Maximilian Mossner, B.S., Susanne Ganepola, M.D., Arne Müßig, M.D., Kristina Allers, Ph.D., Thomas Schneider, M.D., Ph.D., Jörg Hofmann, Ph.D., Claudia Kücherer, M.D., Olga Blau, M.D., Igor W. Blau, M.D., Wolf K. Hofmann, M.D., and Eckhard Thiel, M.D.

nature

HIV-1 remission following CCR5Δ32/Δ32 haematopoietic stem-cell transplantation

Ravindra K. Gupta[1,2,3,4,5]*, Sultan Abdul-Jawad[1], Laura E. McCoy[1], Hoi Ping Mok[4], Dimitra Peppa[3,6], Maria Salgado[7], Javier Martinez-Picado[7,8,9], Monique Nijhuis[10], Annemarie M. J. Wensing[10], Helen Lee[11], Paul Grant[12], Eleni Nastouli[12], Jonathan Lambert[13], Matthew Pace[6], Fanny Salasc[4], Christopher Monit[1], Andrew J. Innes[14,15], Luke Muir[1], Laura Waters[3], John Frater[6,16], Andrew M. L. Lever[4,17], Simon G. Edwards[3], Ian H. Gabriel[14,15,18,19] & Eduardo Olavarria[14,15,19]

One-shot cure approaches



nature COMMUNICATIONS

Sequential LASER ART and CRISPR Treatments Eliminate HIV-1 in a Subset of Infected Humanized Mice

Prasanta K. Dash[1,4], Rafal Kaminski[2,4], Ramona Bella[2,4], Hang Su[1], Saumi Mathews[1], Taha M. Ahooyi[2], Chen Chen[2], Pietro Mancuso[2], Rahsan Sariyer[2], Pasquale Ferrante[2], Martina Donadoni[2], Jake A. Robinson[2], Brady Sillman[1], Zhiyi Lin[1], James R. Hilaire[1], Mary Banoub[1], Monalisha Elango[1], Nagsen Gautam[3], R. Lee Mosley[3], Larisa Y. Poluektova[3], JoEllyn McMillan[3], Aditya N. Bade[3], Santhi Gorantla[3], Ilker K. Sariyer[2], Tricia H. Burdo[2], Won-Bin Young[2], Shohreh Amini[2], Jennifer Gordon[2], Jeffrey M. Jacobson[2], Benson Edagwa[1], Kamel Khalili[2] & Howard E. Gendelman[1]

Immunity

Adeno-Associated Virus Delivery of Anti-HIV Monoclonal Antibodies Can Drive Long-Term Virologic Suppression

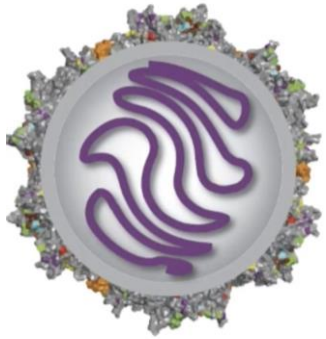
José M. Martinez-Navio,[1,5] Sebastian P. Fuchs,[1,5] Shara N. Pantry,[1] William A. Lauer,[1] Natasha N. Duggan,[1] Brandon F. Keele,[2] Eva G. Rakasz,[3] Guangping Gao,[4] Jeffrey D. Lifson,[2] and Ronald C. Desrosiers[1,6,7,*]

Gene delivery of long-acting antiviral (bANb) or direct *in vivo* gene editing (HIV, CCR5) might eventually lead to durable cure for treated and even untreated people

Aspirational, but theoretically possible

AAV vectors can be used for durable antibody production

Recapitulating "Miami Monkey" in people

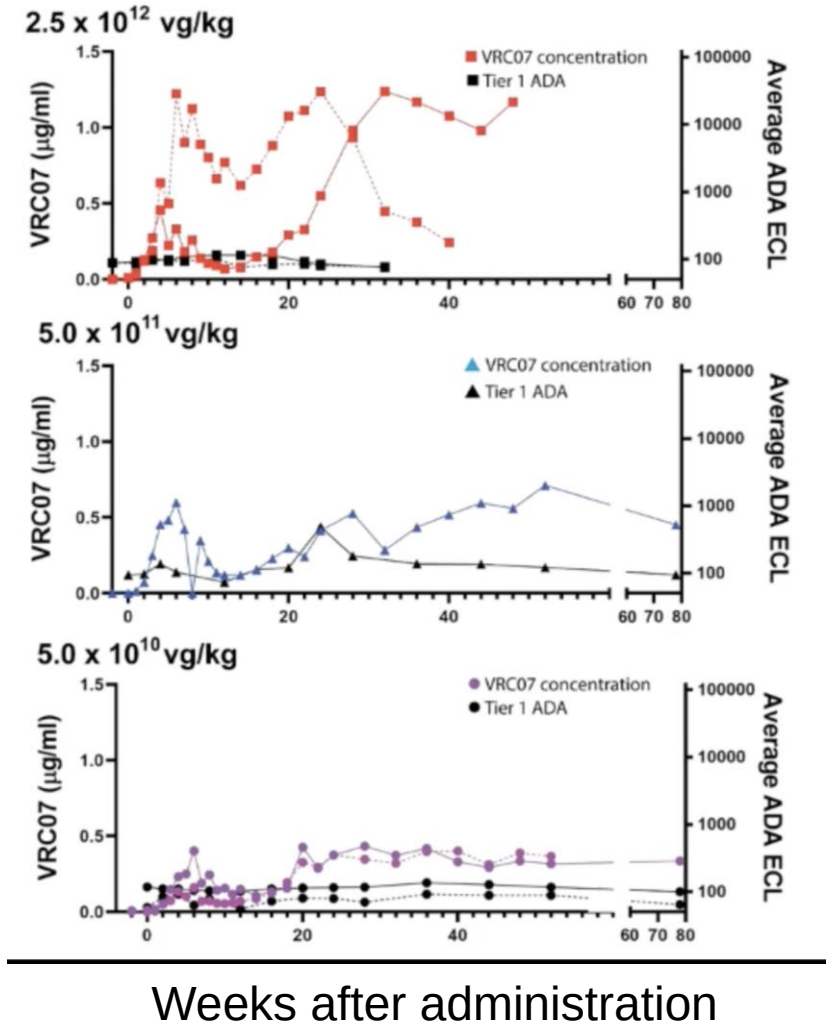


- Adeno-Associated Viral vector
- IM injection
- Episomal (nuclear, stable) DNA
- Safe

=> Encode VRC-07 broadly-neutralizing antibody (bnAb)

Measurable VRC-07 induced in 5/8 participants

(anti-drug antibodies + low [VRC-07] in 3/8 participants)

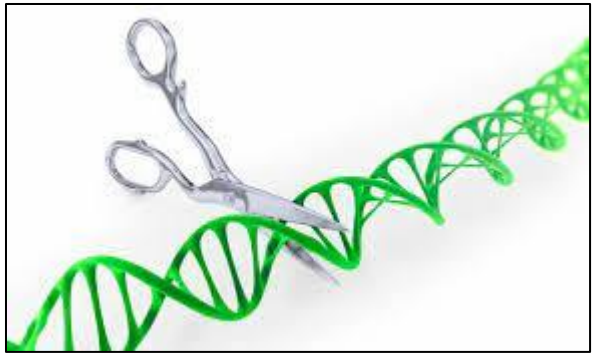


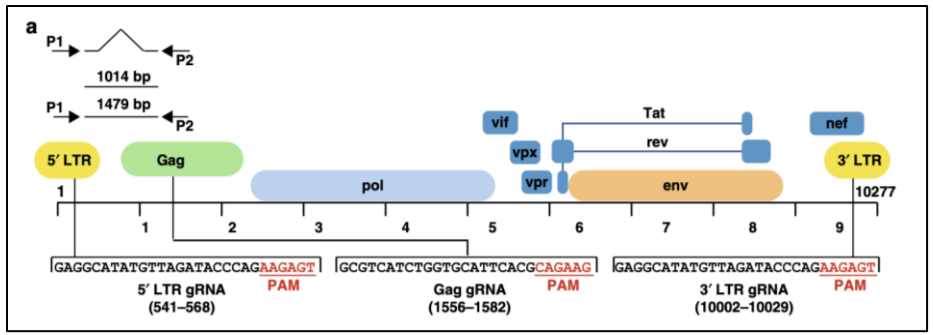
CROI 2021

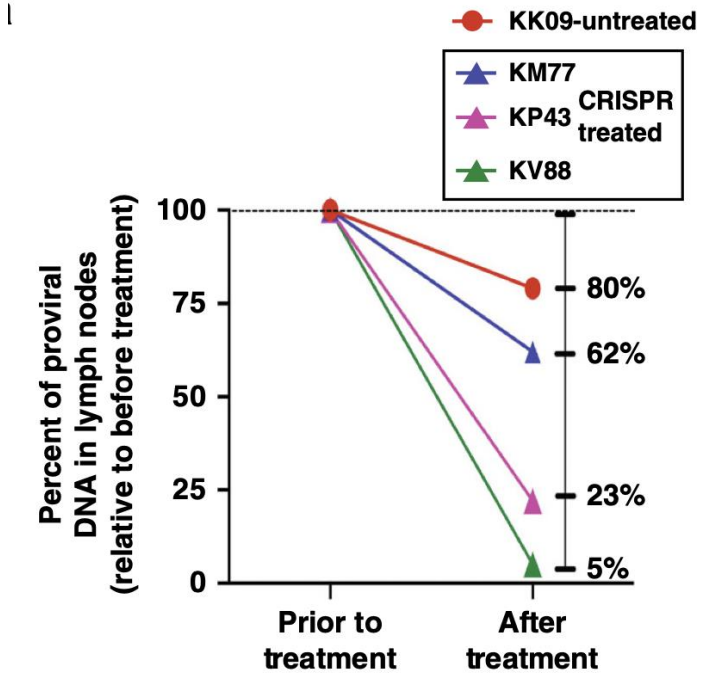
***Joseph Casaza**, Durable HIV-1 Antibody Production in Humans after AAV8-mediated Gene Transfer*

Direct editing of the provirus with vector-delivered enzymes

AAV-delivered CRISP/Cas9 had variable efficacy in disrupting the provirus in macaques receiving ART)







Mancuso et al., Nat Comm 2020

CAR-T cells: Modified cells persist for decades, based on our experience with first generation of CAR-T ells in 1990s

Science

Decade-Long Safety and Function of Retroviral-Modified Chimeric Antigen Receptor T Cells

John Scholler,[1]* Troy L. Brady,[2]* Gwendolyn Binder-Scholl,[1] Wei-Ting Hwang,[3] Gabriela Plesa,[1] Kristen M. Hege,[4] Ashley N. Vogel,[1] Michael Kalos,[1] James L. Riley,[2] Steven G. Deeks,[5] Ronald T. Mitsuyasu,[6] Wendy B. Bernstein,[7] Naomi E. Aronson,[7,8] Bruce L. Levine,[1] Frederic D. Bushman,[2†] Carl H. June[1†]

Science Translational Medicine

Multispecific anti-HIV duoCAR-T cells display broad in vitro antiviral activity and potent in vivo elimination of HIV-infected cells in a humanized mouse model

Kim Anthony-Gonda[1]*, Ariola Bardhi[2]*, Alex Ray[2], Nina Flerin[2], Mengyan Li[2], Weizao Chen[3], Christina Ochsenbauer[4], John C. Kappes[4,5], Winfried Krueger[1], Andrew Worden[1], Dina Schneider[1], Zhongyu Zhu[1], Rimas Orentas[1†], Dimiter S. Dimitrov[6‡], Harris Goldstein[2‡], Boro Dropulić[1‡]

Anti-HIV duoCAR-T cell therapy eliminates cells with HIV

Science Translational Medicine

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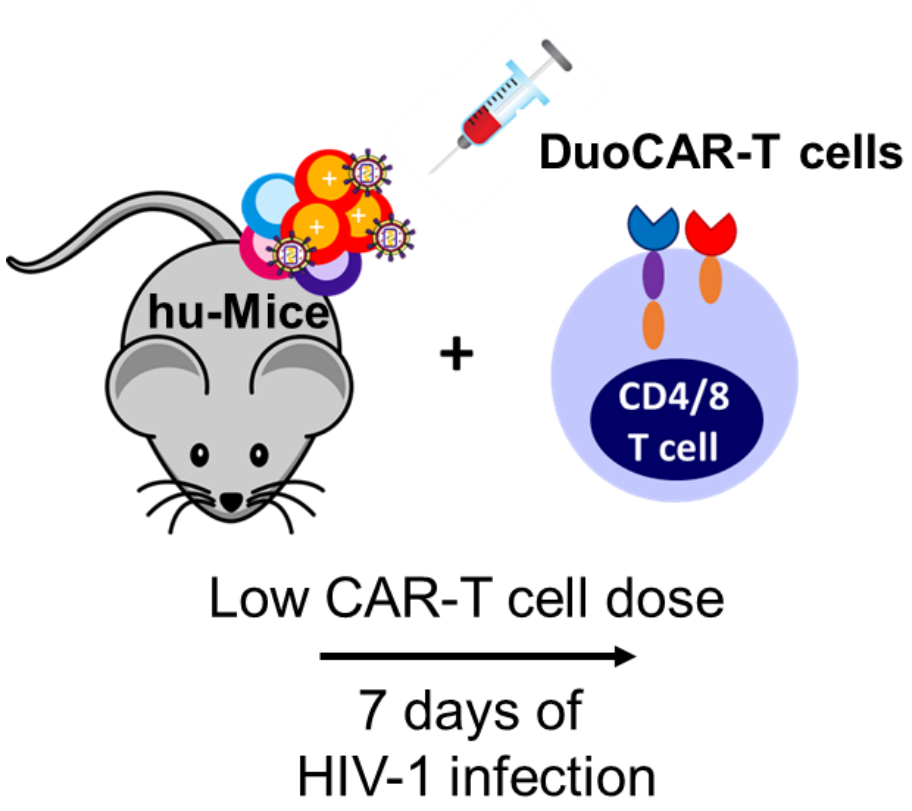
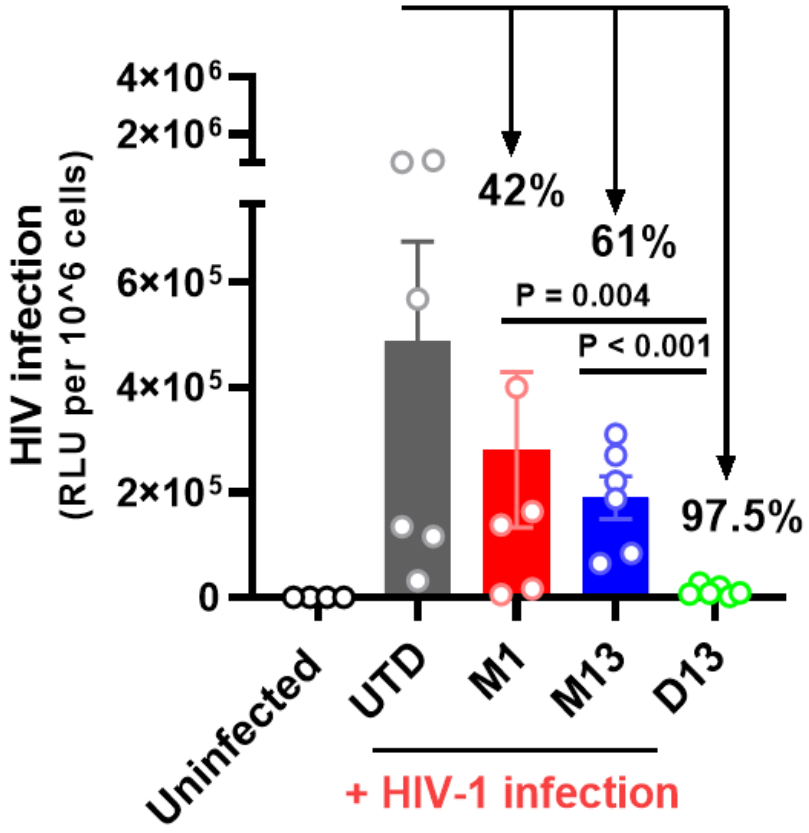
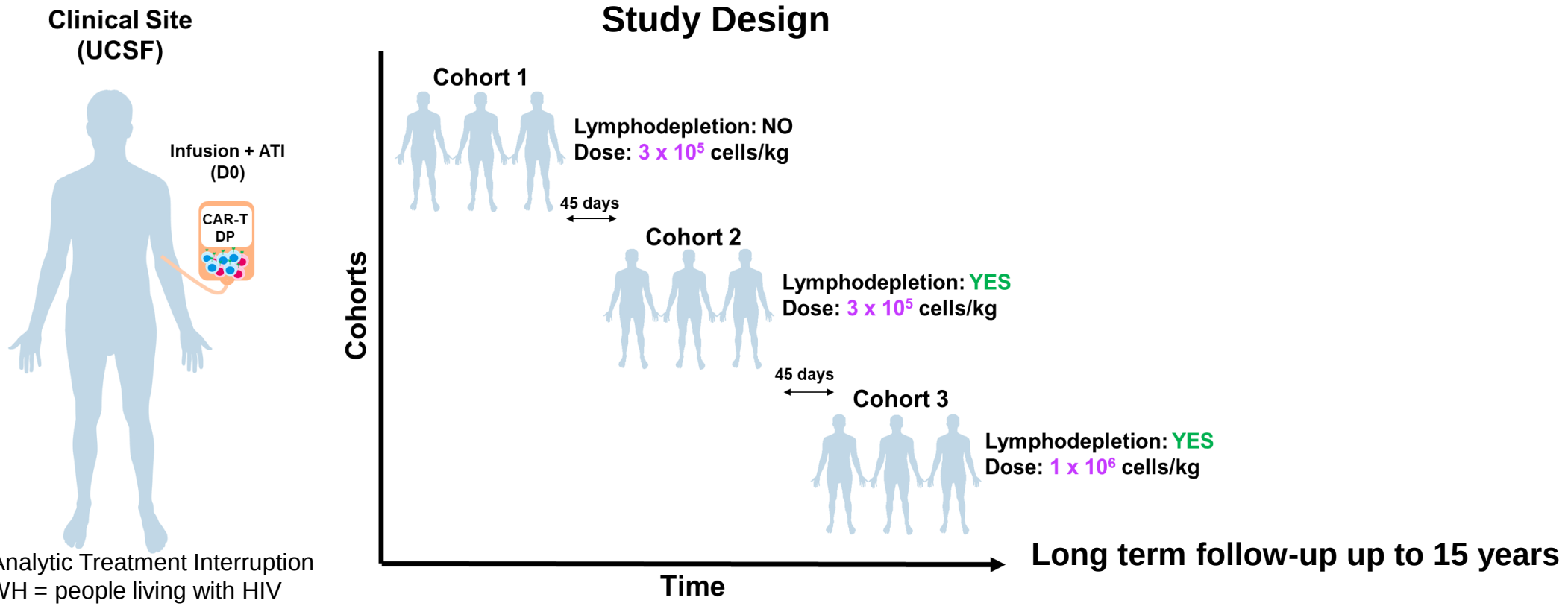
Kim Anthony-Gonda[1]*, Ariola Bardhi[2]*, Alex Ray[2], Nina Flerin[2], Mengyan Li[2], Weizao Chen[3], Christina Ochsenbauer[4], John C. Kappes[4,5], Winfried Krueger[1], Andrew Worden[1], Dina Schneider[1], Zhongyu Zhu[1], Rimas Orentas[1†], Dimiter S. Dimitrov[6‡], Harris Goldstein[2‡], Boro Dropulić[1‡]





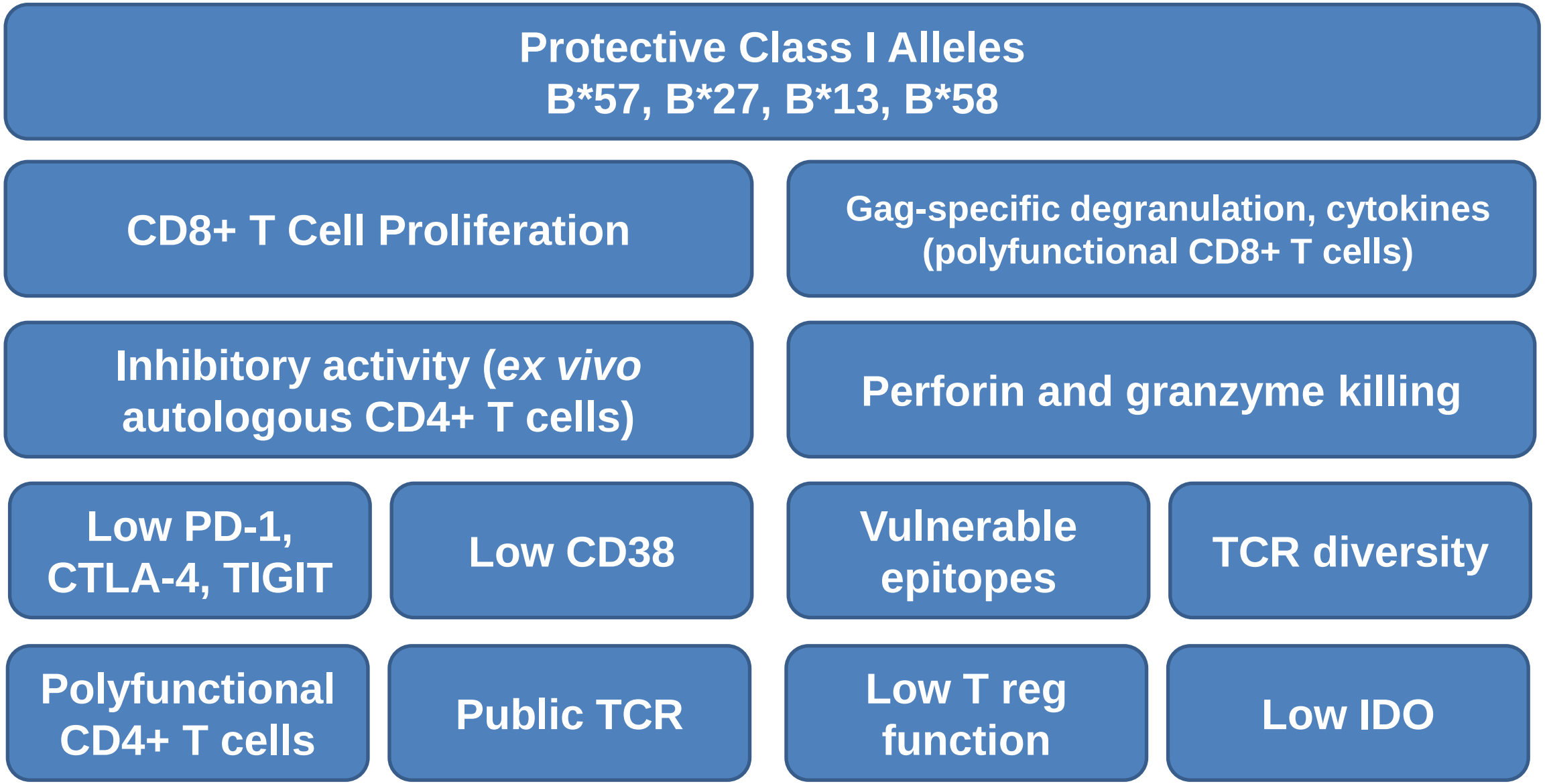
First-in-human phase I/II study to evaluate the safety and efficacy of duoCAR-T cell therapy in ART-suppressed PLWH (NCT04648046)



ATI = Analytic Treatment Interruption
PLWH = people living with HIV

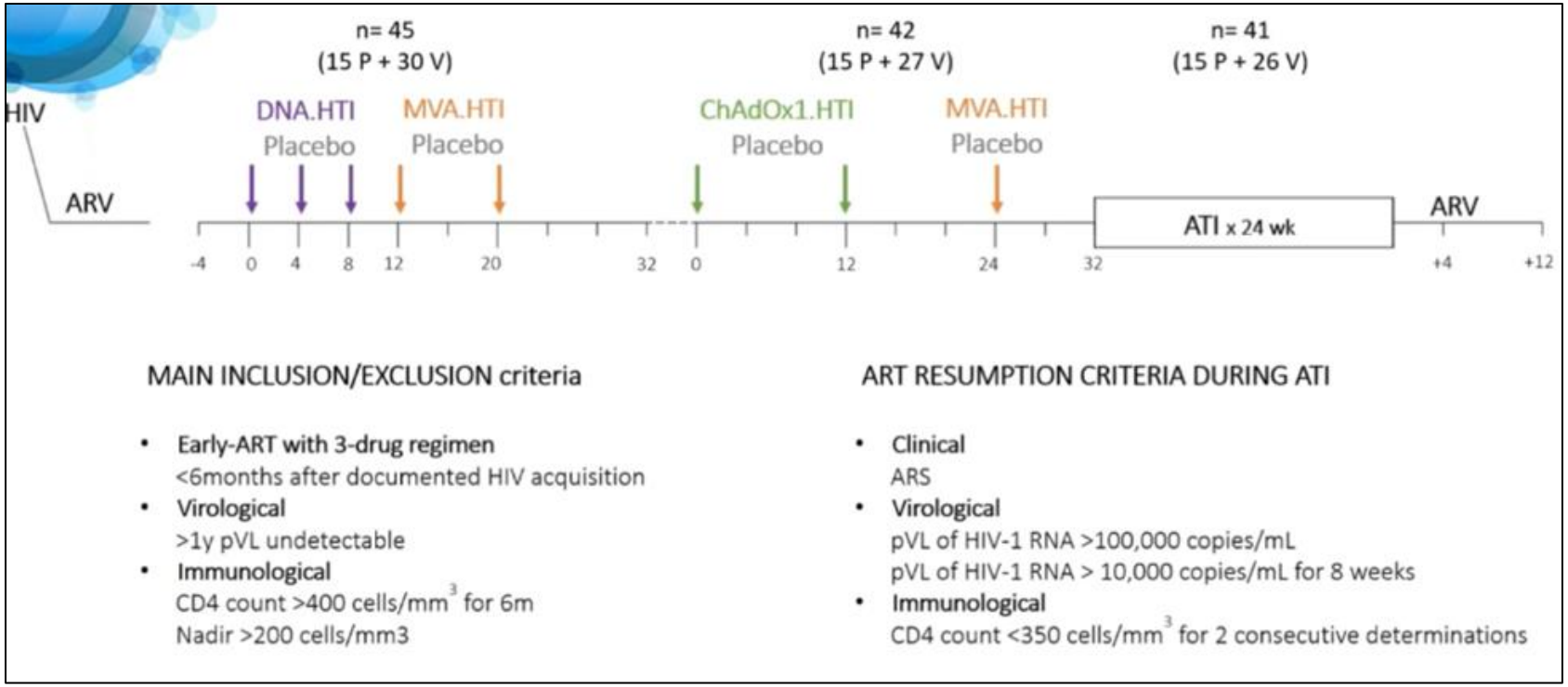
Immunotherapy: Vaccines, broadly neutralizing antibodies, adjuvants, cytokines, and immune checkpoint blockers

“Elite” control is most consistently associated with HIV-specific CD8+ T cell responses, although other pathways are likely involved



AELIX-002 Study Design

Randomized study of multi-vectored therapeutic vaccine



MAIN INCLUSION/EXCLUSION criteria

- **Early-ART with 3-drug regimen**
  <6months after documented HIV acquisition
- **Virological**
  >1y pVL undetectable
- **Immunological**
  CD4 count >400 cells/mm^3 for 6m
  Nadir >200 cells/mm3

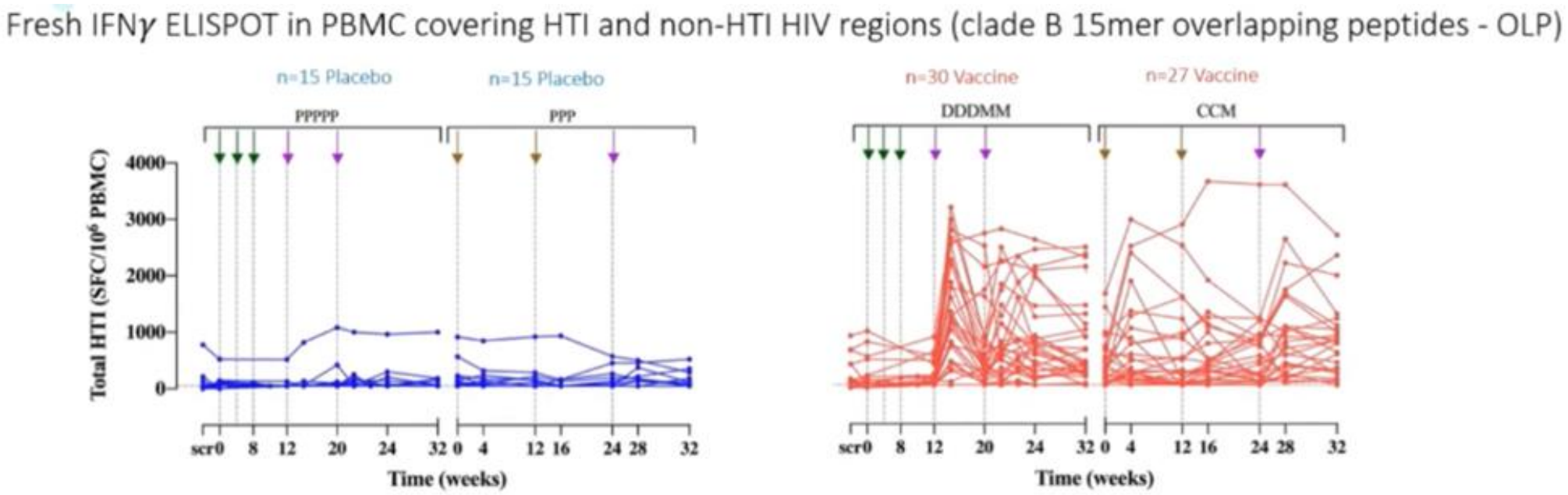
ART RESUMPTION CRITERIA DURING ATI

- **Clinical**
  ARS
- **Virological**
  pVL of HIV-1 RNA >100,000 copies/mL
  pVL of HIV-1 RNA > 10,000 copies/mL for 8 weeks
- **Immunological**
  CD4 count <350 cells/mm^3 for 2 consecutive determinations

Mothe et al., CROI 2021 (LB)

AELIX-002 Study Design

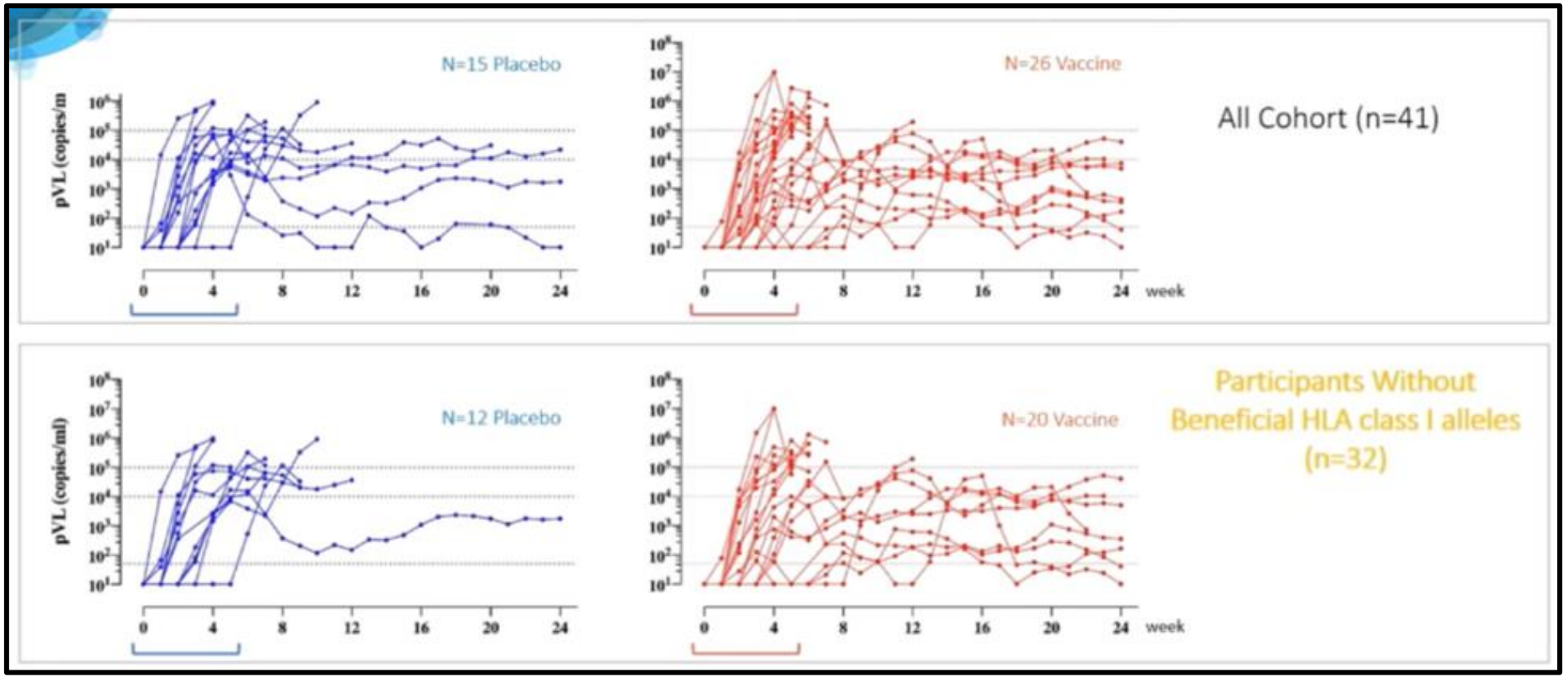
Randomized study of multi-vectored therapeutic vaccine



Mothe et al., CROI 2021 (LB)

AELIX-002 Study Design

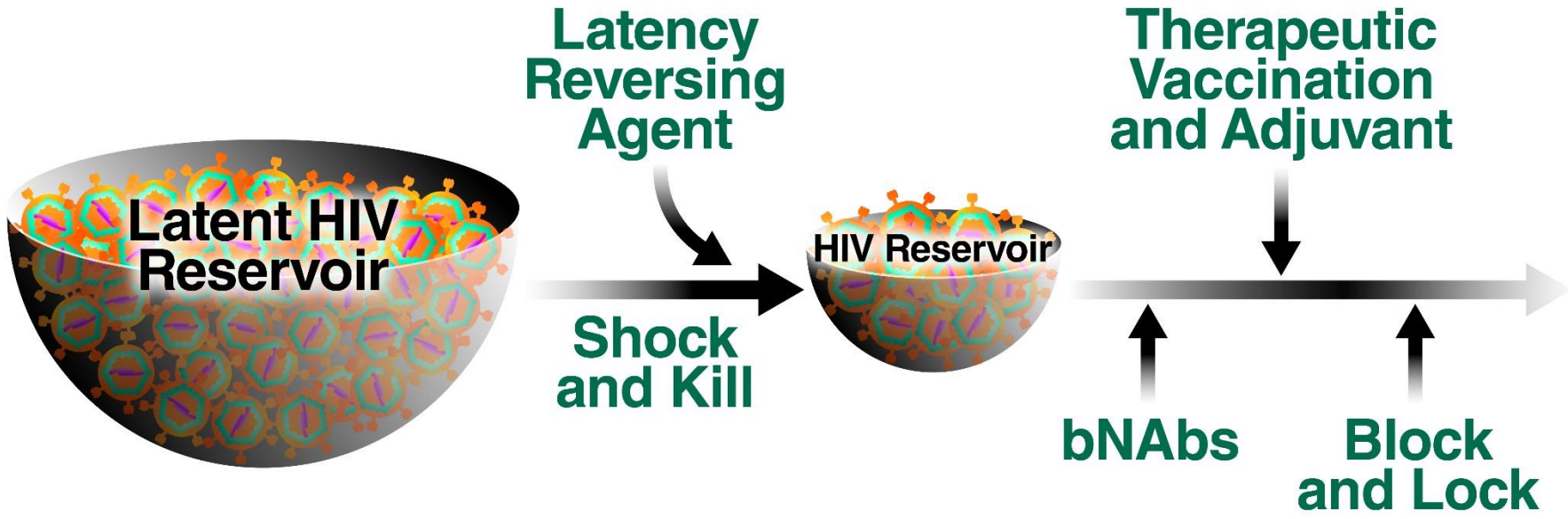
Randomized study of multi-vectored therapeutic vaccine



Mothe et al., CROI 2021 (LB)

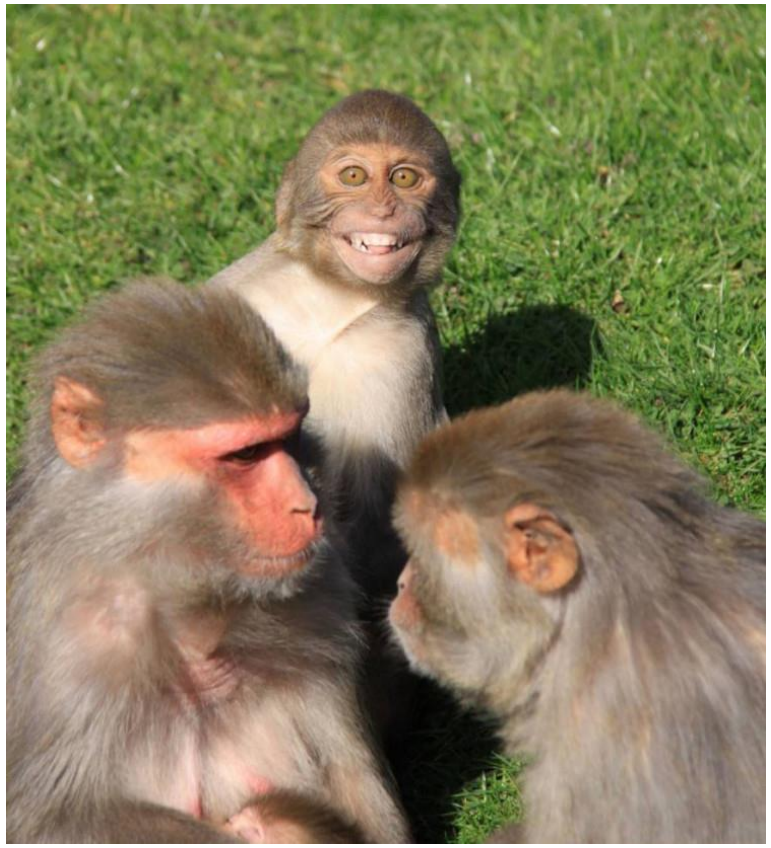
Reduce and Control

Combining Multiple Modalities To Achieve a Sustained Viral Remission in the Absence of ART



Courtesy of Warner Greene

Combination Immunotherapy: Proof-of-concept in monkeys



nature

Immune clearance of highly pathogenic SIV infection

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

nature

Ad26/MVA therapeutic vaccination with TLR7 stimulation in SIV-infected rhesus monkeys

Erica N. Borducchi[1], Crystal Cabral[1], Kathryn E. Stephenson[1], Jinyan Liu[1], Peter Abbink[1], David Ng'ang'a[1], Joseph P. Nkolola[1], Amanda L. Brinkman[1], Lauren Peter[1], Benjamin C. Lee[1], Jessica Jimenez[1], David Jetton[1], Jade Mondesir[1], Shanell Mojta[1], Abishek Chandrashekar[1], Katherine Molloy[1], Galit Alter[2], Jeffrey M. Gerold[3], Alison L. Hill[3], Mark G. Lewis[4], Maria G. Pau[5], Hanneke Schuitemaker[5], Joseph Hesselgesser[6], Romas Geleziunas[6], Jerome H. Kim[7]†, Merlin L. Robb[7], Nelson L. Michael[7] & Dan H. Barouch[1,2]

nature

Early antibody therapy can induce long-lasting immunity to SHIV

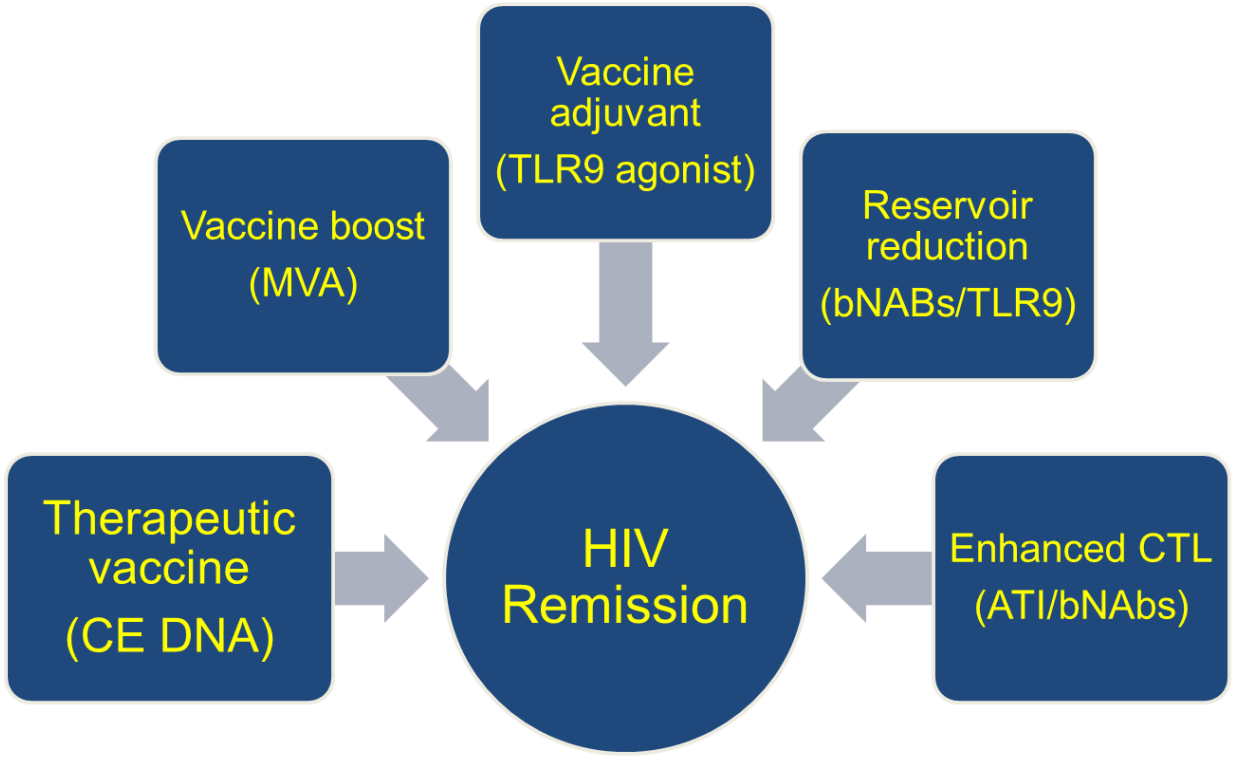
Yoshiaki Nishimura[1], Rajeev Gautam[1], Tae-Wook Chun[2], Reza Sadjadpour[1], Kathryn E. Foulds[3], Masashi Shingai[1], Florian Klein[4,5], Anna Gazumyan[6], Jovana Golijanin[6], Mitzi Donaldson[3], Olivia K. Donau[1], Ronald J. Plishka[1], Alicia Buckler-White[1], Michael S. Seaman[7], Jeffrey D. Lifson[8], Richard A. Koup[3], Anthony S. Fauci[2], Michel C. Nussenzweig[6,9] & Malcolm A. Martin[1]

nature

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]*

Combinatorial therapy with a therapeutic conserved element DNA/MVA vaccine strategy, a TLR9 agonist and broadly neutralizing antibodies: A pilot study aimed at inducing an HIV remission (IND 18488)



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Conclusions

- Progress continues to be made, primarily in animal models
- Multiple approaches are being tested
  - All are likely to initially be less effective than optimally delivered ART
  - Iterative process expected with multiple “shots on goal” and ultimate optimization for addressing the needs of the global pandemic
- Massive synergies exist with HIV prevention (vaccines, bNAbs) and non-HIV immunotherapies (cancer, transplant, autoimmunity)