Caraconference 2023

Transcending Barriers to Ending the HIV Epidemic

September 11–15

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We are Greater Cincinnati's HIV nonprofit devoted to positively changing lives in the fight against HIV/AIDS through:

Prevention

Promoting health and well-being in at-risk communities through evidence-based approaches to prevent disease and reduce the spread of HIV

Housing

Offering a variety of permanent housing support to prevent homelessness and to stabilize individuals living with HIV and their families

Care

Helping individuals living with HIV access the health care they need through medical case management and pharmacy services

Learn more: caracole.org

AETC Midwest

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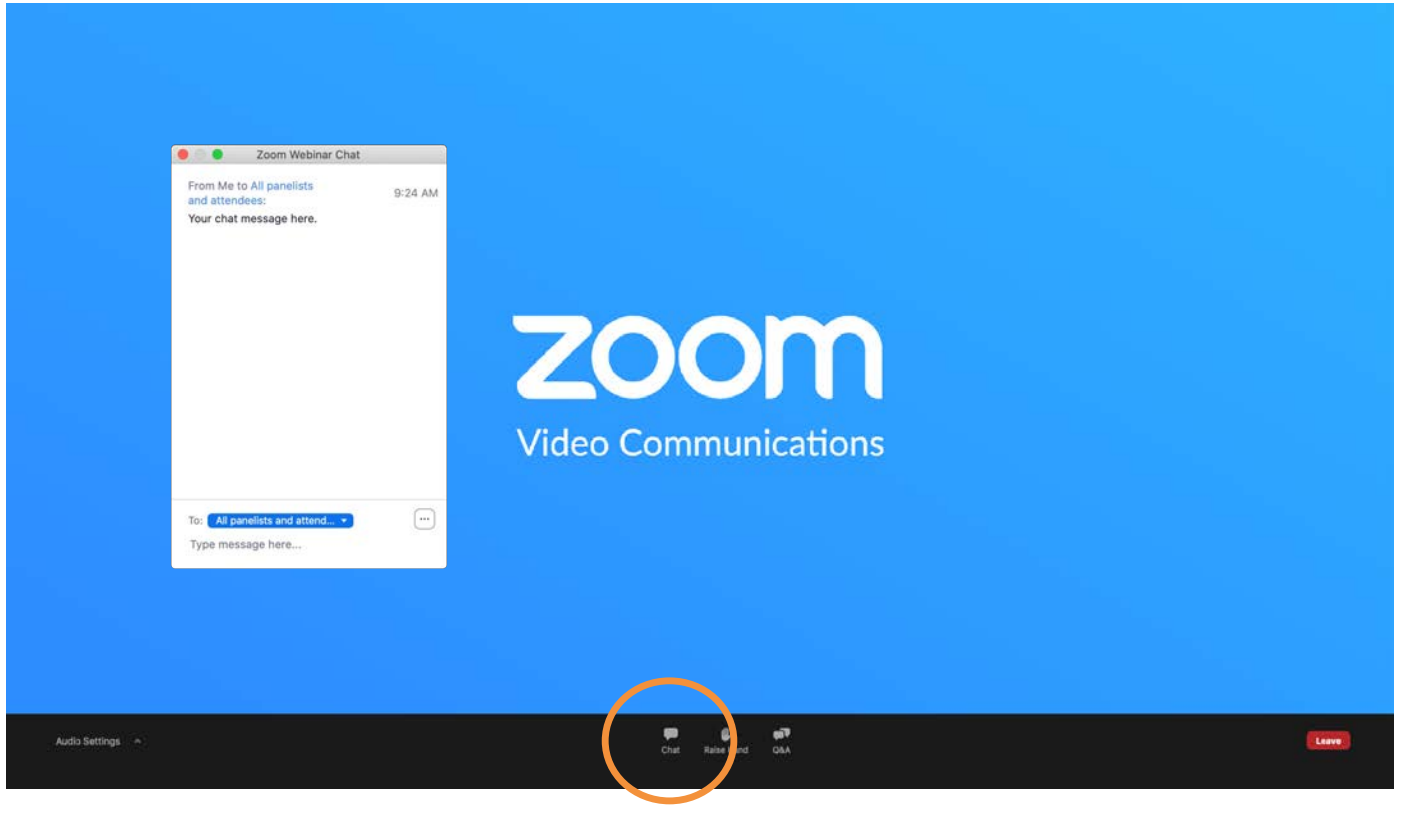
How to participate in today's webinar:

Use "Chat" for technical questions.



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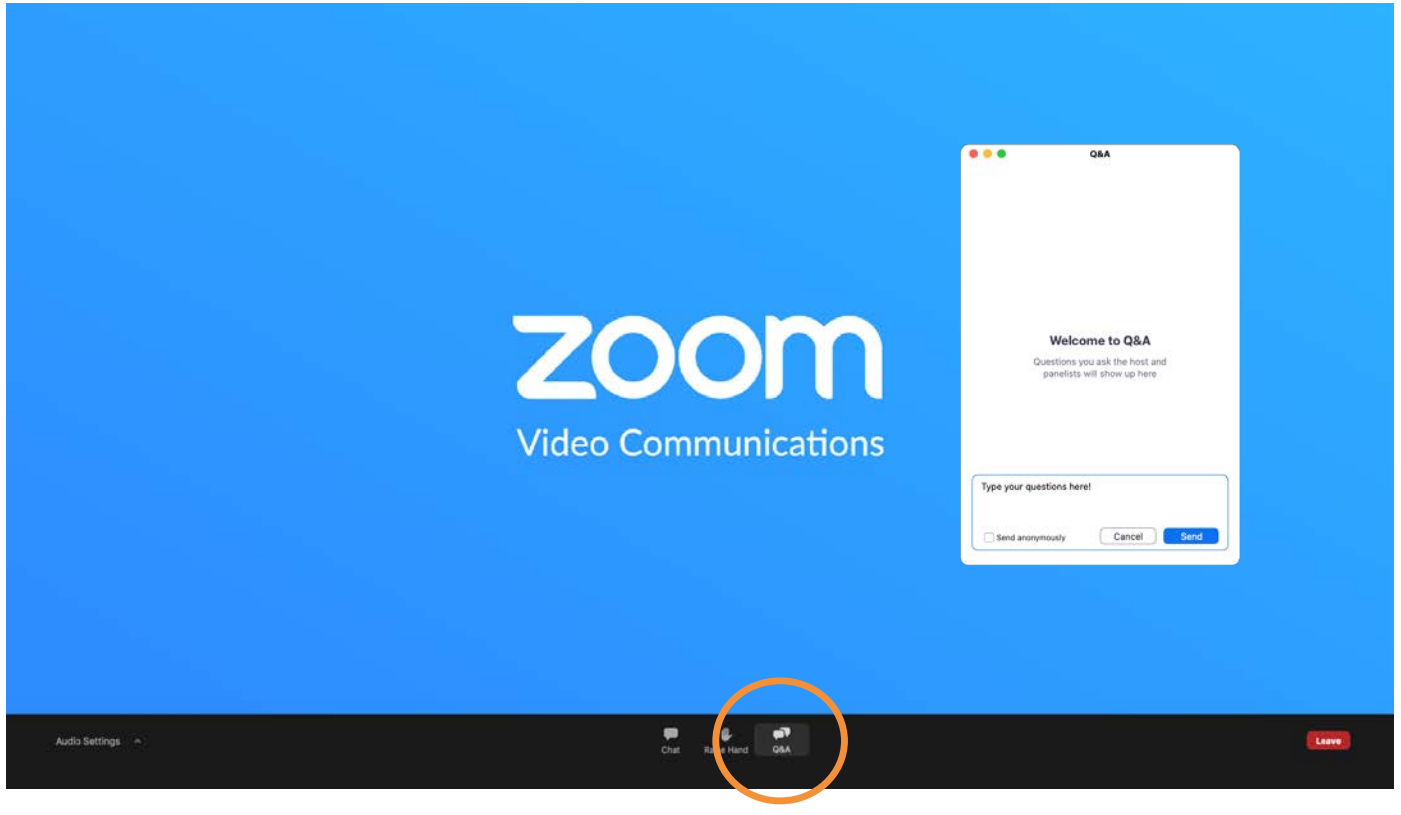
How to participate in today's webinar:

Use "Q&A" for presenter questions.



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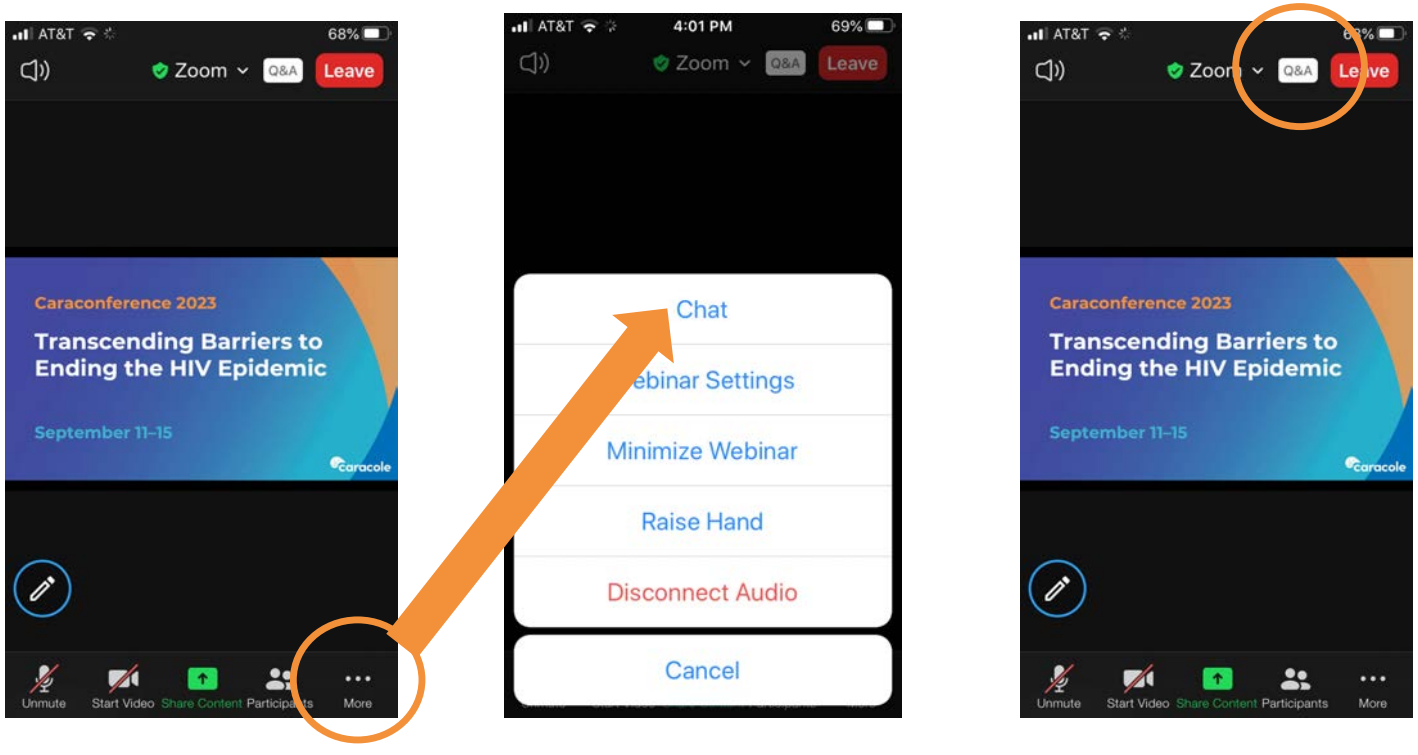
How to participate in today's webinar:

Use the same options for "Chat" and "Q&A" on your mobile device.



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Special thanks!

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Evaluations and Credits

Evaluations recommended for all attendees

Required for CECs

- Link in program and today's chat
- Must be completed by end of business day (5:00 PM EST) today

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MATEC Resources

- National Clinician Consultation Center
  http://nccc.ucsf.edu/
  - HIV Management
  - Perinatal HIV
  - HIV PrEP
  - HIV PEP line
  - HCV Management
  - Substance Use Management
- AETC National HIV Curriculum
  https://aidsetc.org/nhc
- AETC National HIV-HCV Curriculum
  https://aidsetc.org/hivhcv
- Hepatitis C Online
  https://www.hepatitisc.uw.edu
- AETC National Coordinating Resource Center
  https://aidsetc.org/
- Additional Trainings
  https://matec.info

AETC AIDS Education & Training Center Program Midwest

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Disclosures

- None to report

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Monday, September 11

Reflections: TRAILBLAZER Study

Introduction: Linda Seiter & Suzanne Bachmeyer

Presenter: Dr. Carl Fichtenbaum

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Monday, September 11

Objectives for **Today**

1. Gain an understanding of the TRAILBLAZER Study and how this effort accompanies the overall national goal to end the HIV epidemic.
2. Learn how evidence-based approaches that engage the community and those impacted by HIV lead to better interventions and health outcomes.
3. Learn what key findings have been discovered and how researchers feel these can be implemented as next generation strategies to prevent new HIV infections and ensure those living with HIV are able to maintain an undetectable status.

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Searching for a Cure for HIV – What will it take?

Carl J. Fichtenbaum, MD
Gregory W. Rouan Professor of Internal Medicine
University of Cincinnati
September 11, 2023

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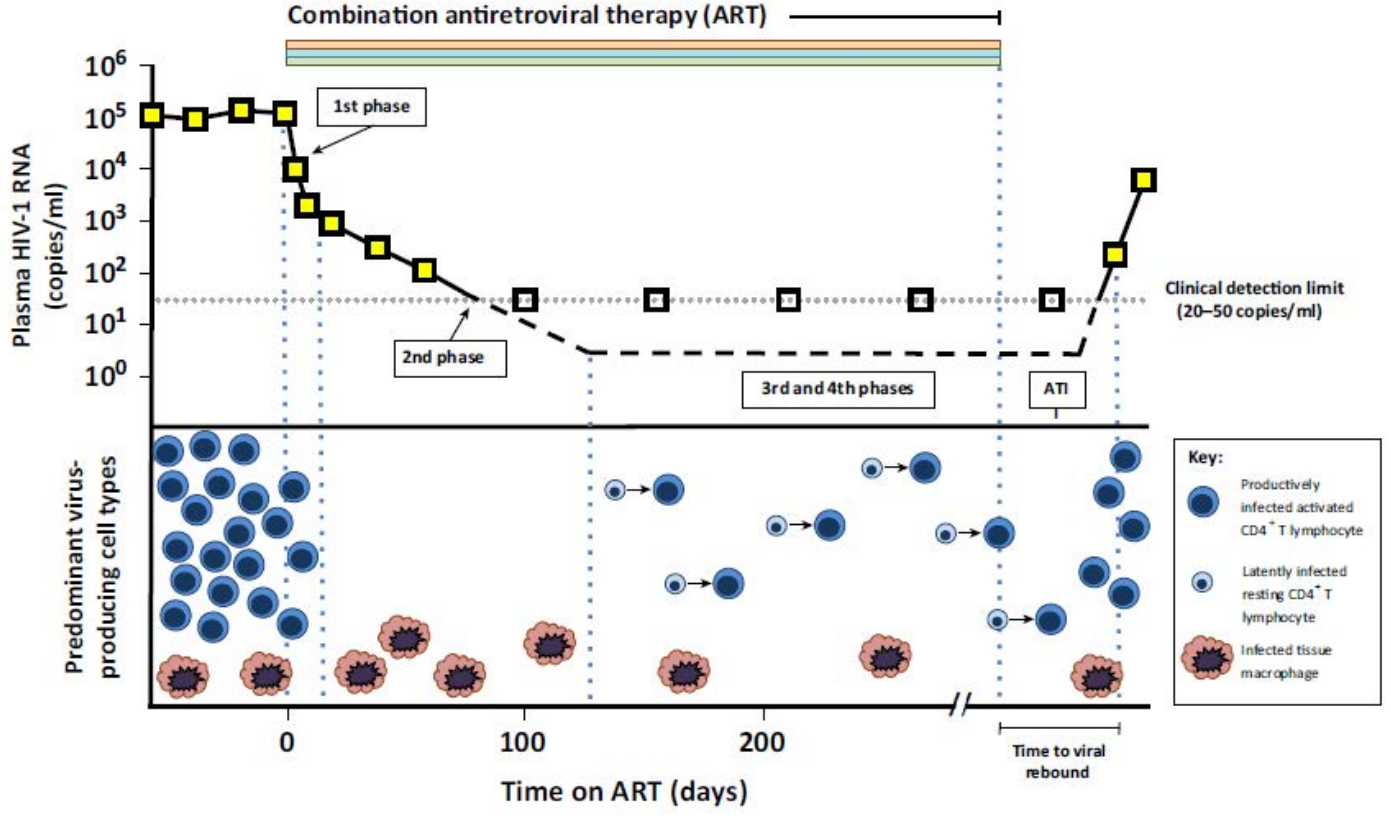
HIV Cure

- HIV treatment (Antiretroviral therapy) does not get rid of HIV despite keeping HIV at very low levels – NOT ZERO!!!!



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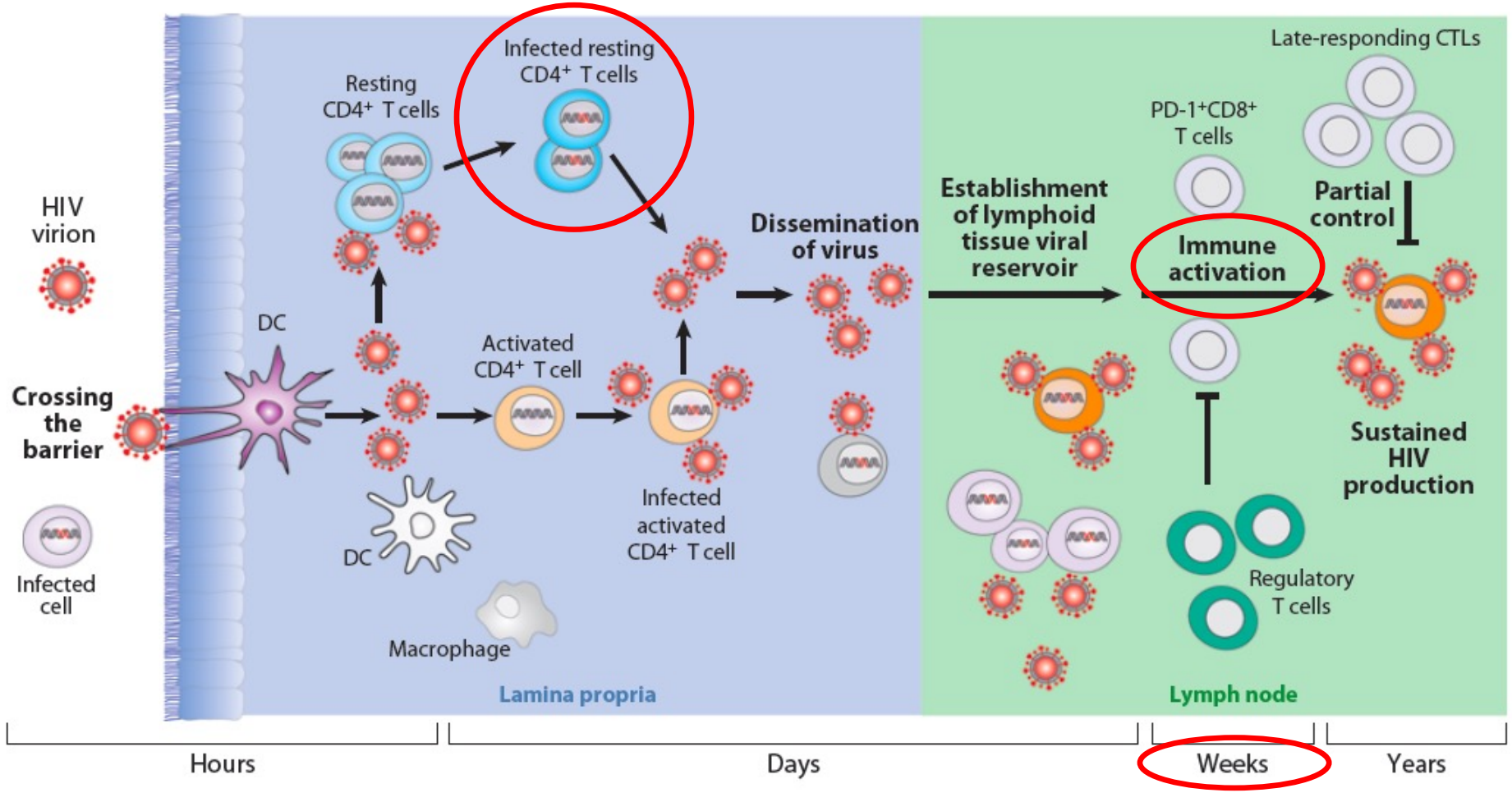


HIV establishes a reservoir within weeks of transmission and cells activated by the immune system leads to HIV replication

Moir, Annu Rev Pathol Mech Dis, 2011

The Significance of the Reservoir

The reservoir is the barrier to the cure.

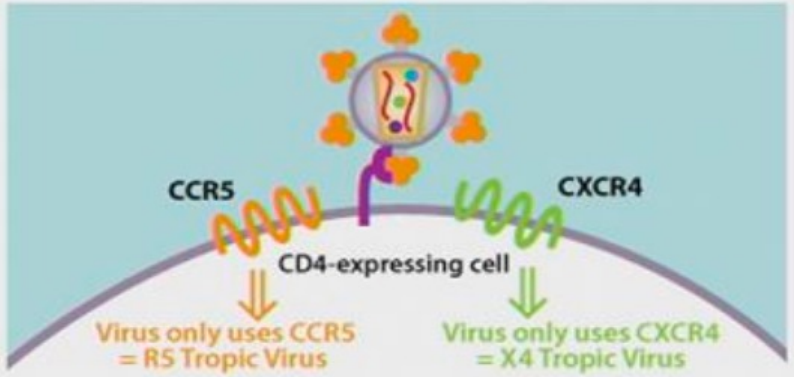
Sterilizing Cure:

Means permanent removal of HIV replication-competent virus, i.e. reservoir elimination

Functional Cure:

Permanent viral suppression without HIV treatment to levels that prevent immunodeficiency and transmission

HIV-1 and CCR5 as a target for remission



- CCR5 is the most commonly used coreceptor used to enter CD4+ target cells
- △ 32 mutation is a 32 base pair deletion in CCR5, preventing expression.
- 1% of Europeans are △32 homozygous and resistant to R5 HIV-1

Samson, Parmentier et al, Nature 1996; Deng, Landau et al, Nature 1996; Liu, Landau et al, Cell 1996

The NEW ENGLAND JOURNAL of MEDICINE

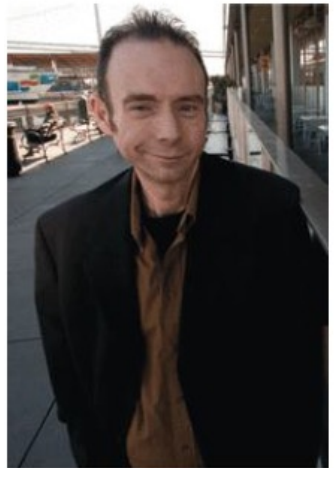
BRIEF REPORT

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.

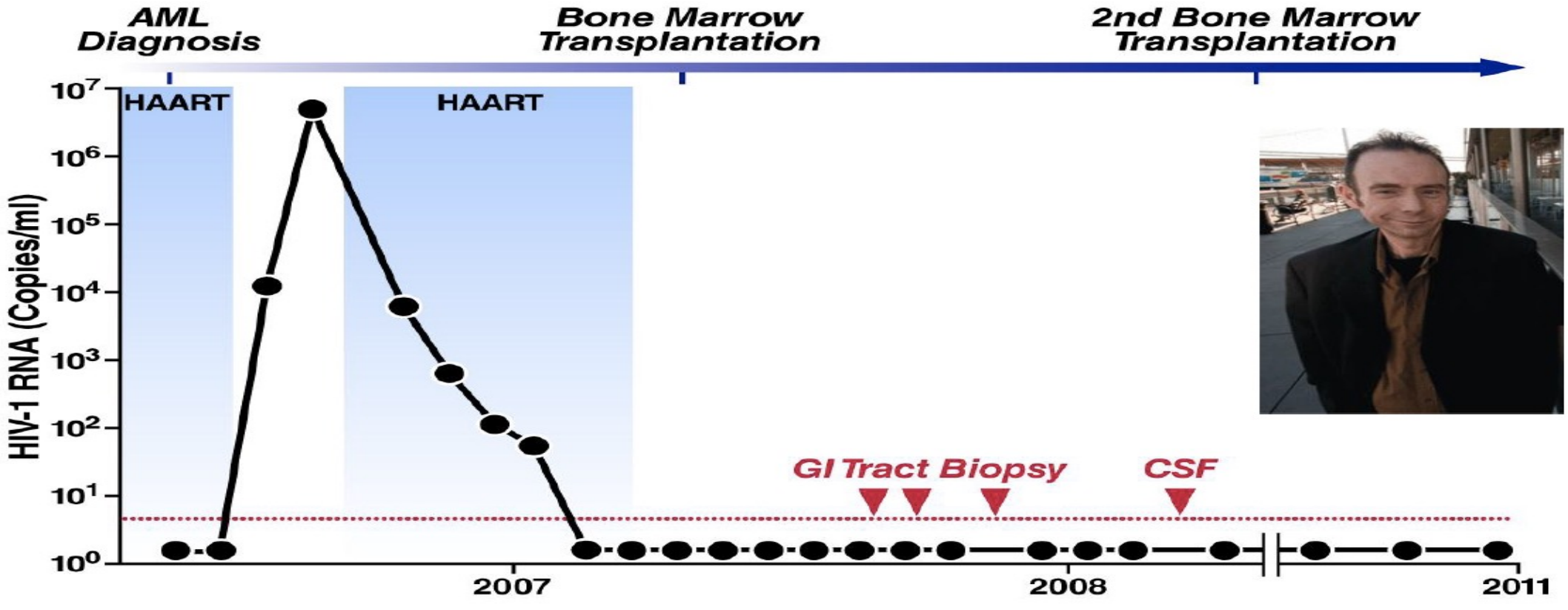
The Berlin Patient

- 40 year old diagnosed with HIV 10 years prior to presentation
  - HIV treatment x 4 years, CD4+ count 415/mm^3, undetectable viral load
- Diagnosed with leukemia (AML)
- Induction chemotherapy x 2, consolidation chemotherapy, brief ART interruption
  - Leukemia relapsed
- Bone Marrow Transplant done to treat Leukemia
  - Stopped ART 1 day before transplant
  - Rabbit antithymocyte globulin day -3, -2, -1 and cyclosporine day -1
  - Received CD34+ peripheral blood stem cell transplant from CCR5 Δ32 homozygous donor
  - Mycophenolate mofetil post-transplant
  - Engraftment 13 days later
  - Complicated by some rejection (Grade I skin graft-versus-host disease
- Leukemia relapsed after 332 days
  - Reinduction with cytarabine and gemtuzumab
  - Whole body irradiation x 1
  - 2nd transplant from same donor on day 391



Hütter, NEJM, 2009; Allers, Blood, 2011

CCR5 Δ32 Stem-Cell Transplantation



CCR5 Δ32 SCT results in undetectable plasma HIV-1 RNA levels in the absence of ART

Courtesy of S. Deeks

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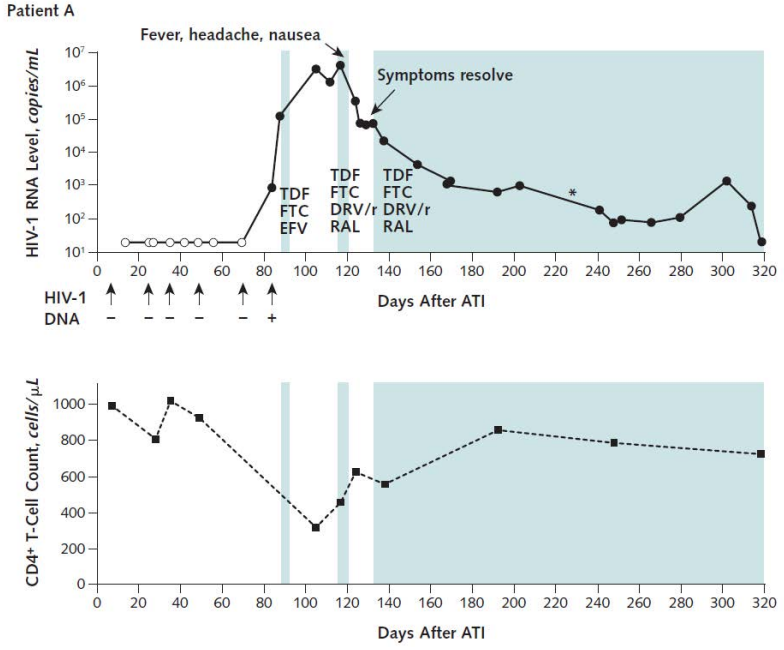
Summary of HIV Cure Successes

TABLE 1 | Differences between the Berlin and London Patients and other Patients.

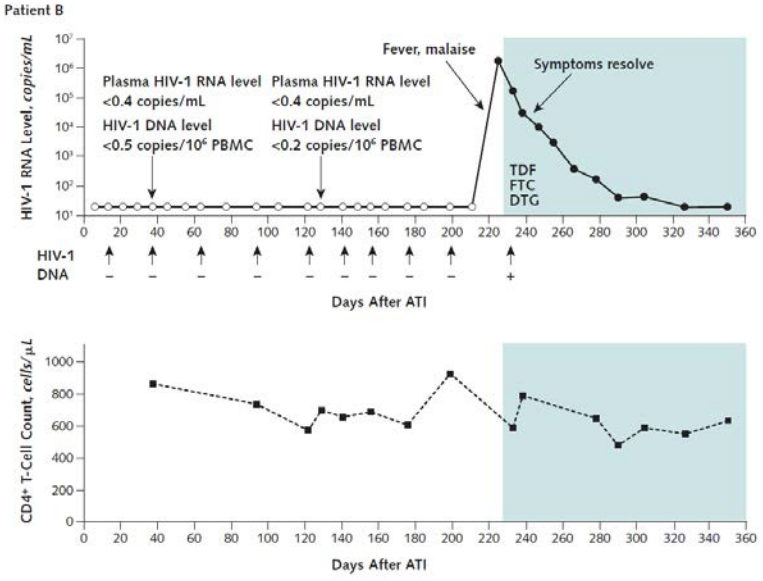
Patients	Malignancy types	ART regimen	Conditioning regimen	HSC donor	Viral load after HSCT	ART interruption	Viral remission	Viral rebound
Berlin Patient	Acute myeloid leukemia	EFV, FTC, TDF	HSCT #1: FLAMSA, CTX, ATG, TBI; HSCT #2: Ara-C, GO, TBI	10/10 HLA match; homozygous for *CCR5* delta*32*	Undetectable	Day of HSCT	Over 12 years	No
London Patient	Hodgkin lymphoma	EFV, FTC, TDF, RAL,RPV, 3TC, DTG	LACE, anti-CD52	9/10 HLA match; homozygous for *CCR5* delta*32*	Undetectable	16 months after HSCT	Over 3 years	No
Düsseldorf Patient	Acute myeloid leukemia	FTC, TDF, DRV, RAL, ABC, 3TC, DTG	Flu, Treo	10/10 HLA match; *CCR5* delta*32*	Undetectable	4 years after HSCT	NA	No
Minnesota Patient	Acute lymphoblastic leukemia	AZT/3TC IDV/rtv AZT/LAM, TDF/FTC, ATV/rtv, RAL, etravirine	RIC (Flu/Mel)	8/8 HLA-matched, ABO-matched; wild-type *CCR5*	Detectable at 56 days after HSCT. Undetectable at 91 days after HSCT	2 years after HSCT	288 days	Yes
Boston Patients	A: Hodgkin lymphoma	A: EFV, FTC, TDF, RAL, DRV/r	A: RIC chemotherapy (busulfan, Flu)	A: 7/8 HLA match; without *CCR5* delta*32*	A: Undetectable	A: 4.3 years after HSCT	A: 84 days	A: Yes
	B: Diffuse large B-cell lymphoma	B: EFV, FTC, TDF, NFV, ABC, RAL	B: RIC chemotherapy (busulfan, Flu)	B: 8/8 HLA match; without *CCR5* delta*32*	B: Undetectable	B: 2.6 years after HSCT	B: 225 days	B: Yes
Essen Patient	Anaplastic large-cell lymphoma	LPV/r, TDF, FTC, 3TC, ABC, RAL	ATG, CSA MTX	10/10 HLA match; homozygous for *CCR5* delta*32*	Undetectable	7 days before HSCT	20 days	Yes
Mississippi baby		AZT, 3TC, NVP, LPV/r; began receiving ART 30 hours after birth				18 and 23 months of age	27 months	Yes

Front. Immunol. 12:688747. doi: 10.3389/fimmu.2021.688747

Failures of Bone Marrow Transplantation



2 Patients got Allogenic HSCT
Both were Heterozygotes for CCR5 gene
Got wild-type donor cells for CCR5



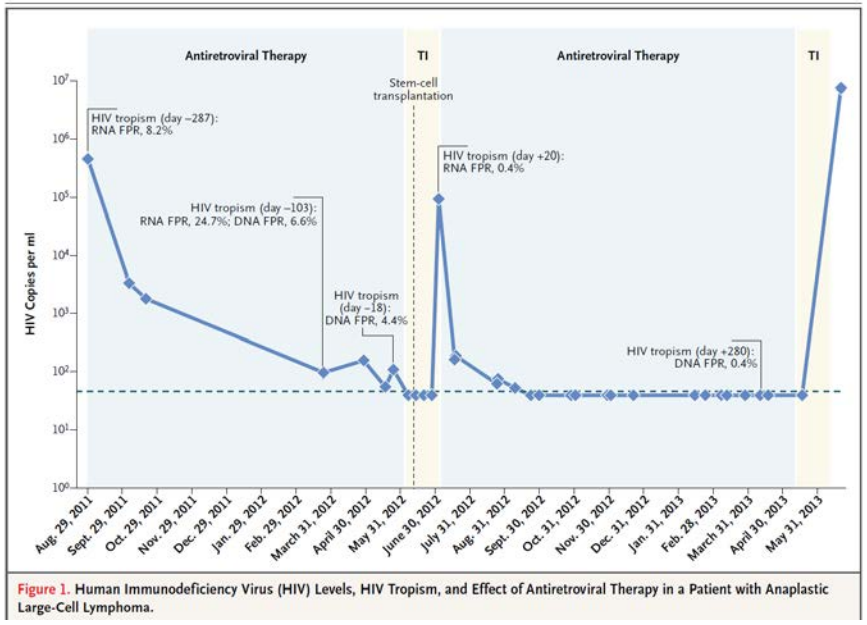


Figure 1. Human Immunodeficiency Virus (HIV) Levels, HIV Tropism, and Effect of Antiretroviral Therapy in a Patient with Anaplastic Large-Cell Lymphoma.

NEJM 2014; 371: 881-2
Ann Intern Med. 2014;161:319-327.

Summary of Allogeneic Transplants for HIV

Table 1. Men with Human Immunodeficiency Virus Type 1 (HIV-1) Infection Who Received an Allogeneic Transplant from a Stem-Cell Donor Who Was Homozygous for the *CCR5* delta32/delta32 Mutation.*

Location of Transplantation	Age of Patient	Type of Cancer	Type of Graft	Outcome after Transplantation
	yr			
Berlin†	40	Acute myeloid leukemia	HLA-matched unrelated	Alive after 7 yr, no viral rebound, no ART
Utrecht, the Netherlands‡	53	Myelodysplastic syndrome	Combined haploidentical bridge with umbilical-cord blood	Died from relapse of the myelodysplastic syndrome and pneumonia after 2 mo
Münster, Germany§	51	Non-Hodgkin's lymphoma	HLA-mismatched unrelated	Died from infection after 4 mo
Essen, Germany¶	30	Non-Hodgkin's lymphoma	HLA-matched unrelated	CXCR4-tropic HIV-1 rebound, died from relapse of non-Hodgkin's lymphoma after 12 mo
Minneapolis§	12	Acute lymphoblastic leukemia	Umbilical-cord blood	Died from GVHD after 3 mo
Santiago, Chile§	46	Non-Hodgkin's lymphoma	HLA-matched related	Died from pneumonia shortly afterward
Barcelona§	37	Non-Hodgkin's lymphoma	Combined haploidentical bridge with umbilical-cord blood	Died from relapse of non-Hodgkin's lymphoma after 3 mo

NEJM 2014; 371: 2437-38

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Summary of Marrow Transplantation

- Very Expensive >$500,000 per transplant
- Hard to find matched donors with CCR5 delta-32 deletion
- Lots of side effects with mortality substantial (~50%)
  - Antiretroviral treated individuals can live into their 70's and 80's
- Good for proof of principle but not a long-term solution that is widely applicable.

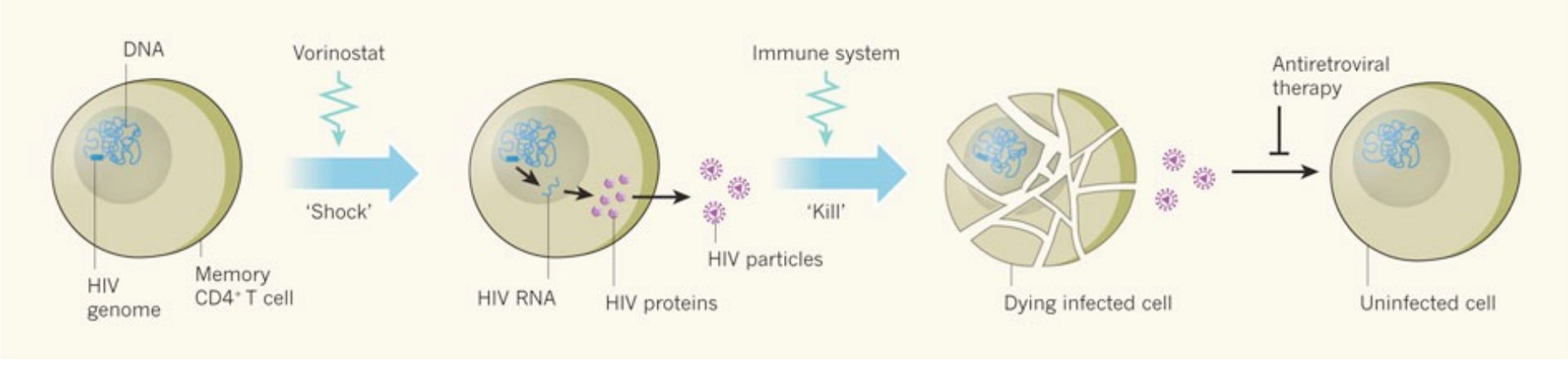
Approaches to a Cure

- Shock and Kill (wake up the reservoir – eliminate HIV infected cells)
- Therapeutic HIV vaccines
- Broadly neutralizing antibodies
- Gene-Modified T Cells (CRISPER / Zinc finger endonuclease)
- CAR-T Cells

Shock and Kill

The idea:

- Latently infected cells are “invisible” to the immune system
- **Shock:** Activate HIV replication, making the cells targets
- **Kill:** Once HIV-specific CD8+ T cells are stimulated, kill infected cells
- HIV treatment prevents released HIV from infecting other cells
- End result: The reservoir is eradicated

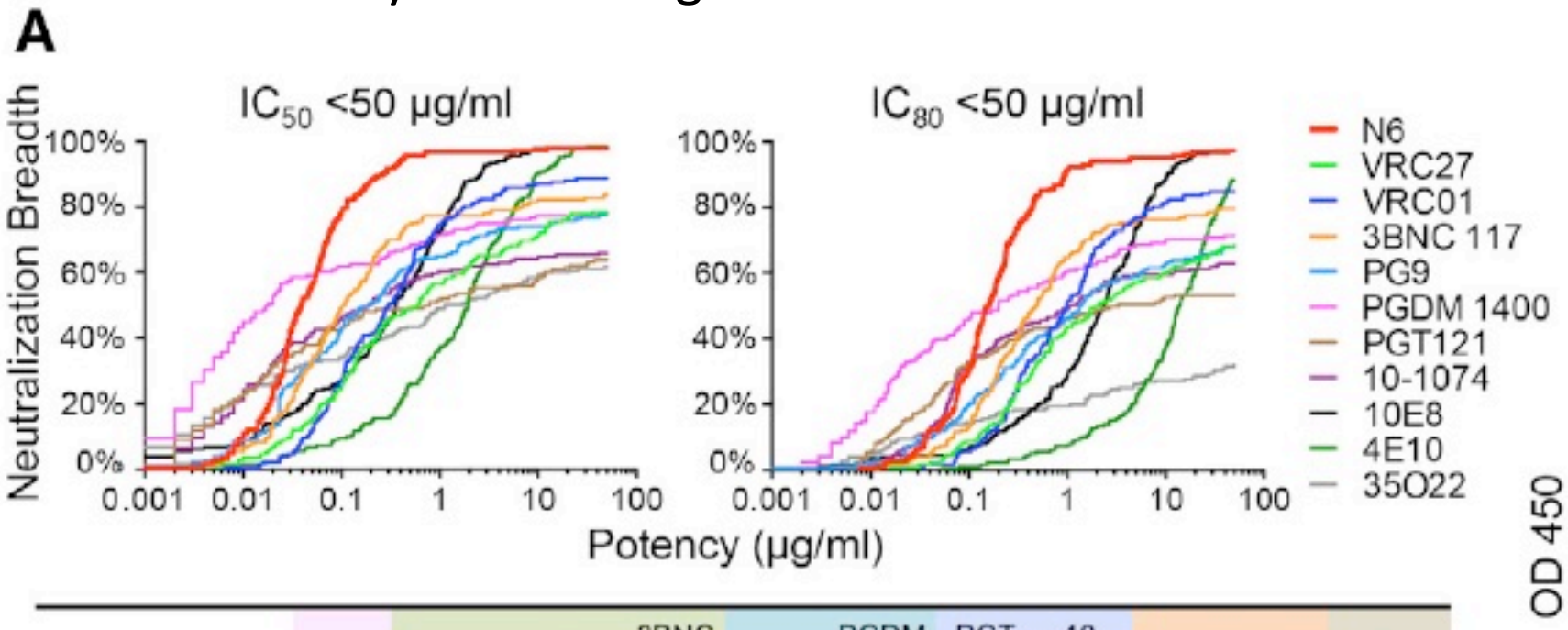


Deeks, Nature, 2012

Shock & Kill

- 45+ Studies done but it does not work.
- Sometimes we can activate cells (Shock them).
- Sometimes we can clear cells infected with HIV (Kill).

Broadly neutralizing antibodies – N6



	N6	VRC27	VRC01	3BNC 117	PG9	PGDM 1400	PGT 121	10-1074	10E8	4E10	35O22
No. of viruses	181	175	177	181	177	171	177	178	180	181	181
IC_{50} <50 µg/ml	98%	78%	89%	83%	78%	78%	64%	66%	98%	98%	62%
IC_{50} <1 µg/ml	96%	56%	73%	76%	64%	70%	50%	60%	72%	37%	48%
GM IC_{50}*	0.044	0.297	0.250	0.094	0.109	0.015	0.051	0.036	0.222	1.303	0.058
Median IC_{50}	0.038	0.217	0.248	0.073	0.088	0.008	0.022	0.022	0.352	1.920	0.033
Binding site		CD4-binding site			V1V2		V3		gp41 MPER		gp120-gp41

* Geometric Mean IC_{50} concentration is µg/ml.

N Engl J Med 2016;375:2037-50.DOI: 10.1056/NEJMoa1608243

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BNABS –Broadly Neutralizing Antibodies

- Despite many studies, no control of HIV when stopping HIV treatment
- Studies focused now on giving BNABs every 3-6 months to control HIV sometimes along with other long-acting HIV treatment.

A COMPARATIVE STUDY OF AUTOLOGOUS CD4+ T CELLS GENETICALLY MODIFIED AT THE CCR5 GENE BY ZINC FINGER NUCLEASES SB-728 VERSUS *EX VIVO* EXPANDED UNMODIFIED AUTOLOGOUS CD4+ T CELLS IN TREATED HIV-1 INFECTED SUBJECTS

Protocol Number: U01 AI 131295

Principal Investigator: Rafick Sekaly, PhD (Case Western)

Lead Clinical Investigator: Carl J. Fichtenbaum, MD (UC)

Research Sites: Case Western, Cincinnati, San Francisco (UCSF)

TRAILBLAZER STUDY

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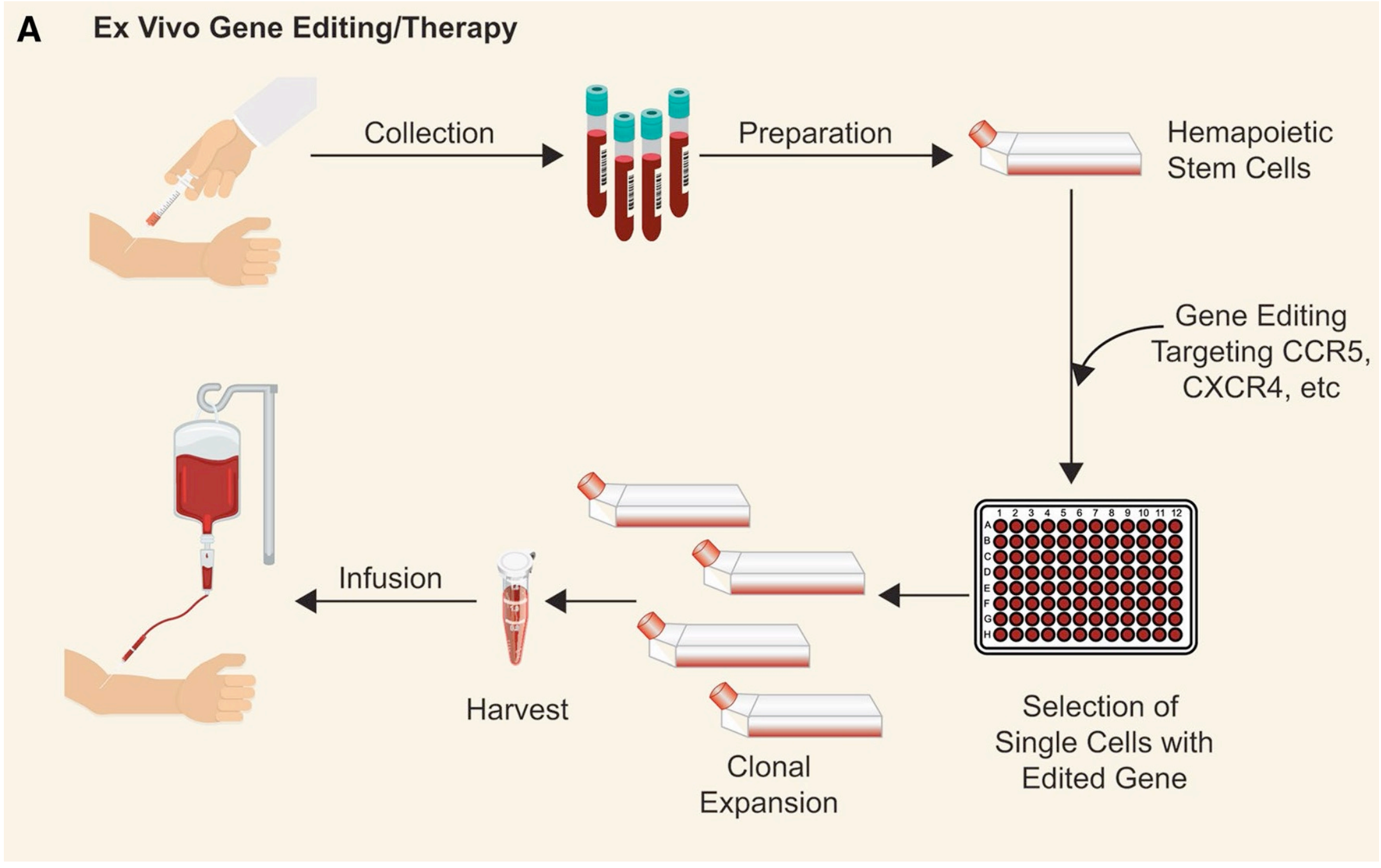
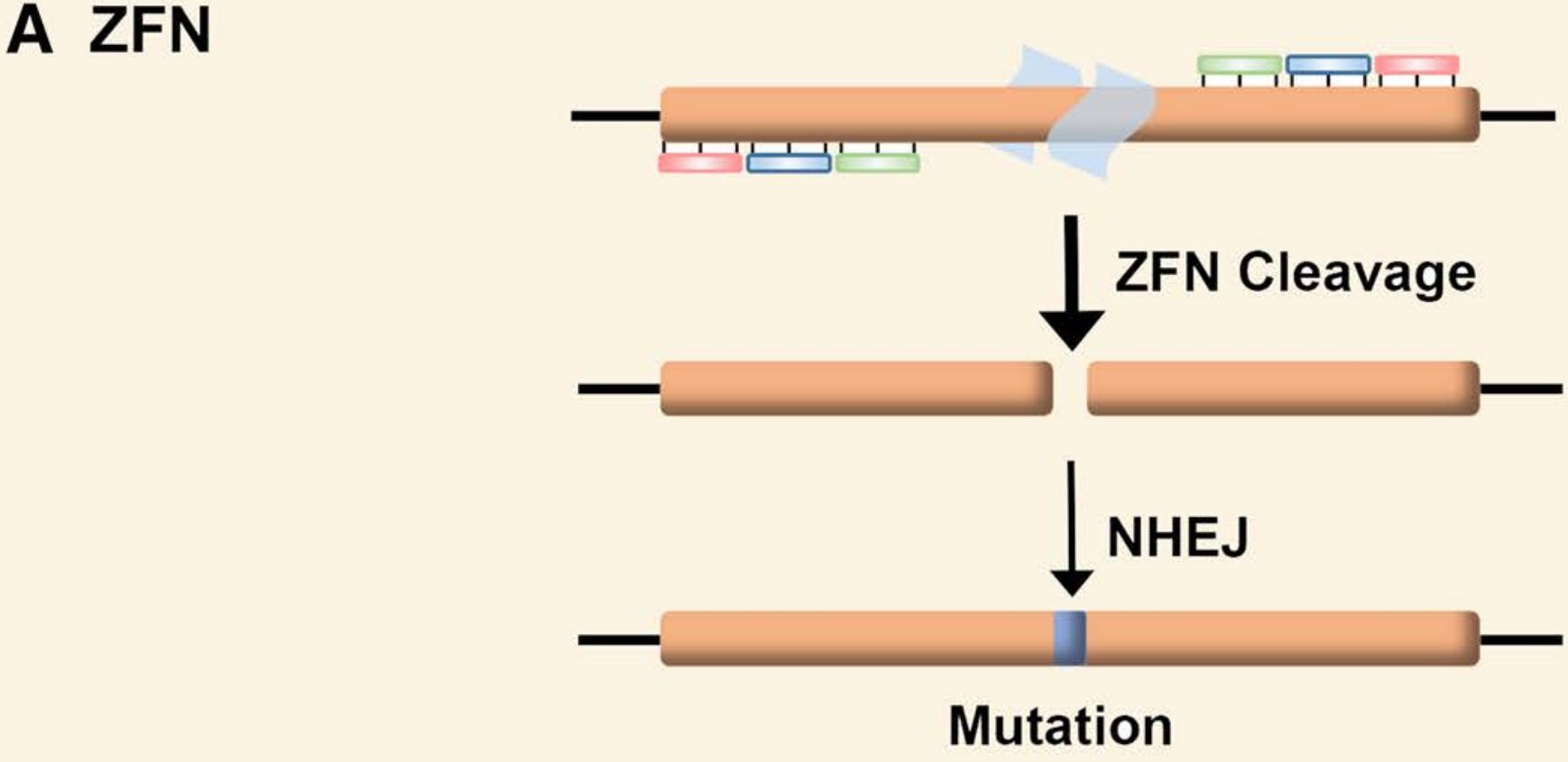
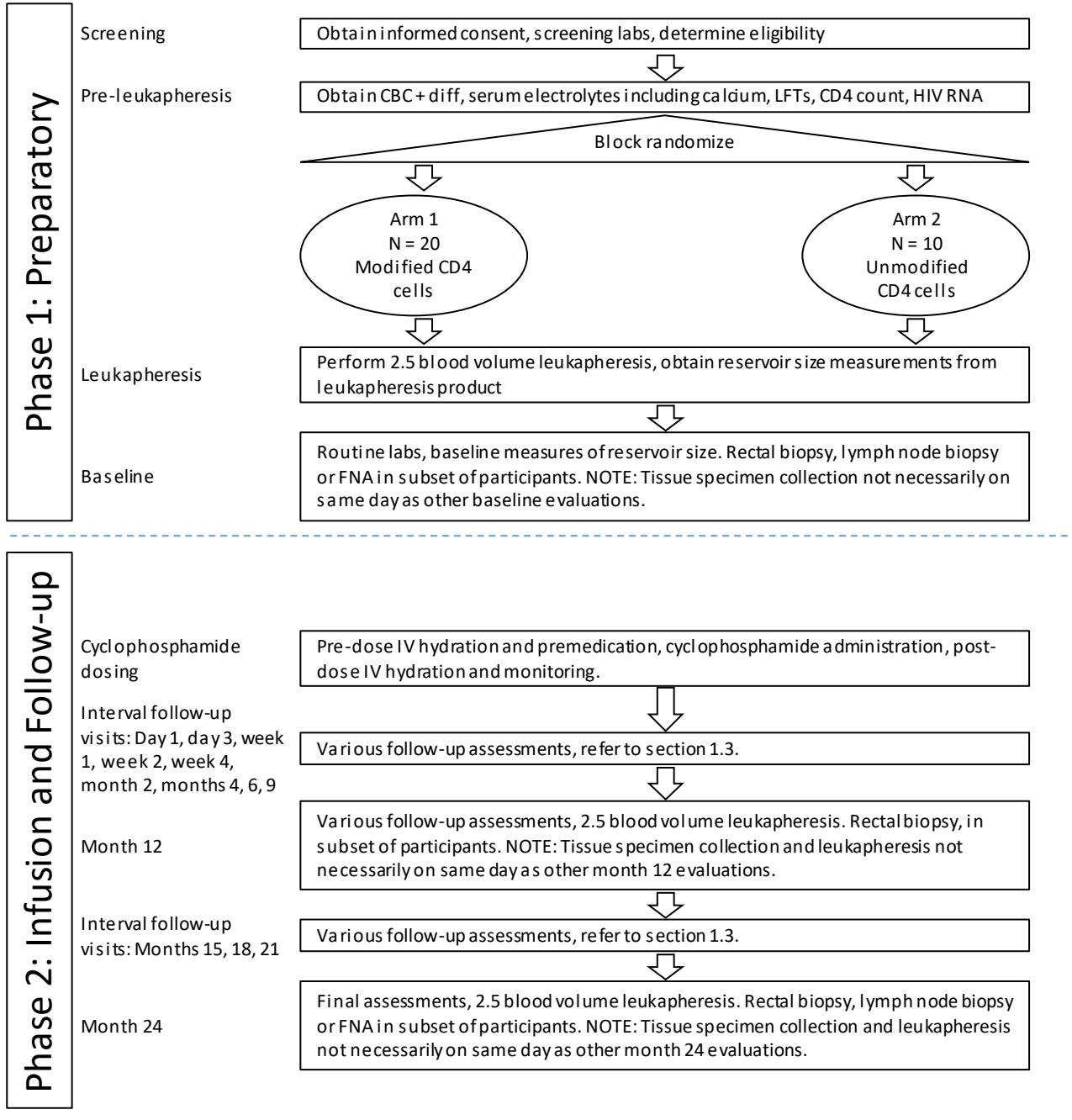


Cell. Mol. Life Sci. (2017) 74:2439–2450

Schematic of Zinc Finger Nuclease Cleavage



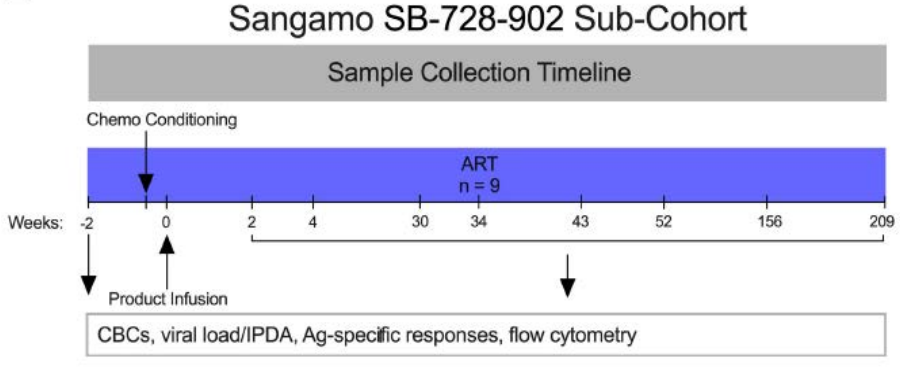
Cell. Mol. Life Sci. (2017) 74:2439–2450

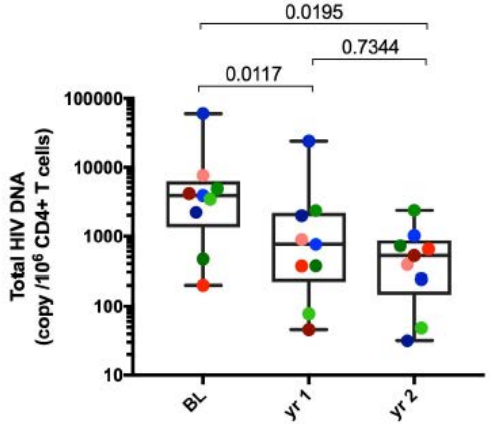


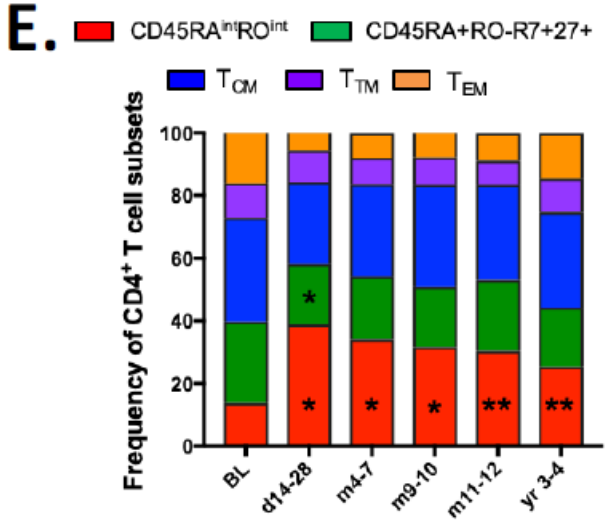
TRAILBLAZER Study

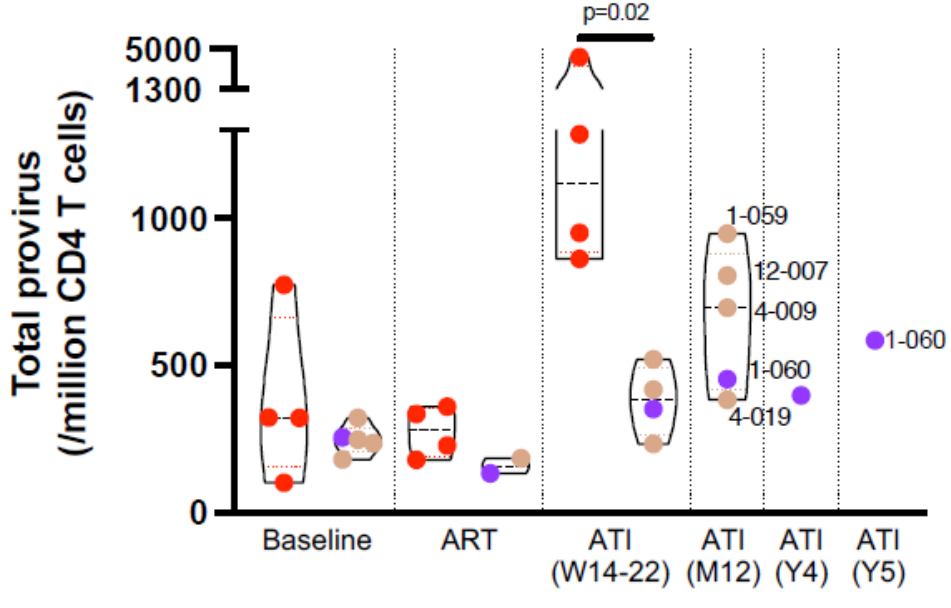
- Will be finished December 2023
- 30 participants
  - Cincinnati – 14
  - Cleveland – 10
  - San Francisco – 6
- Collecting samples from blood, lymph nodes, intestines and spinal fluid
- Will transformed cells lower amount of HIV in the reservoir?

Some Hope From TBZ Technology









Courtesy of Rafick Sekaly

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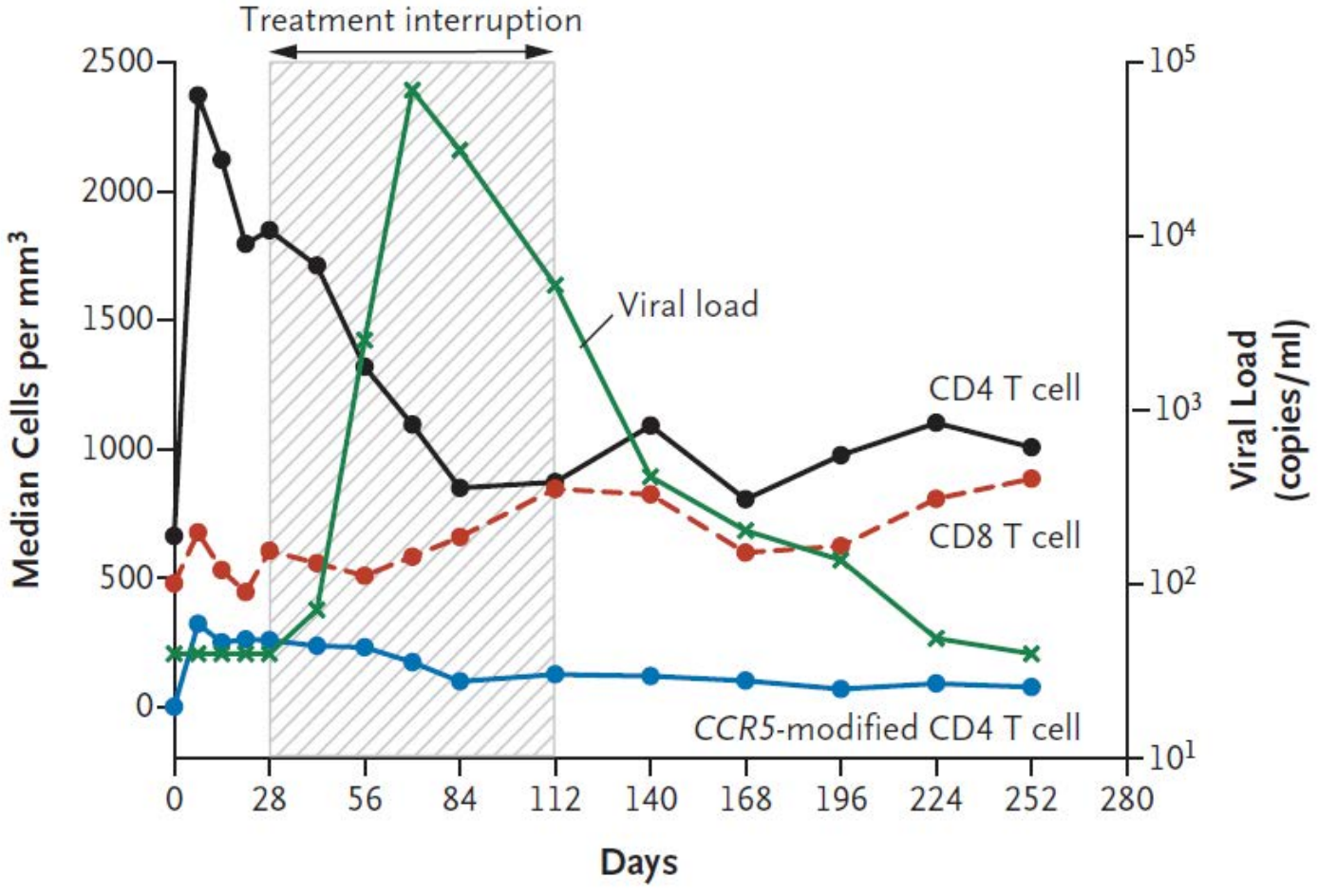
TBZ Technology Study Fails to Control HIV



Tebas et al. N Engl J Med 2014;370:901-10. DOI: 10.1056/NEJMoa1300662

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A Cautionary Note from an Advocate

- "H.I.V. is not going away anytime soon. I've been living with it for more than 20 years and have seen the overhyped stories promising a cure around the corner pop up regularly, particularly around the time of big AIDS conferences. The news last week that a second person seems to have gone into long-term remission from H.I.V. after a stem cell transplant is a real scientific advance. But I fear the sensationalism with which this report was received could do more harm than good. It obscures the actual struggles we face in combating this epidemic." *NY Times Opinion 3/9/2019*
  - Gregg Gonsalves, Assistant Professor of Public Health, Yale University

https://www.nytimes.com/2019/03/09/opinion/sunday/cure-hiv-aids.html

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HIV Cure

Will likely require a multi-pronged approach

- Suppress HIV replication in entire body (cellular compartments)
- Wake-up HIV expression in latently infected CD4+ cells
- Clearance of cells with HIV
  - Will likely require enhancement of HIV-1 specific immune responses