

Primer on Cure

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National Institute of
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Infectious Diseases

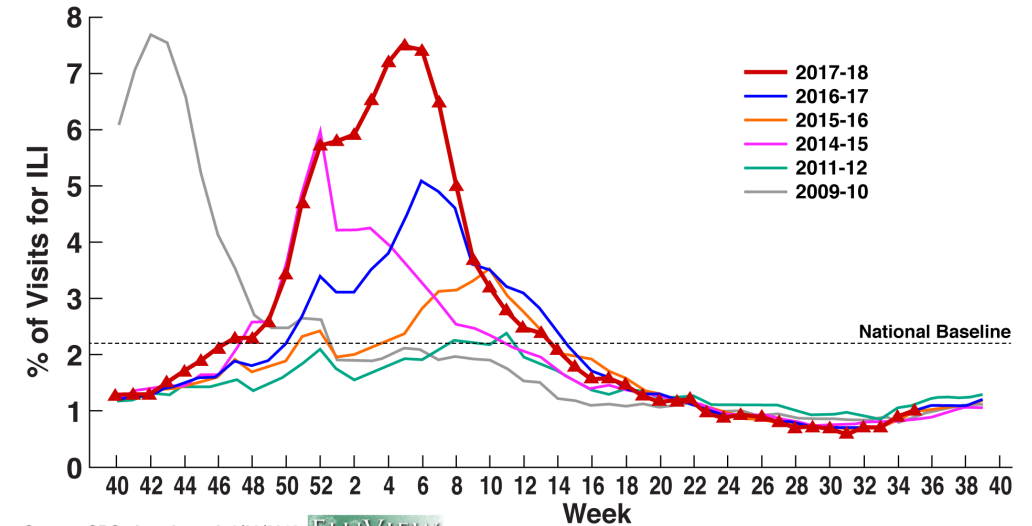
What Does Cure Mean?

- **Merriam-Webster says:**
 - A complete or permanent solution or remedy
 - To bring about recovery from
 - To permanently restore to health, soundness
- **For well known viral infections what is cure?**
 - Influenza
 - Hepatitis C
 - HIV

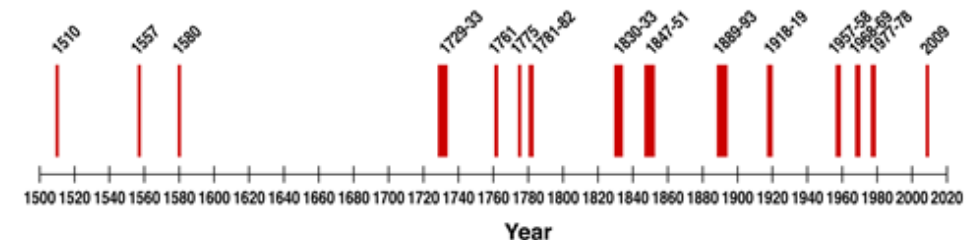
Influenza

- Uncomplicated flu
- After exposure, short incubation (1-2 days)
- Fever (3-4 days)
- Weakness and/or fatigue (up to 2-3 weeks)
- Clear virus within 10-14 days
- As influenza evolves, susceptibility to infection recurs

Weekly Reporting of Influenza-Like Illness in the United States by Season

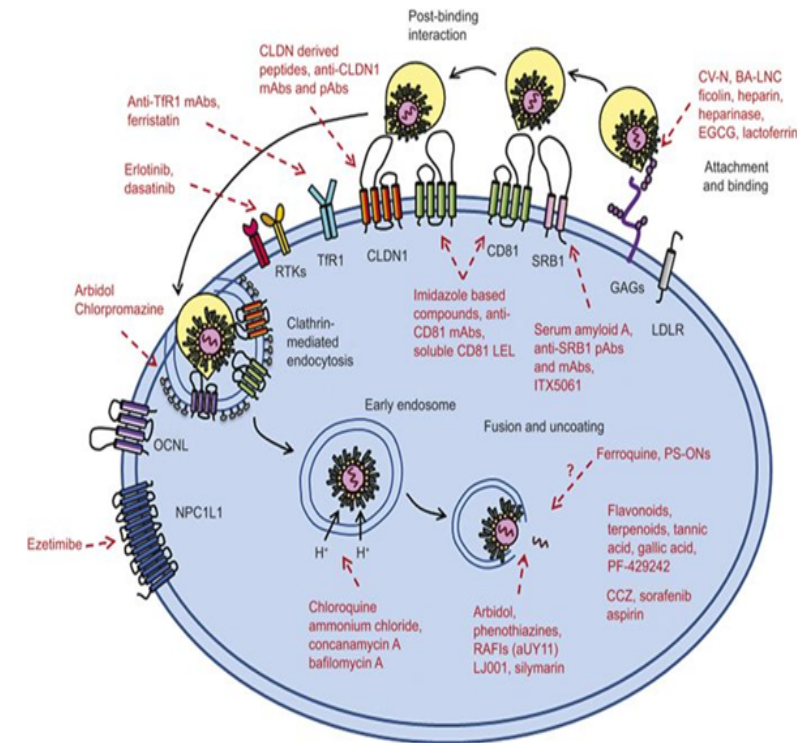


500 Years of Likely and Documented Influenza Pandemics



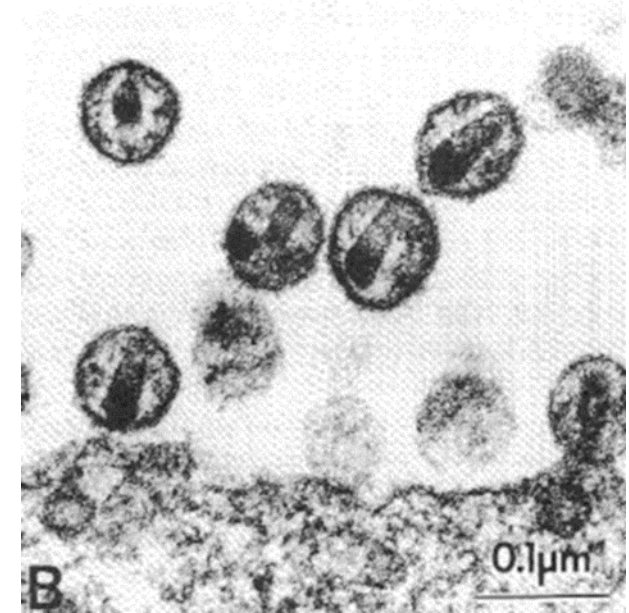
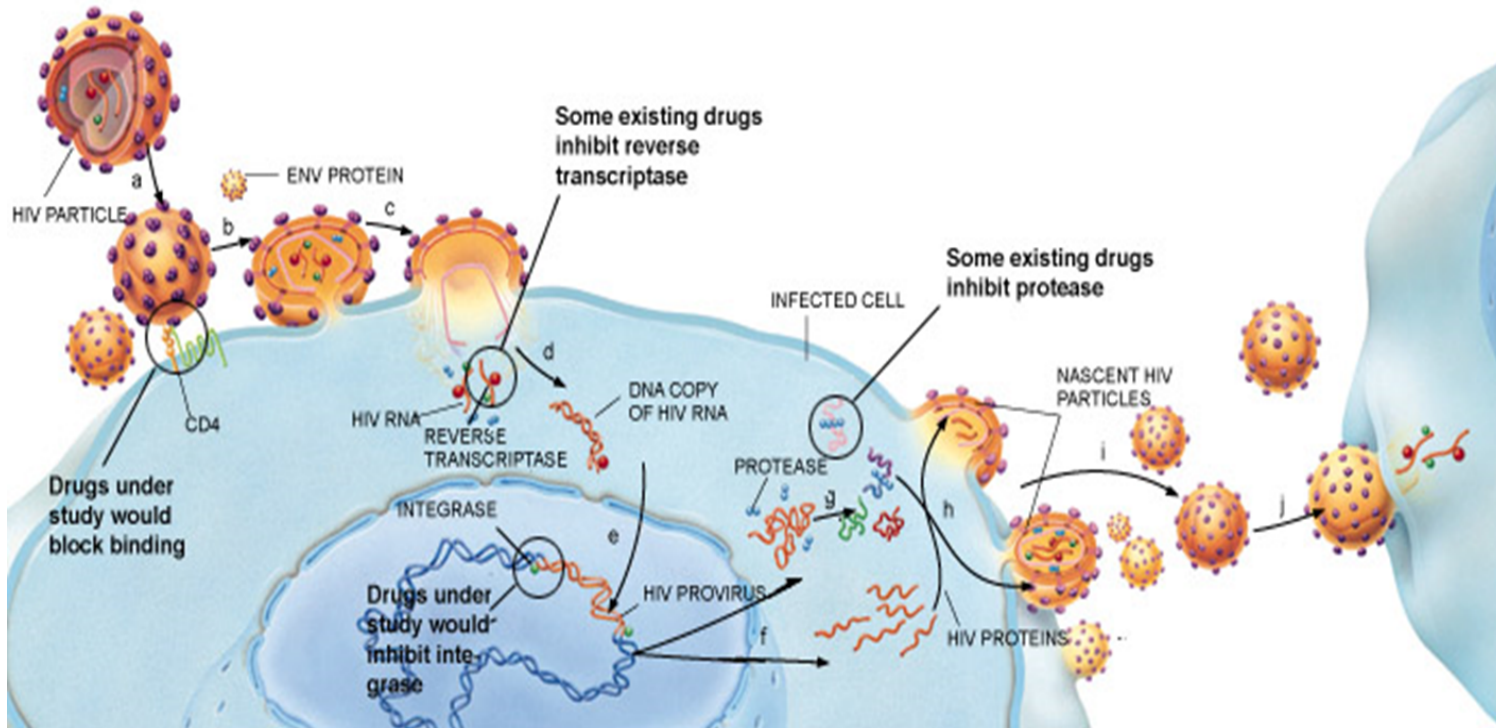
Hepatitis C Virus

- Approximately 15- 25% of people infected with HCV clear their infection within the first 6 months of infection
- Early in infection most people are asymptomatic
- Progression to liver disease takes time and is accelerated by cofactors such as excessive alcohol consumption
- Curable in greater than 90% of people with HCV with current medications
- If cured by drug treatment, reinfection is possible



What Makes HIV Unique

- A central tenet in immunology is activate and respond, create memory and rest, poised to respond should the pathogen return
- By becoming part of the CD4 cell DNA, HIV thrives by exploiting the process that works against other pathogens



The Importance of Accurate Measurement

UPDATE

National Cancer Institute/Office of Cancer Communications

January 11, 1985

Blood Test for AIDS Proves Reliable and Practical

A team of National Cancer Institute (NCI) and collaborating scientists has demonstrated that a simple blood test for the virus called HTLV-III, the probable cause of AIDS, is a reliable, specific, and sensitive tool for screening large numbers of blood samples for antibodies to HTLV-III.

Immediate Importance of Blood Test for HIV

- **Protect blood supply**
- **Diagnosis, especially early in disease**
- **Demonstration of extent of asymptomatic disease**
- **Epidemiological and natural history studies**

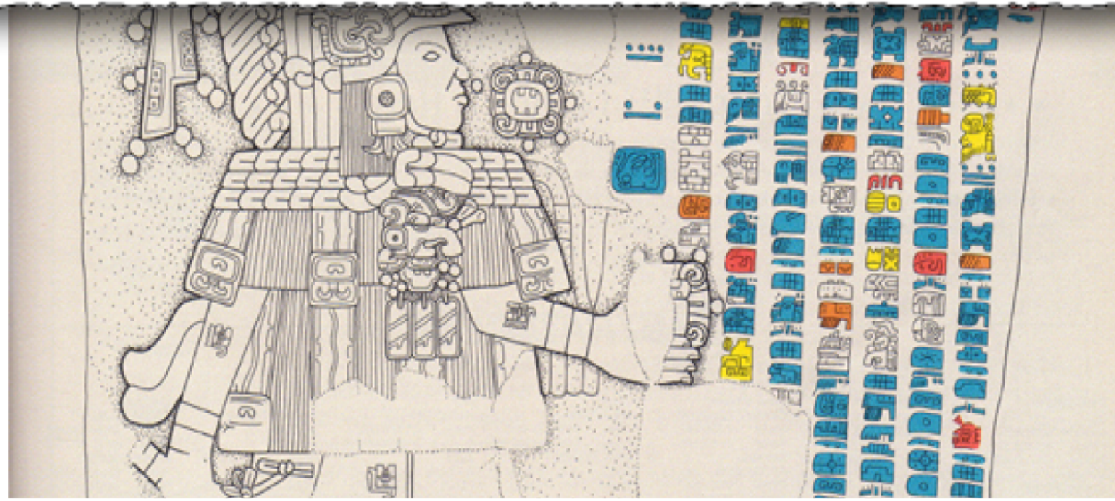
AMERICAN
ASSOCIATION FOR THE
ADVANCEMENT OF
SCIENCE

19 March 1993
Vol 259

SCIENCE

High Levels of HIV-1 in Plasma During all Stages of Infection Determined by Competitive PCR

M Piatak Jr., JD Lifson, et al.



January 12, 1995

International weekly journal of science

nature

Rapid Turnover of Plasma Virions and CD4 Lymphocytes in HIV-1 Infection

DD Ho, M Markowitz, et al.

Viral Dynamics in Human Immunodeficiency Virus Type 1 Infection

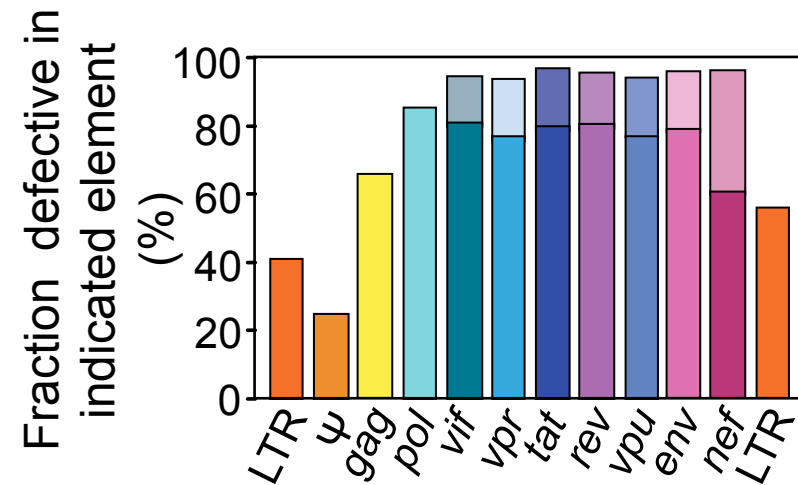
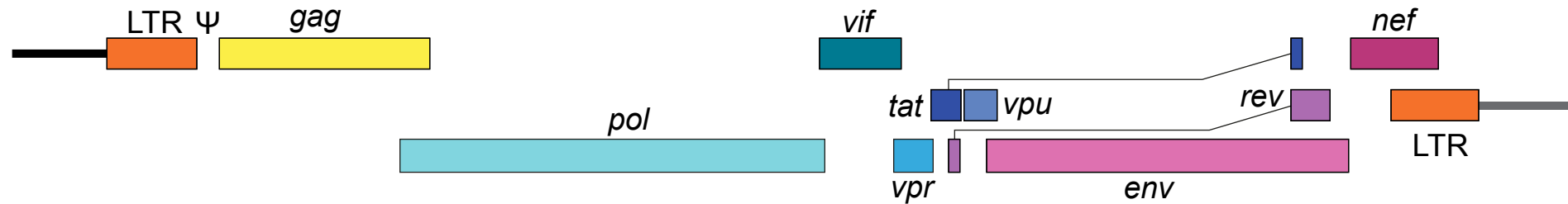
X Wei, GM Shaw, et al.

A quantitative approach for measuring the reservoir of latent HIV-1 proviruses

Katherine M. Bruner, Zheng Wang, Francesco R. Simonetti, et al.

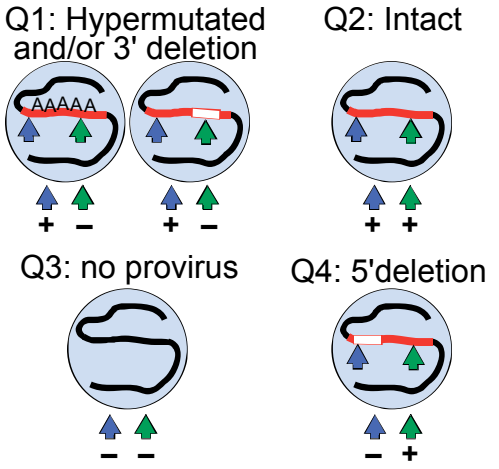
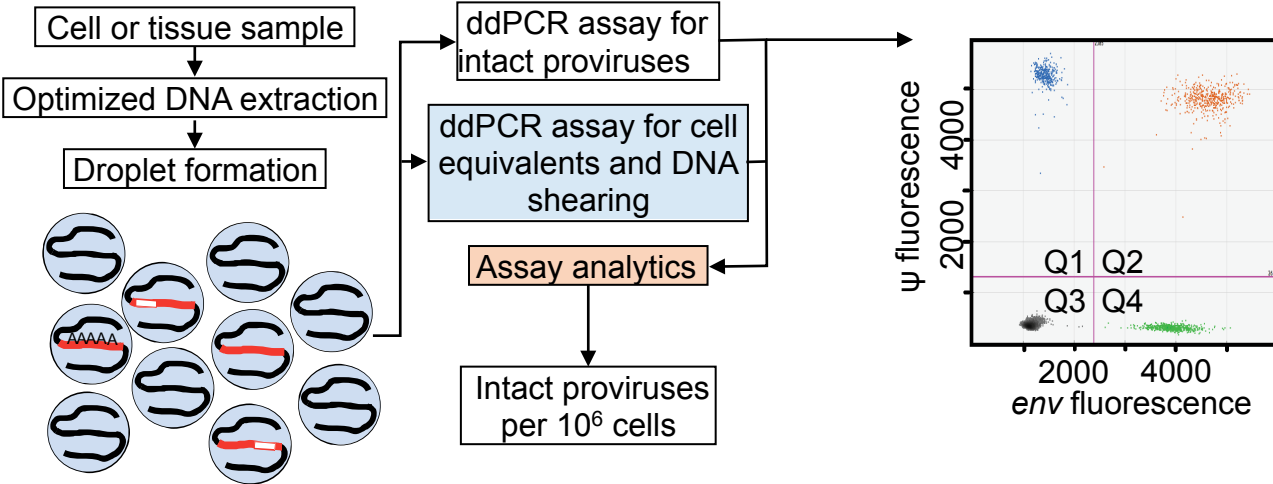
Nature 566, 120-125 (2019)

Most Proviruses Are Defective

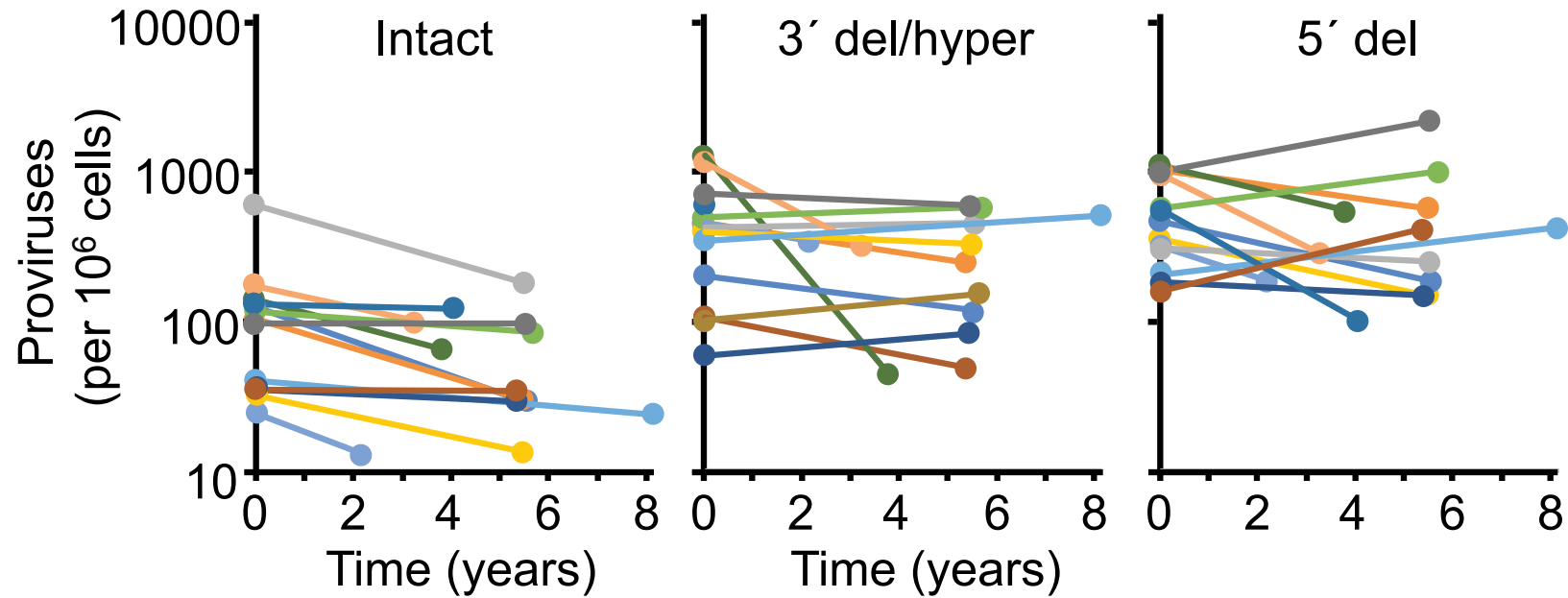


- Most proviruses are defective in most viral genes
- Cells with defective and intact proviruses may be affected differently by shock and kill interventions

Intact Proviral DNA Assay



Decay of Intact and Defective Proviruses



Pathways to Sustained ART-Free HIV Remission

Eradicate the replication-competent HIV reservoir – classic **“cure”**



Control viral rebound without eradication of HIV in the absence of ART – **“sustained virologic remission”**

Pathways to Sustained ART-Free HIV Remission

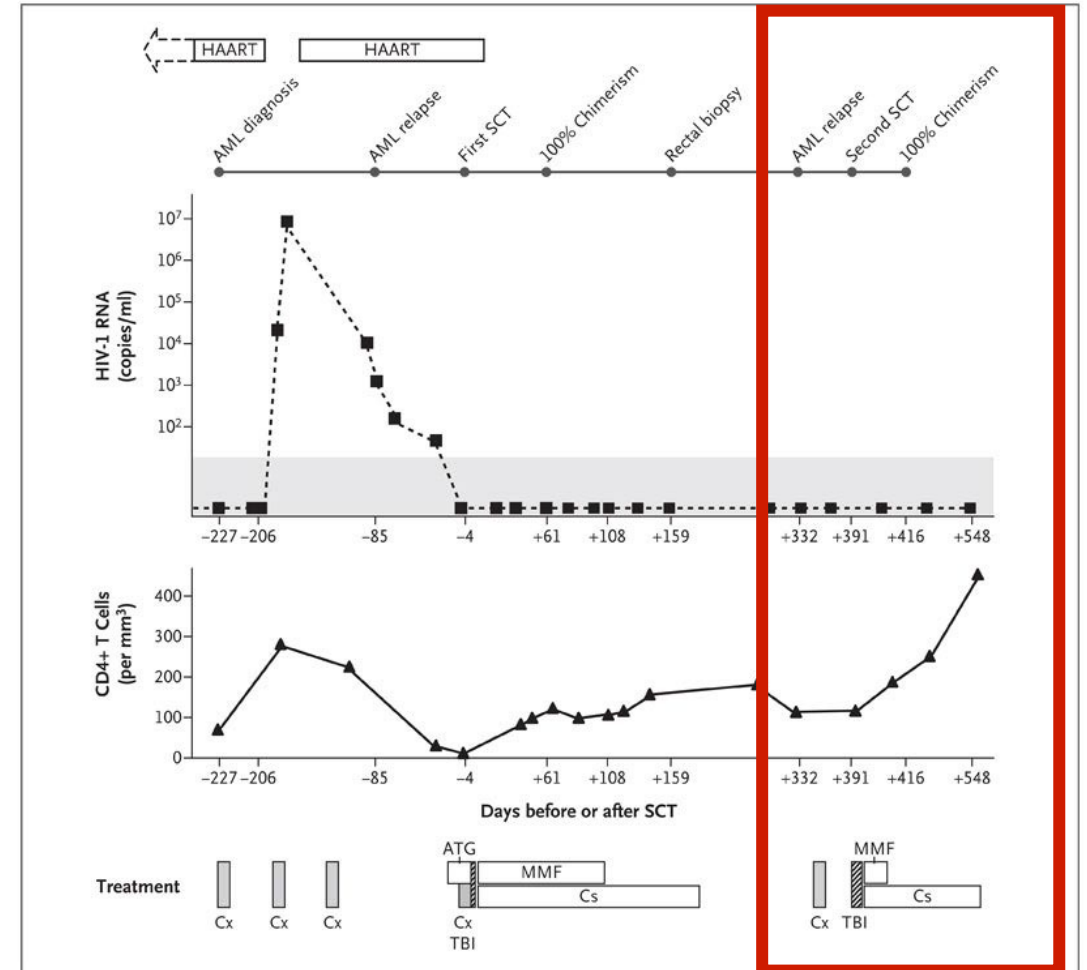
Eradicate the replication-competent HIV reservoir – classic **“cure”**



Control viral rebound without eradication of HIV in the absence of ART – **“sustained virologic remission”**

What Can We Still Learn From TRB?

- Eradicate the replication competent HIV reservoir required replacement, twice of Timothy's immune system
- Once to clear HIV, the second to clear his leukemia
- This sledgehammer strategy is applicable when faced with a lethal cancer



Latency-reversing agents to deplete HIV reservoirs

Modified antibodies and/or effector cells directed at reservoir

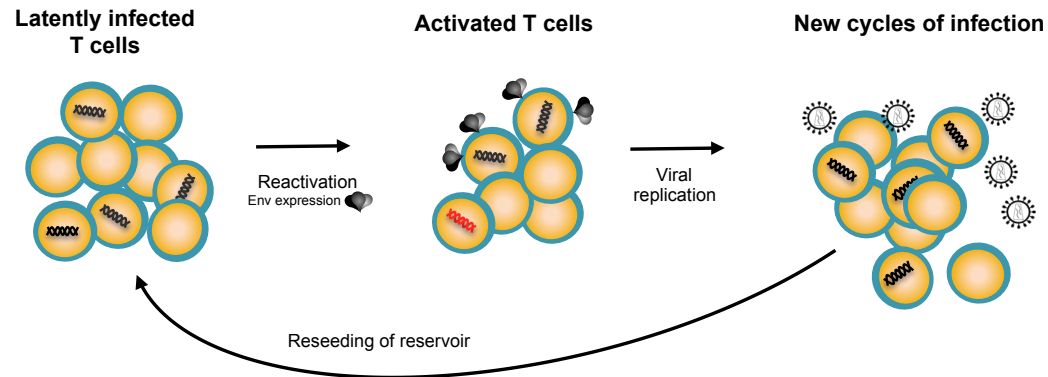
Potential Strategies to Eradicate HIV from an HIV-Infected Individual

Stem cell transplantation

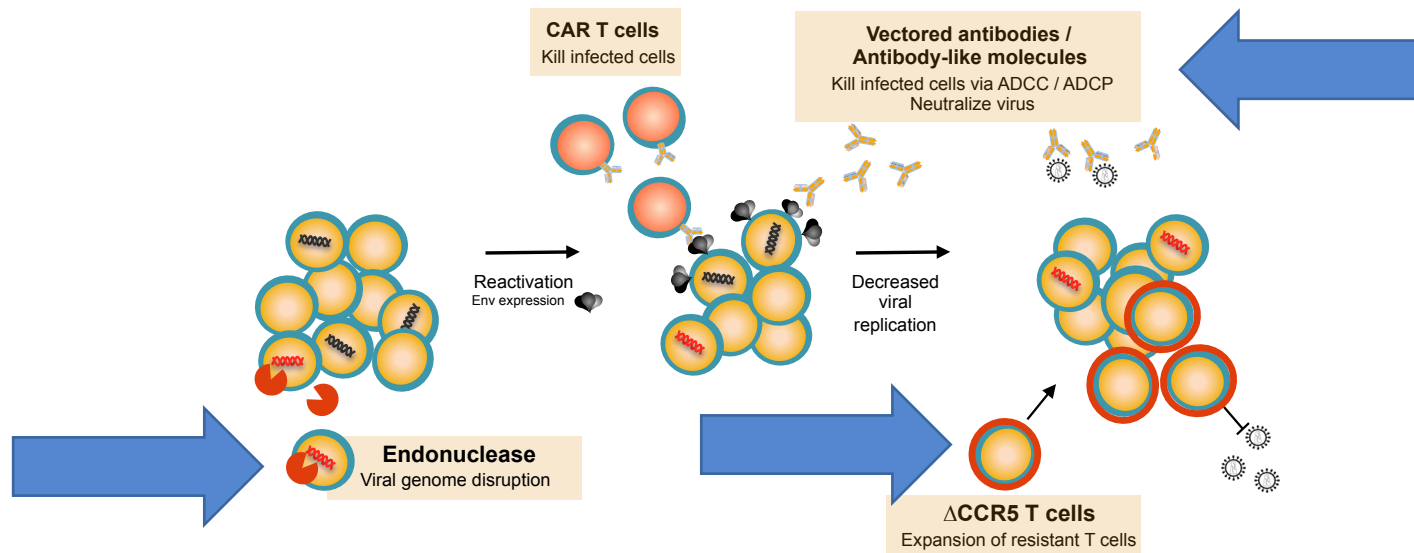
Gene editing

Multiple Targets for Anti-HIV Gene Therapy

A



B



Pathways to Sustained ART-Free HIV Remission

Eradicate the replication-competent HIV reservoir – classic “cure”



Control viral rebound without eradication of HIV in the absence of ART – “sustained virologic remission”

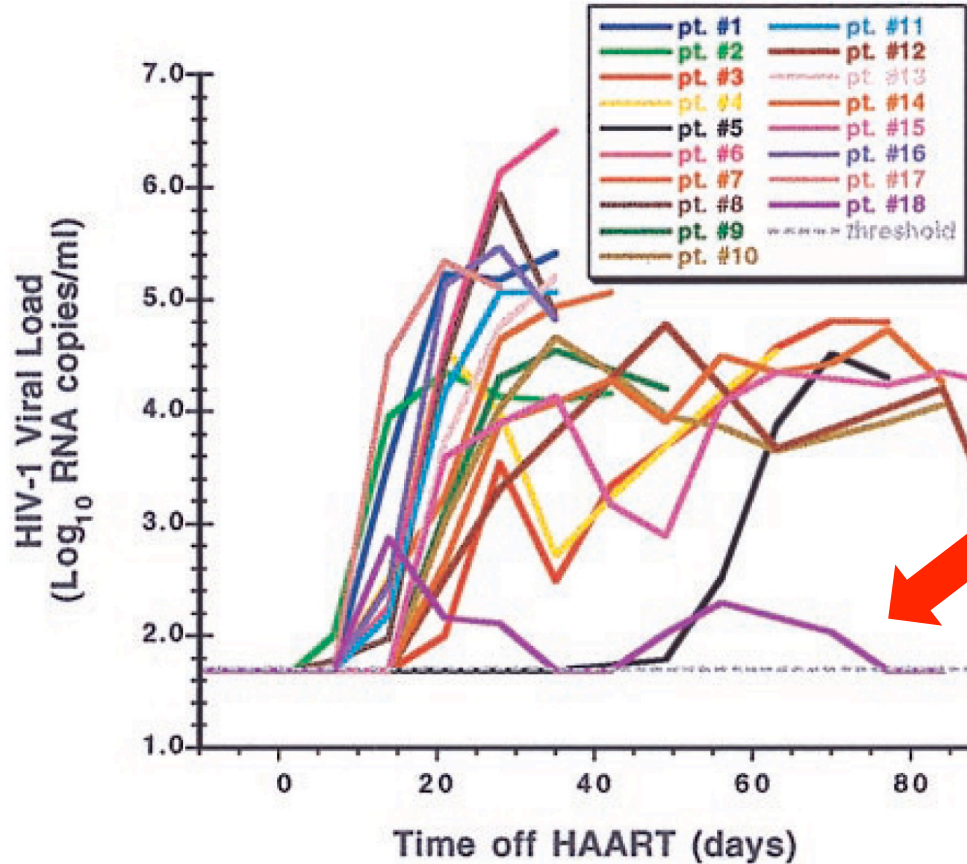
Optimal Criteria for Maintaining ART-Free Remission of HIV Infections Without Direct Eradication of Virus

- **Low risk to patient**
- **Scalable**
- **Potentially leads to induction of durable immune-mediated control of virus**

ART-Free Remission of HIV Infection

- **ART-free remission, but requiring intermittent or continual non-ART intervention**
- **ART-free remission resulting from induction of durable immune-mediated control of virus without further intervention**

“...sustained virologic control...”



HIV-1 and T cell dynamics after interruption of highly active antiretroviral therapy (HAART) in patients with a history of sustained viral suppression

Richard T. Davey, Jr.¹, Niranjan Bhat², Christian Yoder¹, Tae-Wook Chun³, Julia A. Metcalf⁴, Robin Dewar⁵, Ven Natarajan⁶, Richard A. Lempicki⁵, Joseph W. Adelsberger⁵, Kirk D. Miller¹, Joseph A. Kovacs¹, Michael A. Polis¹, Robert E. Walker¹, Judith Falloon¹, Henry Masur¹, Dennis Gee¹, Michael Baseler⁵, Dimitar S. Dimitrov¹, Anthony S. Fauci¹, and H. Clifford Lane¹

¹National Institute of Allergy and Infectious Diseases, (NIAID) and ²Critical Care Medicine Department, National Institutes of Health, Bethesda, MD 20892; ³Science Applications International Corporation (SAIC), Frederick, MD 21702; and ⁴National Cancer Institute/Frederick Cancer Research and Development Center, National Institutes of Health, Frederick, MD 21702

“One patient (patient 18) in this study appeared capable of maintaining significant control of viral replication after discontinuation of drug therapy.”

ART-Free Remission of HIV Infection

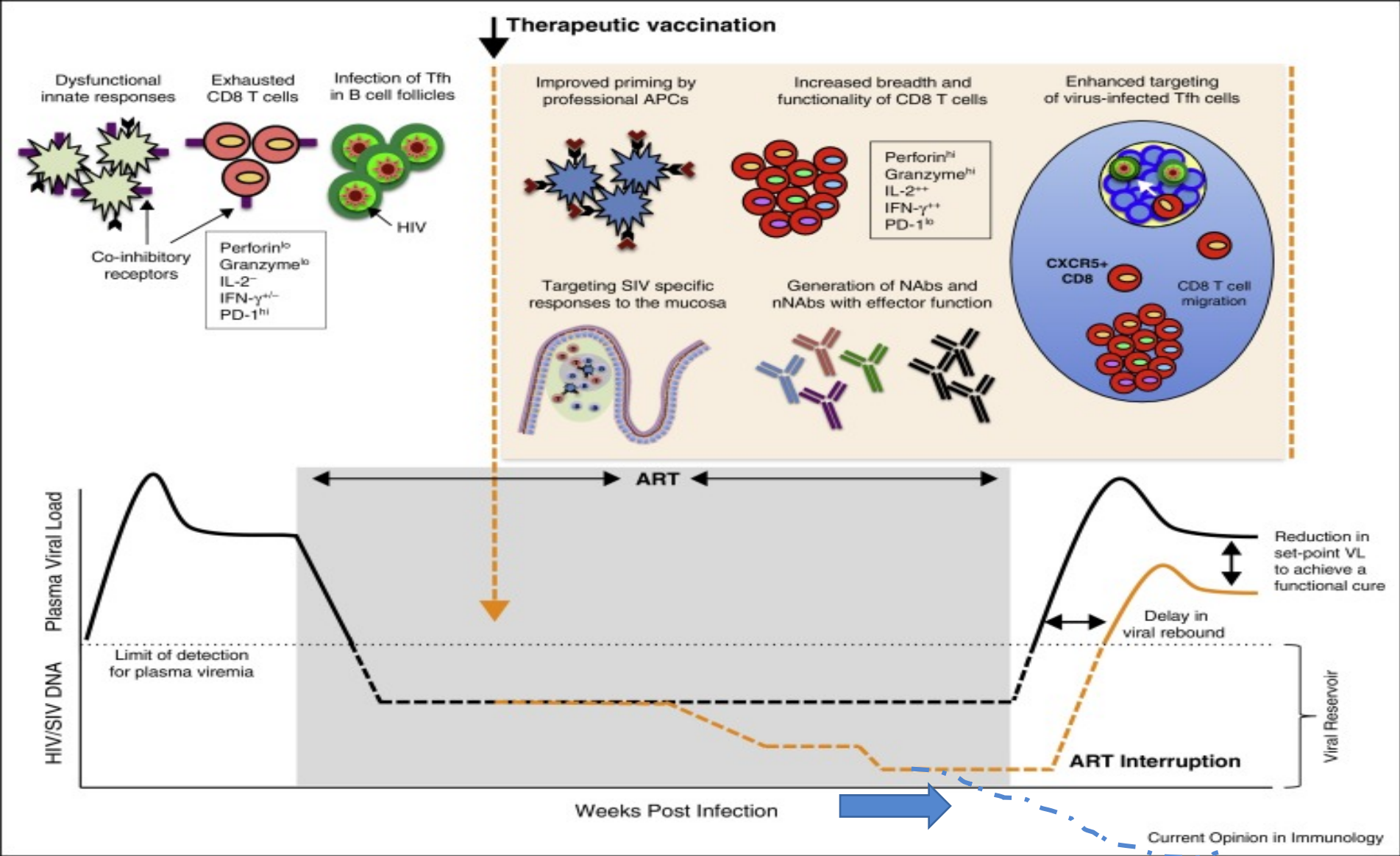
■ **ART-free remission, but requiring intermittent or continual non-ART intervention**

■ **ART-free remission resulting from induction of durable immune-mediated control of virus without further intervention**

ART-Free Approaches Towards Durable Control of HIV Infection Requiring Intermittent or Continual Non-ART Intervention

- **Therapeutic vaccination**
- **Passive transfer of broadly neutralizing anti-HIV monoclonal antibodies (bNAbs)**

Activities of a Therapeutic Vaccine



nature

Accelerated Article Preview

LETTER

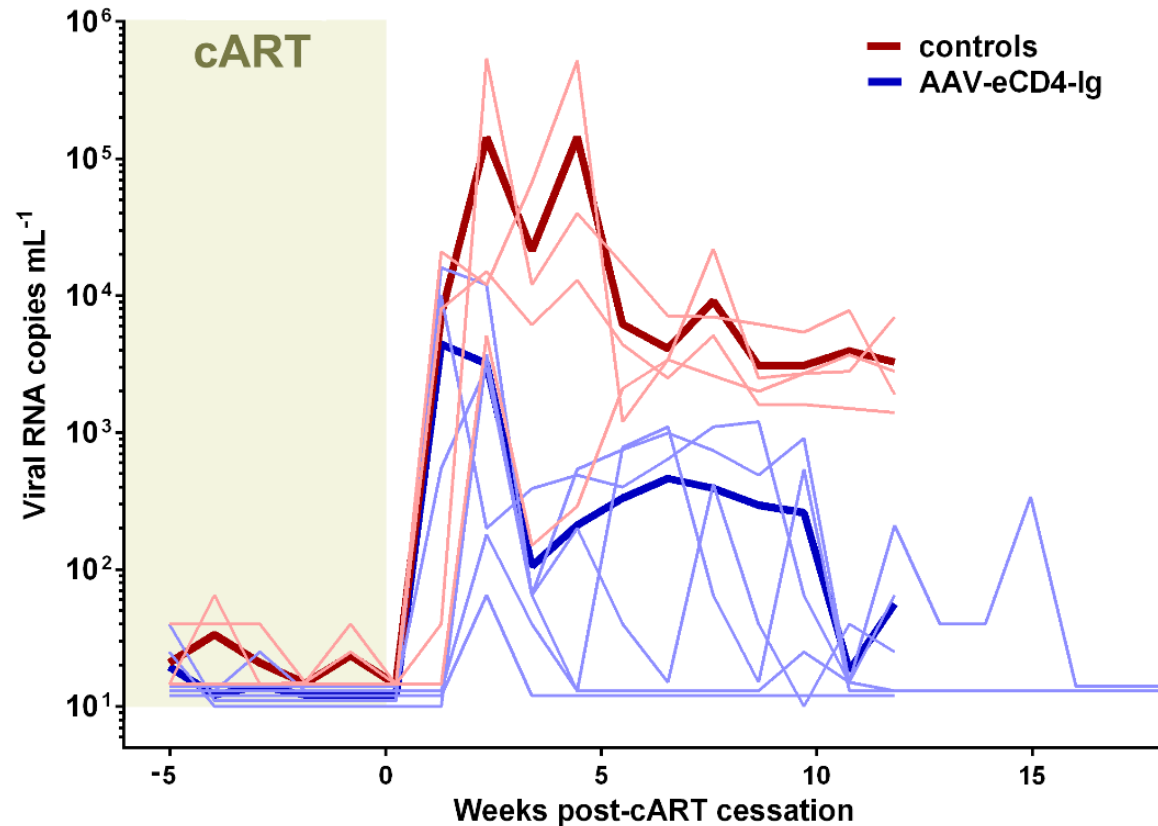
doi:10.1038/nature20583

Ad26/MVA Therapeutic Vaccination with TLR7 Stimulation in SIV-Infected Rhesus Monkeys

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



Summary of a Functional Cure Study with rh-eCD4-Ig



		Most recent values:	
	Macaque	Viral loads (RNA copies/ml)	eCD4-Ig levels (μg/ml)
Controls	r13015	1400	0
	r13044	1900	0
	r13070	7000	0
	r13092	2800	0
AAV-eCD4-Ig	r14057	65	6
	r14089	25	10
	r14058	<15	8
	r14079	<15	19
	r13075	<15	8
	r13084	<15	3

In Conclusion

- **We are approaching the end of the beginning**
- **Do we have a new assay, will it be dynamic enough?**
- **Hints of success are appearing**
- **We will build upon our successes and learn from our failures**
- **Together we can succeed**