

Update on the Cure: From in Between Days to Just Like Heaven



Katharine J. Bar, MD
Associate Professor of Medicine
University of Pennsylvania
Philadelphia, PA



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Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years

Dr Bar reported serving as a consultant for ViiV Healthcare,
Merck & Co, Inc, and AbbVie, Inc. (Updated October 27,
2025)



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Learning Objectives

After attending this presentation, learners will be able to:

- Identify examples of HIV cure from stem cell transplant and natural immunity
- Describe several gene therapy strategies for HIV cure
- Explain results from recent trials of bnAbs given at the time of ART initiation
- Communicate with patients about research in HIV cure



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Hey Doc – What’s going on with HIV Cure? I know ART is great and improving, but *am I going to have to keep taking ART forever?*



Hypothetical young person with HIV at a routine clinic visit

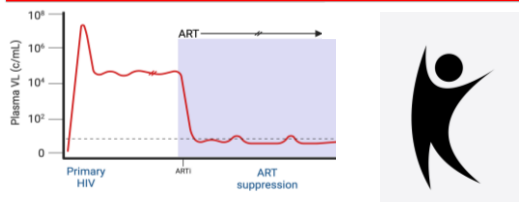
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Outline

- Brief Reminder of HIV Persistence
- HIV Cure examples
 - Gene therapy strategies
- Natural HIV Control
 - Elite Control & Post-Treatment Control
 - Immunotherapy strategies
- Clinical Trials of bnAbs at ART Initiation

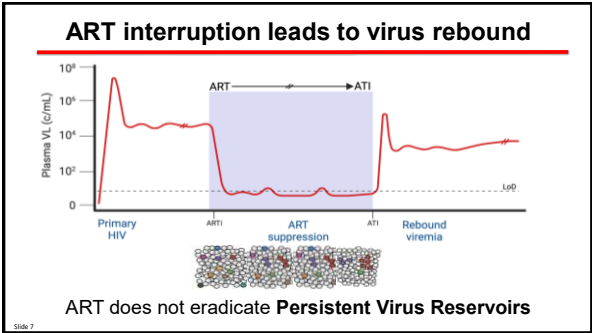
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ART stops virus replication

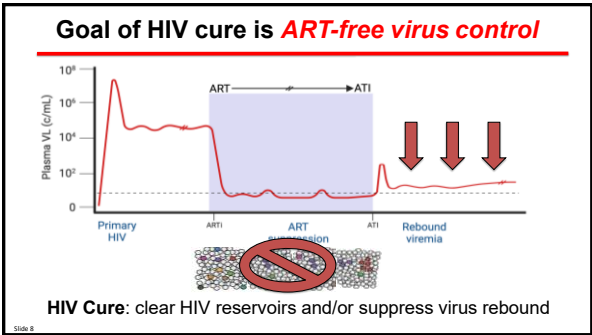


- ART blocks virus replication, enables return to health, prevents ongoing transmission

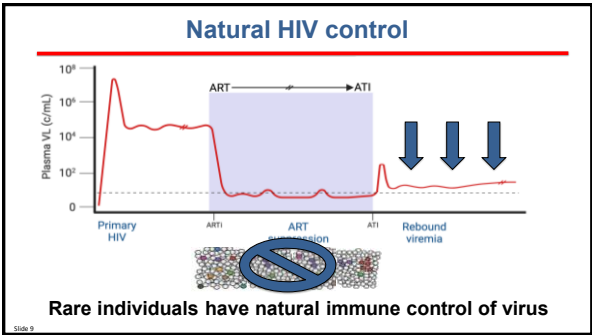
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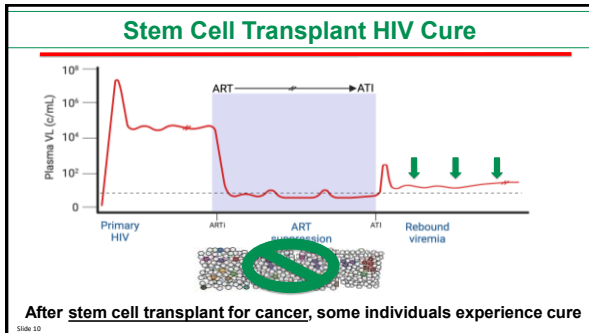
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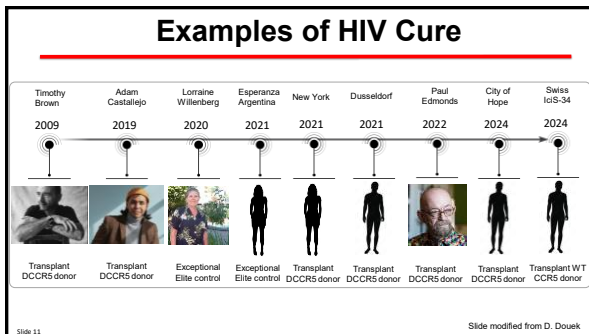
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Stem Cell Transplant w CCR5 Δ 32 donor

- In PWH **and cancer** – where SCT was indicated for cancer
 - Donor with HIV-resistant cells
 - Systemic chemotherapy
 - Graft vs. Host Disease
 - Immunotherapeutics
- Reservoir measures negative
- ART stop → Durable remission
- Not scalable – but proof of concept

Gene therapy: ex vivo and in vivo editing of CD4 T cells to knockout CCR5 expression and become resistant to HIV

Slide 12

Haworth, Peterson, Kiern, Cryotherapy 2017

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Gene Therapy Approaches

CAR-T cells

bnAb delivery

CRISPR-Cas9

- CAR-T cells:** CAR-NK cells
 - A5419: Phase 1 study of DuoCAR-T cell + vaccine to enhance durability
- Delivery of bnAbs** by DNA/RNA, LNP, AAV, B cells
 - Casazza NIH Phase 1; A5430: Phase 1 study of AAV9-bnAb
- CRISPR** or other recombinase HIV excision
 - EBT-101 – Phase 1 trial AAV9-delivery CRISPR-Cas9 (safe, no change rebound)

Slide 13
Casazza Nat Med 2019, Maldini Nat Med 2020, Burdo Gene Therapy, 2023

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Durable vectored delivery of bnAbs to infant macaques

AAV9-bnAb delivery to infant NHP – prevents oral infection

Maternal exposure + AAV9 delivery to infant NHP

Durable bnAbs prevented rectal infection in adolescence

HIV prevention and cure in infants, children & adults

- AAV-9 bnAb delivery to infant rhesus macaques**
 - Long-lived production of bnAbs; no ADA in young animals
 - Protection against oral, rectal challenge; suppression of viremia

Slide 14
Ardeshir et al., Nature 2025

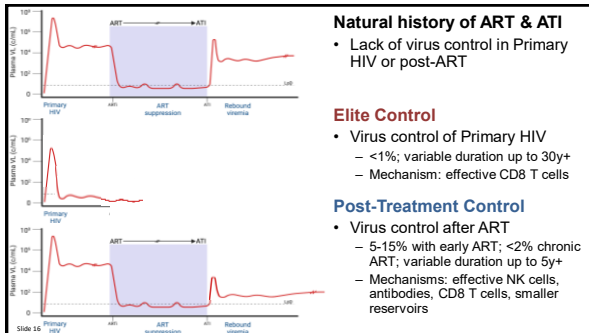
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Examples of HIV Cure

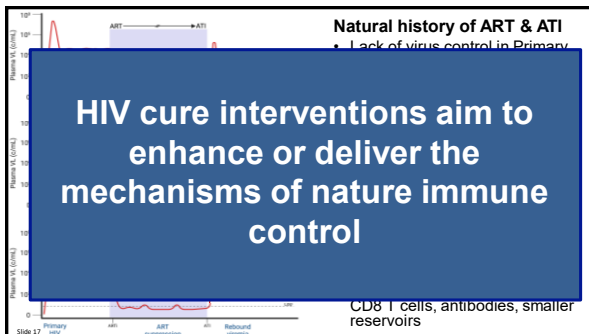
Individual	Year	Notes
Timothy Brown	2009	Transplant DCCR5 donor
Adam Castelleo	2019	Transplant DCCR5 donor
Lorraine Willenberg	2020	Exceptional Elite control
Esperanza Argentina	2021	Exceptional Elite control
New York	2021	Transplant DCCR5 donor
Dusseldorf	2021	Transplant DCCR5 donor
Paul Edmonds	2022	Transplant DCCR5 donor
Swiss ICI-34	2024	Transplant WT CCR5 donor

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Slide modified from D. Douek

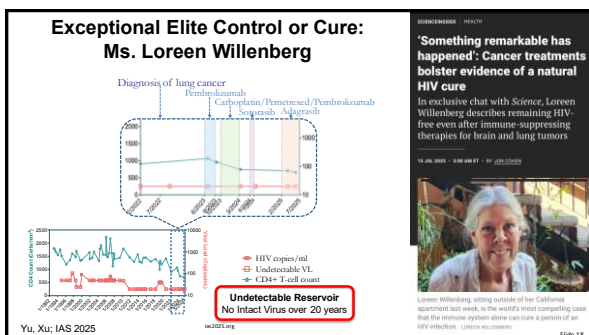
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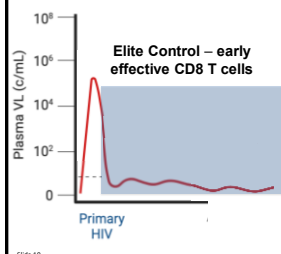


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Elite Control – early, effective CD8 T cell response



Cure Strategies to elicit Elite Control:

1. Boost CD8 T cell responses
 - Therapeutic vaccines, checkpoint inhibition, CAR-T cells
2. Early ART
 - Limit size, diversity of reservoir
 - Limit immune exhaustion

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SPARTAC ATI substudy

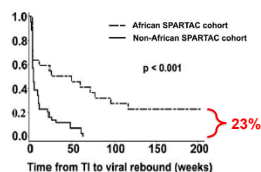
- SPARTAC – showed benefit of early ART in two cohorts: African women and Western MSM
- **SPARTAC ATI** – can early ART increase rates of post-treatment control?
- **Yes, but only in African women**
 - 5/22 (23%) of African women ppts with early ART maintained VL < 400 over a median of 188 weeks follow up

Highlights:

- **Early ART: improves virus control**
 - Mechanisms: smaller, less diverse reservoir & more functional HIV-specific immunity
- **Importance of conducting studies in diverse populations:** sex, geography, virus clade, ART timing, other factors

Virological remission after antiretroviral therapy interruption in female African HIV seroconverters

Morgane Gosses¹, Genevieve Elizabeth Martin¹, Matthew Pace², Gila Ranjeet³, Anamika Premraj⁴, Pontiano Kaleebu⁵, Helen Rees⁶, Jamie Inshaw⁷, Wolfgang Kuster⁸, Jodi Meyerowitz⁹, Emily Hopkins¹⁰, Matthew Jones¹¹, Jacob Hurst¹², Khouloud Porter¹³, Abdel Bahler¹⁴, Sarah Fidler¹⁵, John Frater^{16,17}, on behalf of the SPARTAC Trial Investigators

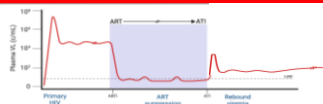


Gosses, AIDS 2018

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Post-Treatment Control



- **Early ART** – limits reservoir, preserves functional immunity
- Multiple **immune mechanisms** correlate:
 - Immune function: NK cells, Antibodies, CD8 T cells.
- **Intervention: bnAbs at ART initiation**

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Rationale for bnAbs at ART initiation

Reservoir is largely formed when ART is started

- Stable immunity allows long-lived HIV+ memory CD4 T cells to survive
- Feasible clinical juncture

Kill HIV+ Cells via antibody effector functions

- Limits initial formation of the reservoir

Enhance immunity via vaccinal effect of IC presentation

- Ample virus for immune complexes, but no replication to develop resistance

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Abrahams, STM 2020; Halper-Sternberg, 2018

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Recent Clinical Trials

bnAbs at early ART initiation

RIO

Increased frequency of post-treatment control

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RIO: +/- bnAbs at early ART initiation

72 participants

Randomise

Group A: bnAbs (n=36)

Stop ART

Monitor until viral rebound *

Restart ART and monitor

Group B: placebo (n=36)

Stop ART

Monitor until viral rebound *

Restart ART

bnAbs plus ART for 24 weeks

Monitor until viral rebound *

Restart ART and monitor

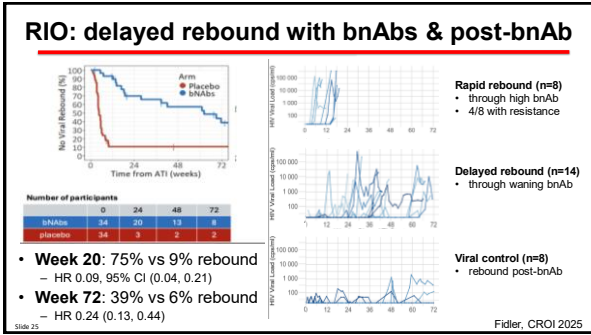
Preliminary Results on Stage 1

Placebo recipients receive delayed intervention

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Fidler, CROI 2025

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Thanks, Doc – great to hear the progress towards HIV cure.

1. *Better understanding of how HIV persists through ART*
2. *Gene therapy holds promise for HIV cure.*
3. *Some people control HIV naturally – Elite and Post-treatment Control*
4. *Early ART and bnAbs at ART initiation show promise in leading to ART-free virus control.*

Hypothetical young person with HIV at a routine clinic visit

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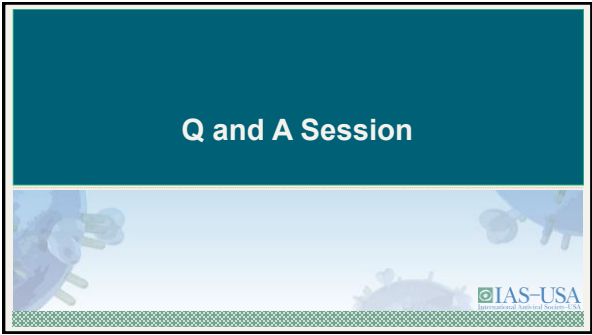
Thank you!

**Participants
Study Teams**

Content: Drs. Danny Douek, Sarah Fidler

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