

Advances Toward a Cure for HIV: Getting Beyond N = 2

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Learning Objectives

After attending this presentation, learners will be able to:

- Define the mechanisms behind HIV persistence
- Describe challenges in achieving HIV eradication and remission
- List ongoing efforts and strategies for inducing HIV remission

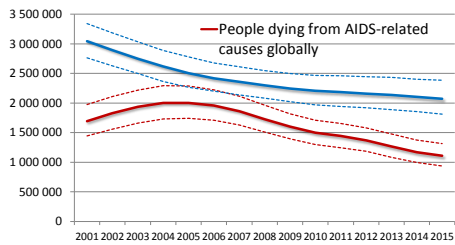
Slide 3 of 53

Overview

- Status of the HIV epidemic
- Mechanisms behind HIV persistence
- Success stories
 - The Berlin and London patients
 - Post-treatment controllers
- Strategies for inducing HIV remission

Slide 4 of 53

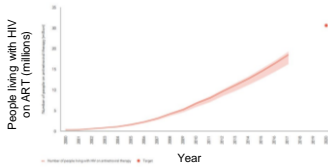
Decline in HIV incidence and mortality over time



Slide 5 of 53 Source: UNAIDS/WHO estimates.

Update on the Epidemic

- 37 million people living with HIV
- 22 million people on ART
- 1.8 million new infections yearly
- 1 million AIDS-related deaths yearly



Slide 6 of 53 Source: UNAIDS/WHO estimates.

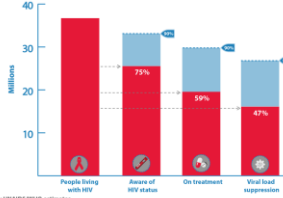
Why Do We Need a Cure?



Slide 7 of 53 POZ.com

Challenges in ART Initiation and Adherence

HIV testing and care continuum (2017)



Source: UNAIDS/WHO estimates

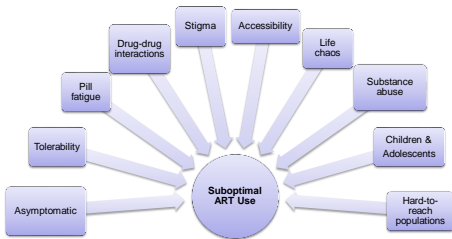
<http://www.who.int/hiv/data/>



Slide 8 of 53

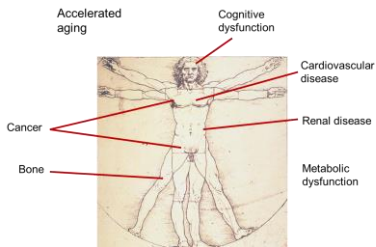
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Issues Surrounding Long-Term ART



Slide 9 of 53

Complications of Long-Term ART Despite ART



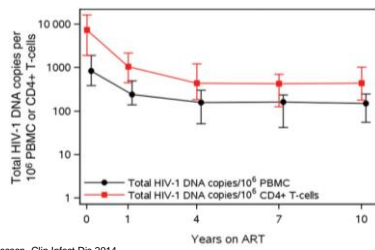
Slide 10 of 53

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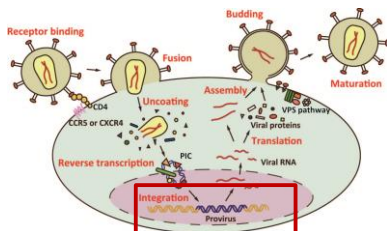
Slide 11 of 53

HIV Persists Despite Long-Term ART



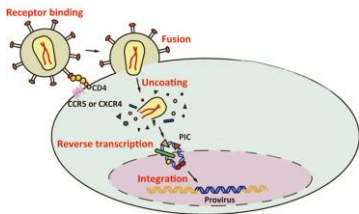
Slide 12 of 53 Besson, Clin Infect Dis 2014

HIV Life Cycle Leads to Persistence



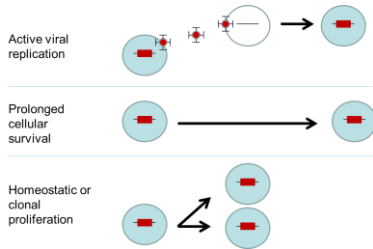
Slide 13 of 53

HIV Can Become Latent (Silent)



Slide 14 of 53

Mechanisms of HIV Persistence



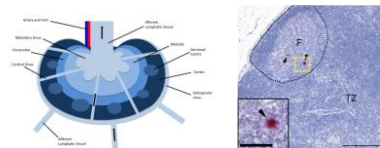
Slide 15 of 53

Don't Forget the Tissues

ARTICLES

B cell follicle sanctuary permits persistent productive simian immunodeficiency virus infection in elite controllers

nature
medicine



Slide 16 of 53 Fukazawa, Nat Med 2015

Overview

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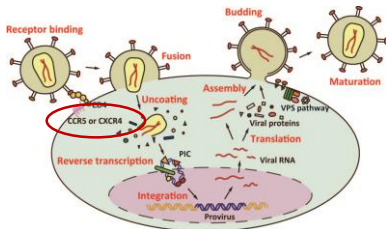
Slide 17 of 53

Is HIV Cure Possible?



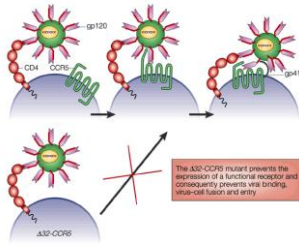
Slide 18 of 53

HIV Requires a Co-Receptor for Cell Entry



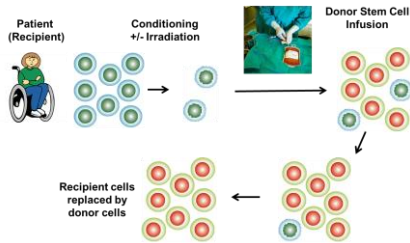
Slide 19 of 53

CCR5 Deletion Prevents HIV Entry



Slide 20 of 53

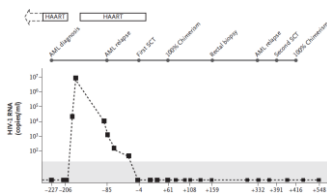
Allogeneic Stem Cell Transplantation (ASCT)



Slide 21 of 53

HIV Remission after CCR5- $\Delta 32$ Donor HSCT

THE NEW ENGLAND JOURNAL OF MEDICINE
Long-Term Control of HIV by CCR5 $\Delta 32/\Delta 32$ Stem-Cell Transplantation



Slide 22 of 53 Hutter, N Engl J Med 2009

The screenshot shows a news article from the Bay Area Reporter. The headline is "Berlin Patient' HIV-free for 10 years". The author is La Rightman. The article mentions a 10-year anniversary of the Berlin patient and a conference on HIV research in San Francisco. A photo shows a group of people at a celebratory event.

Slide 23 of 53

The screenshot shows a Nature Accelerated Article Preview. The title is "HIV-1 remission following CCR5 Δ 32/ Δ 32 haematopoietic stem-cell transplantation". The article includes a line graph showing viral load (VL) and CD4 count over time. The graph shows VL dropping to undetectable levels and CD4 count increasing after transplantation.

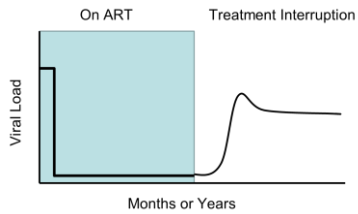
Slide 24 of 53

Differences between Berlin and London patients

Berlin patient	London patient
Heterozygous for Δ 32	Homozygous for wild type CCR5
Acute myelogenous leukemia	Hodgkin lymphoma
Two HSCT	Single HSCT
Total body irradiation	No irradiation
Full intensity conditioning	Reduced intensity conditioning
T cell depletion with ATG	T cell depletion with aCD52

Slide 25 of 53

HIV Suppression Requires Life-long ART



Slide 26 of 53

Fun Poll #1

In the average patient, how quickly does HIV return to detectable levels in the blood after ART is discontinued?

1. <48 hours
2. 2-4 days
3. 2-4 weeks
4. 2-4 months
5. >4 months

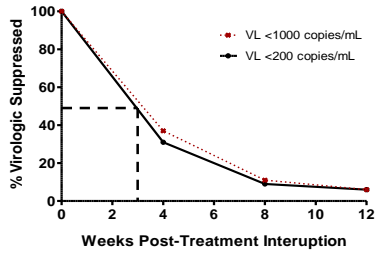
Slide 27 of 53

HIV Rebound after Treatment Interruption (TI)

- Assess the timing of HIV rebound in a pooled analysis of 6 AIDS Clinical Trials Group (ACTG) TI studies
- Inclusion criteria
 - On combination ART
 - HIV-1 RNA <50 copies/mL at time of ATI
 - No immunologic intervention (e.g., therapeutic vaccination)
- Viral rebound threshold definitions
 - Confirmed HIV-1 RNA ≥ 200 copies/mL or a single HIV-1 RNA $\geq 1,000$ copies/mL

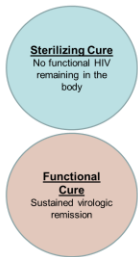
Slide 28 of 53

Most Patients will Rebound Between 2-4 Weeks



Slide 29 of 53

Definitions of an HIV Cure



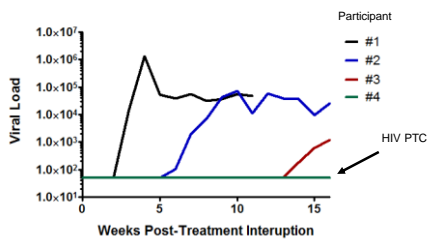
Examples

- Timothy Ray Brown (Berlin patient)
- HIV controllers or long-term non-progressors
- HIV post-treatment controllers (PTCs)

Slide 30 of 53

Adapted from Cillo, Curr Opin Virol 2016

The Timing of HIV Rebound is Not Uniform

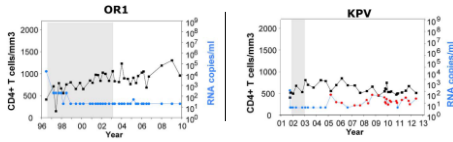


Slide 31 of 53

HIV Post-Treatment Controllers (PTCs)

ORCID iD [0009-0001-7849-9246](https://orcid.org/0009-0001-7849-9246) [PLOS](https://pubs.plos.org/plosone) [PLOS ONE](https://pubs.plos.org/plosone)

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



Slide 32 of 53 Saez-Cirion, *Plos Pathog* 2013

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Slide 33 of 53

How Do We Transform Our Patients into PTCs?

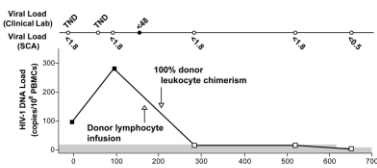
- Bone marrow transplant (with CCR5 wild-type donors)
- Early HIV treatment
- Shock and kill
- Gene therapy

Slide 34 of 53

The "Boston BMT Patients"



Long-Term Reduction in Peripheral Blood HIV Type 1 Reservoirs Following Reduced-Intensity Conditioning Allogeneic Stem Cell Transplantation



Slide 35 of 53 Henrich, J Infect Dis 2013

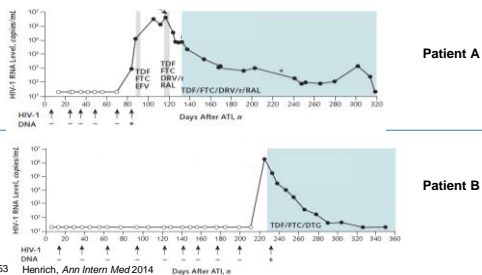
Fun Poll #2

Stem-cell transplant with donor cells containing wild-type CCR5 had what effect after ART interruption?

1. Led to a sterilizing HIV cure
2. Significant delay in HIV rebound, but eventual HIV rebound
3. Rapid HIV rebound

Slide 36 of 53

HSCT Alone Resulted in Delayed HIV Rebound



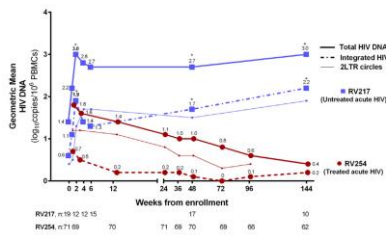
Slide 37 of 53 Henrich, Ann Intern Med 2014

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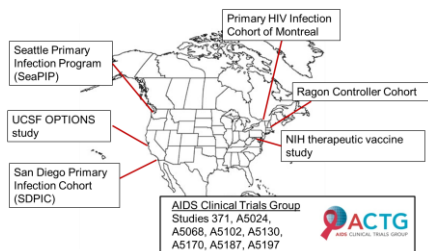
Slide 38 of 53

Early ART Dramatically Decreases HIV Reservoir



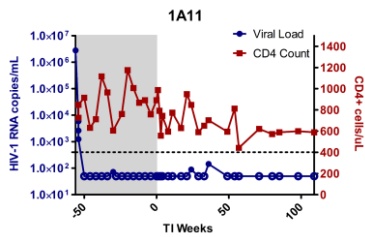
Slide 39 of 53 Ananworanich, EBioMed 2016

The Control of HIV after Antiretroviral Medication Pause (CHAMP) Study



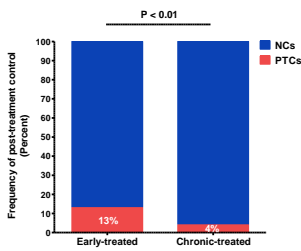
Slide 40 of 53 Namazi, J Infect Dis 2018

Example of a PTC



Slide 41 of 53 Namazi, J Infect Dis 2018

Higher PTC Frequency with Early ART Initiation

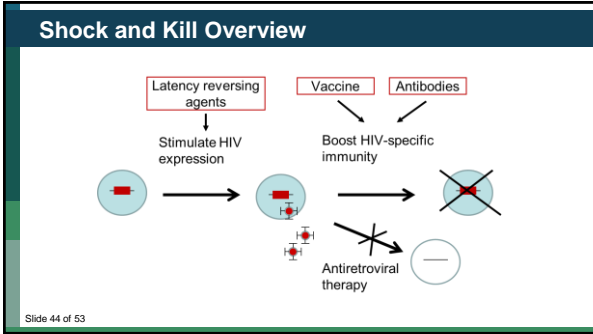


Slide 42 of 53 Namazi, J Infect Dis 2018

How Do We Transform Our Patients into PTCs?

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Slide 43 of 53



nature ARTICLE

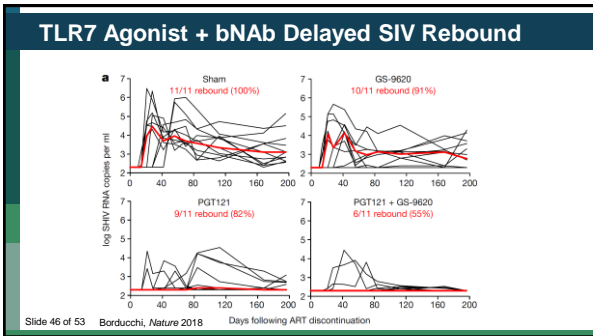
Corrected: Publisher Correction
<https://doi.org/10.1038/s41586-018-0001-6>

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

Erica N. Borducchi^{1,2}, Jeremy Liu^{1,2}, Joseph B. Nankala¹, Anthony M. Casbon¹, Weng Zhao^{1,2}, Stephanie Fischinger¹, Thomas Dinger¹, Peter Akarshin¹, Soe B. Mawardi¹, Abhishek Choudhary^{1,2}, David Lertse¹, Lauren Pitzer¹, Katherine McMahony¹, Edward T. Mendenhall¹, Elvira Bekmeier¹, Joseph Hwang^{1,2,3,4}, Weiqun Li¹, Mark G. Lewis¹, Gail Alter¹, Simon Gulamreza¹ & Dan H. Baruch^{1,2,4}

- Latency reversing agent = TLR7 agonist (GS-9620)
- Reservoir clearing agent = broadly-neutralizing Ab (PGT-121)
- 44 rhesus monkeys randomized to 4 groups:
 - sham (placebo), GS-9620 alone, PGT-121 alone, or both
- ART interruption 16 weeks after end of intervention

Slide 45 of 53 Borducchi, *Nature* 2018



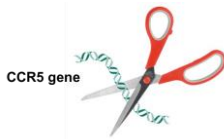
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Slide 47 of 53

Zinc-Finger Nucleases (ZFN)

- Zinc-finger nucleases induce breaks in the gene of interest (e.g., CCR5)
- DNA repair is error-prone and frequently result in disruption and inactivation of the gene

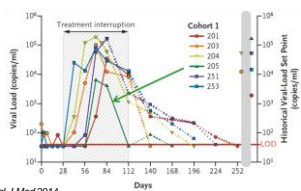


Slide 48 of 53

The NEW ENGLAND JOURNAL of MEDICINE

INTRODUCTION TO DATA MARCH 6, 2014 VOL 370 NO 10

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



Slide 49 of 53 Tebas, N Engl J Med 2014






The Washington Post

Chinese scientist's claim of gene-edited babies creates uproar




Slide 50 of 53

Cure Strategy Score Card

- Stem cell transplant
 - CCR5-Δ32 donor cells 
 - CCR5 wild type donor cells 
- Early HIV treatment 
- Shock and kill 
- Gene therapy 

Slide 51 of 53



"I know in my heart and soul that I will not be the only one cured of AIDS. Hope is alive in me."

Slide 52 of 53

Question-and-Answer

Slide 53 of 53

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