



Introduction to HIV Cure-Related Research



CUREiculum

This research training curriculum is a collaborative project aimed at making the science of HIV cure-related research accessible to the community and the HIV research field.

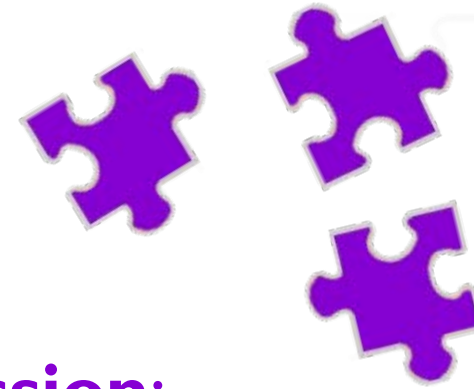
What is the CUREiculum?

- Series of modules and tools to simplify the science of HIV cure-related research
- Designed by **community for community**
- Hope it will lead to meaningful community-centered conversations

6 modules:

- 1. Introduction to HIV cure-related research**
- 2. Analytical treatment interruptions (ATIs)**
- 3. HIV persistence**
- 4. HIV cure-related research strategies**
- 5. Ethics of HIV cure-related research**
- 6. Community, patient & stakeholder engagement**

Glossary of Key Terms



Antiretroviral (ART)-free HIV suppression:

*Control of virus in the absence of HIV treatment
(also: ‘**post-treatment control**’ or ‘**ART-free durable control**’)*

Latency:

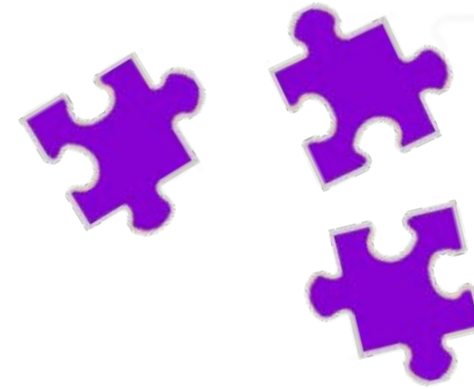
The ability of a virus to stay dormant (inactive) within a cell

Provirus:

*A virus’ genetic material that has become integrated inside the DNA
(deoxyribonucleic acid) of a cell*



Glossary of Key Terms



Reservoirs:

Cells and compartments in the body where HIV can hide and not be found, even in the presence of antiretroviral therapy

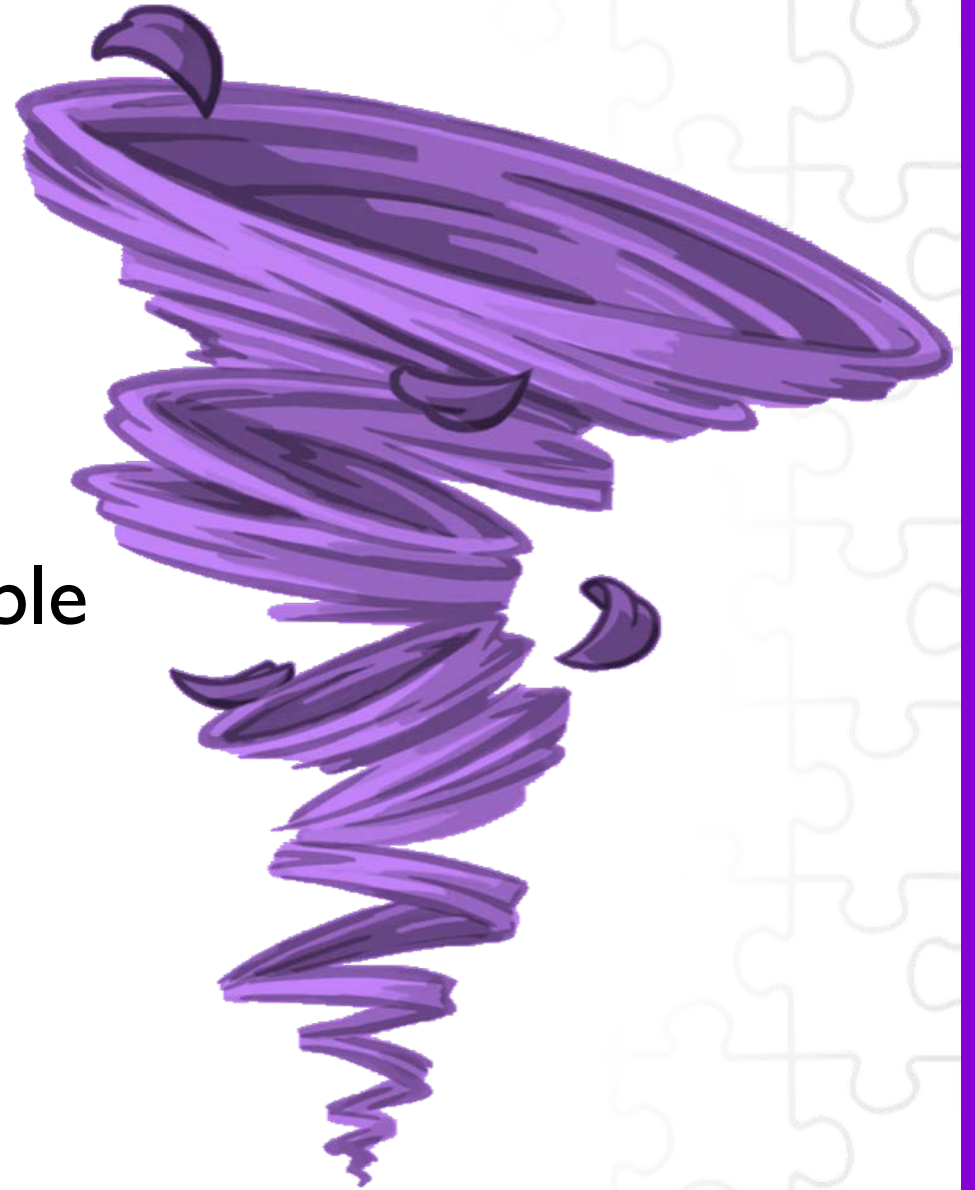
Viral rebound:

When a person has detectable levels of HIV in the blood after a period of having undetectable levels



A Whirlwind Tour

- What do we mean by cure
- Why an HIV cure is needed
- Why we believe an HIV cure is possible
- Path to a cure
- Why is curing HIV so difficult
- Cure strategies being pursued
- Ethical Issues



Why HIV is it so hard to cure in a nutshell!



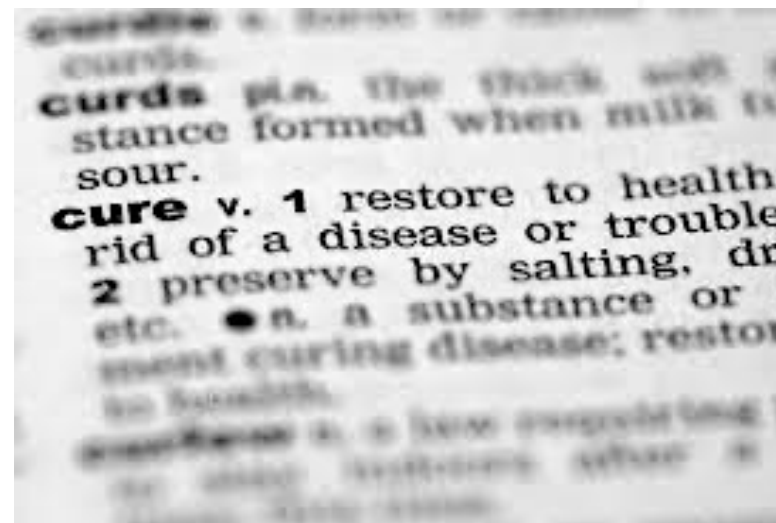
What Would HIV Cure Mean?

“Cure”

A complete or permanent solution or remedy

To bring about recovery from

To permanently restore health



Two main pathways being investigated:

- **“Complete” or “classic” cure** = *complete elimination of the virus from the body*
- **ART-free durable suppression (or control)** = *the ability to control HIV replication without HIV treatment*



What Kind of Cure Do PWH Want?

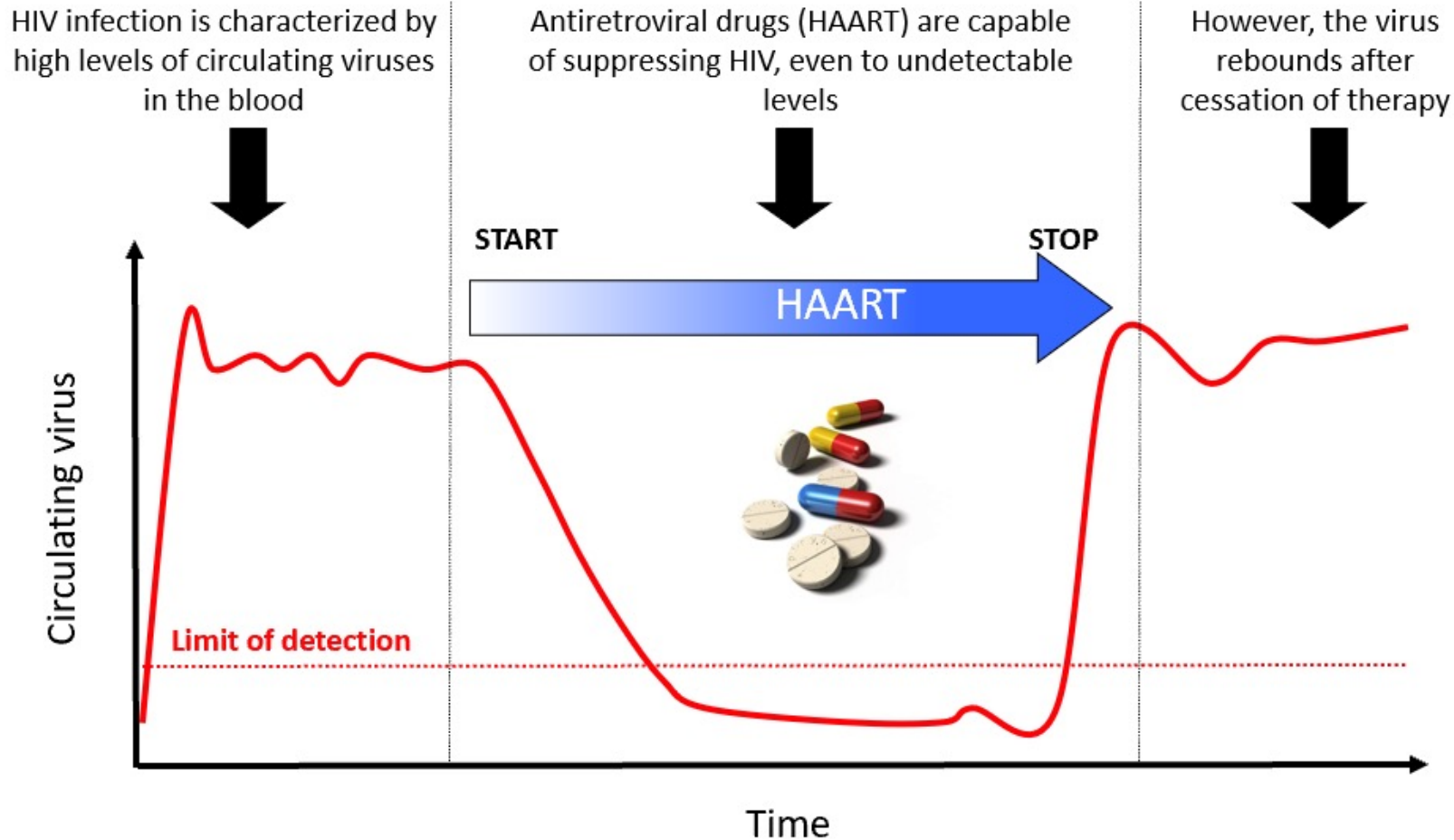
- Safe
- Simple
- Affordable
- Scalable
- Complete
- Durable
- Prevents Transmission
(ideally both ways)



Why do we need a cure?



Current anti-HIV drugs do not eliminate HIV

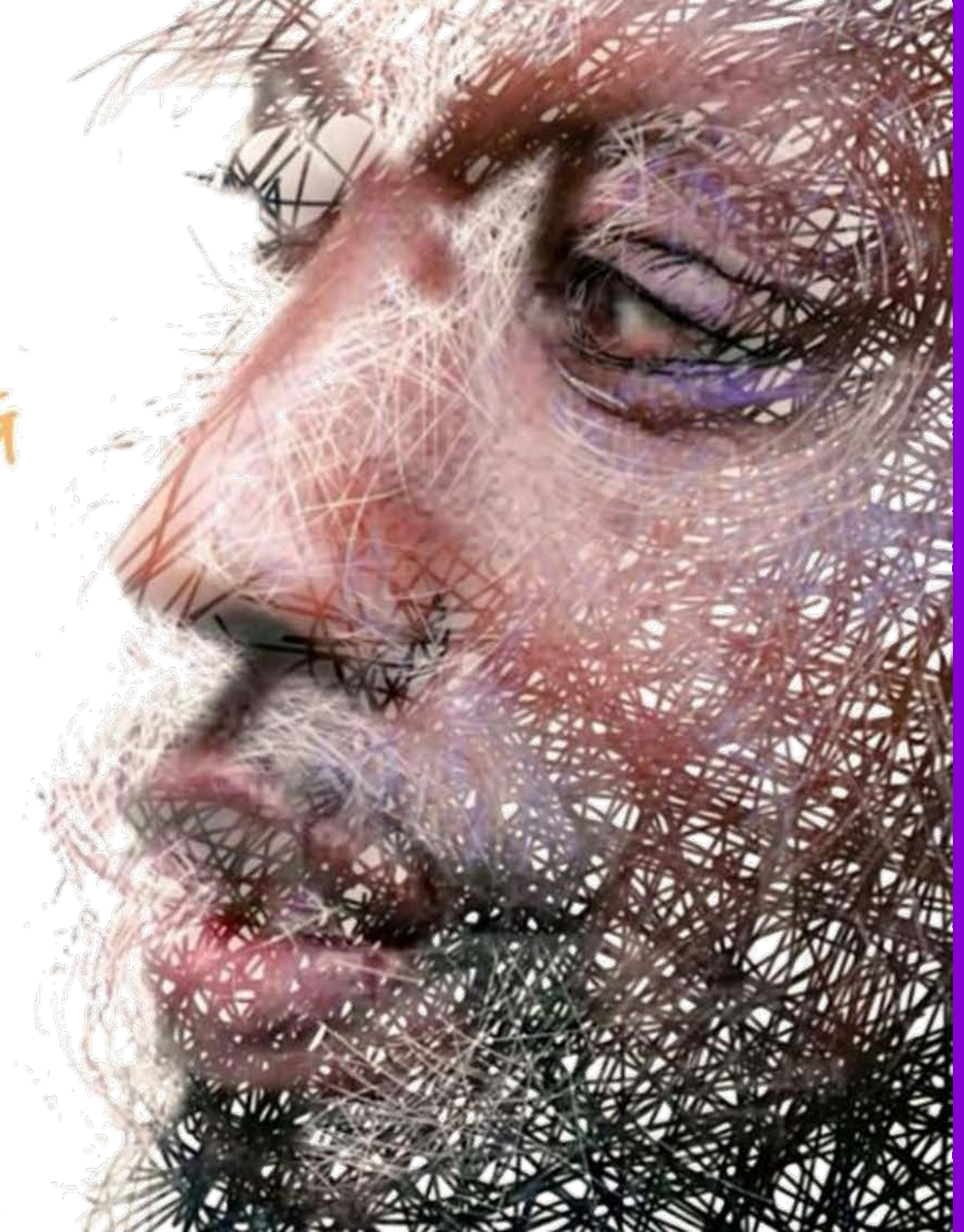


→ *HIV hides in places that are not sensitive to current therapies*



[illegible]

People see
an HIV cure
as **LIBERATING**
for both
individuals
and society.



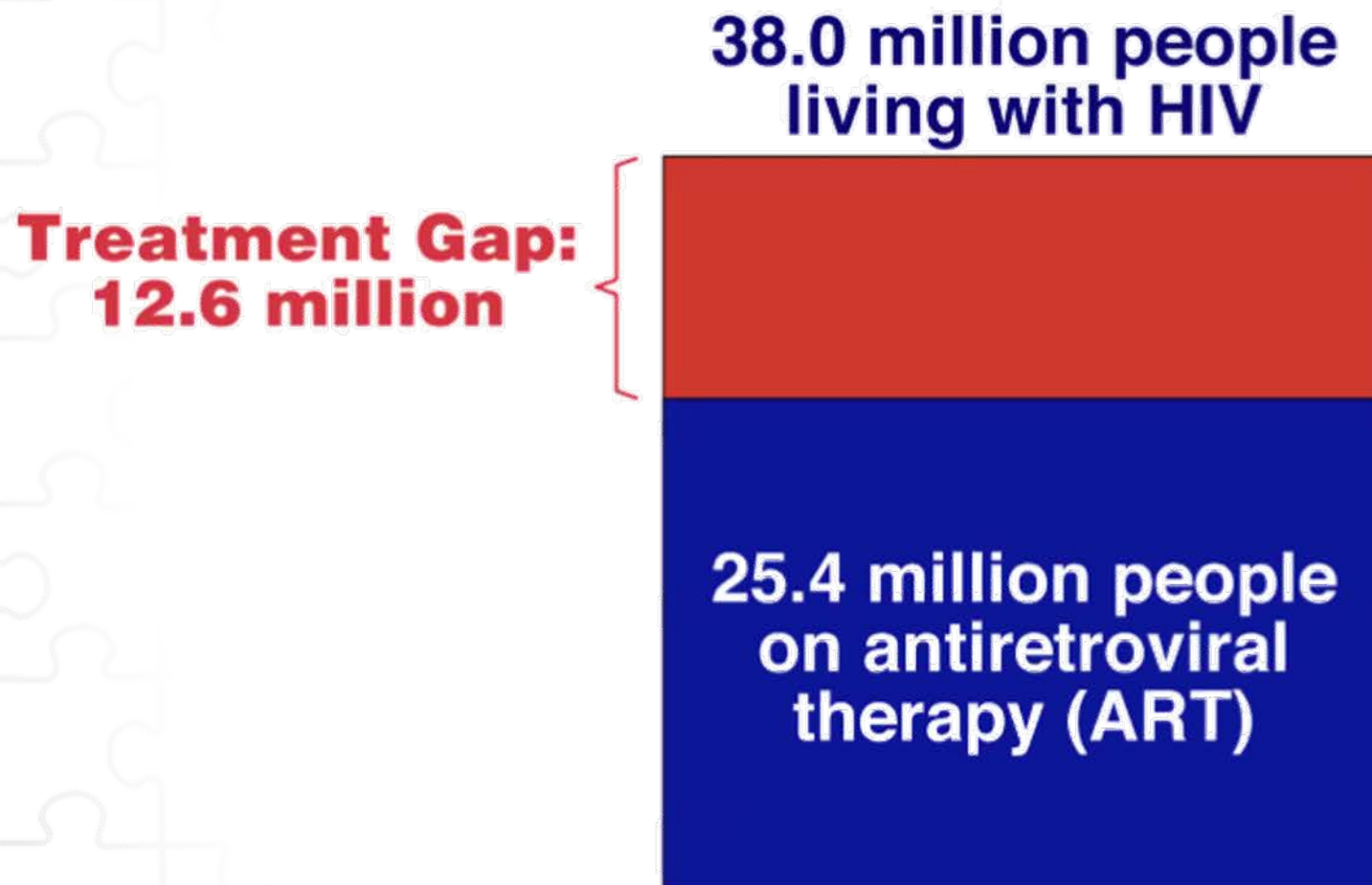
The Holy Grail



Introduction



The Global HIV Treatment Gap

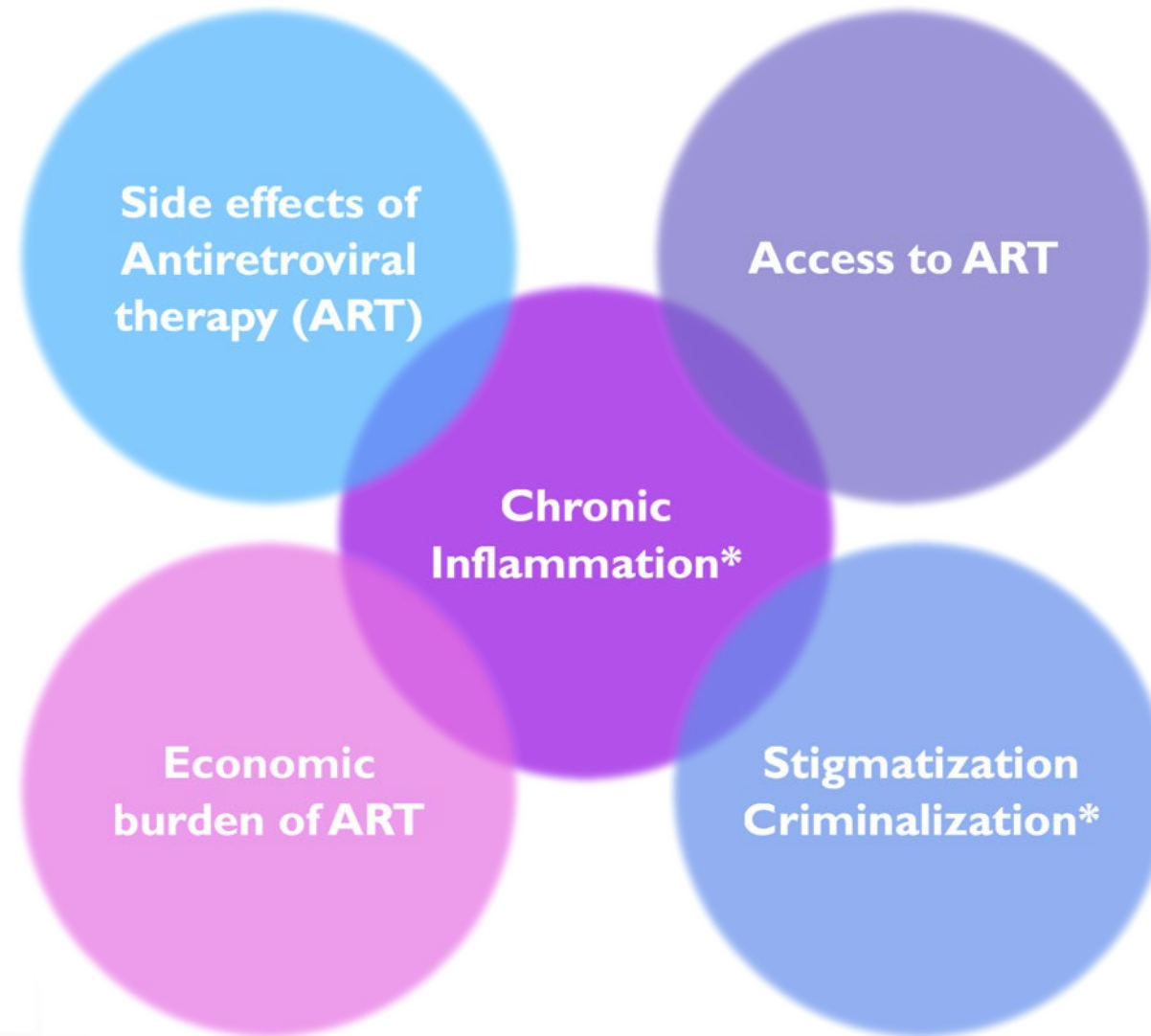


Source: UNAIDS, 7/2020.
Data for 2019.

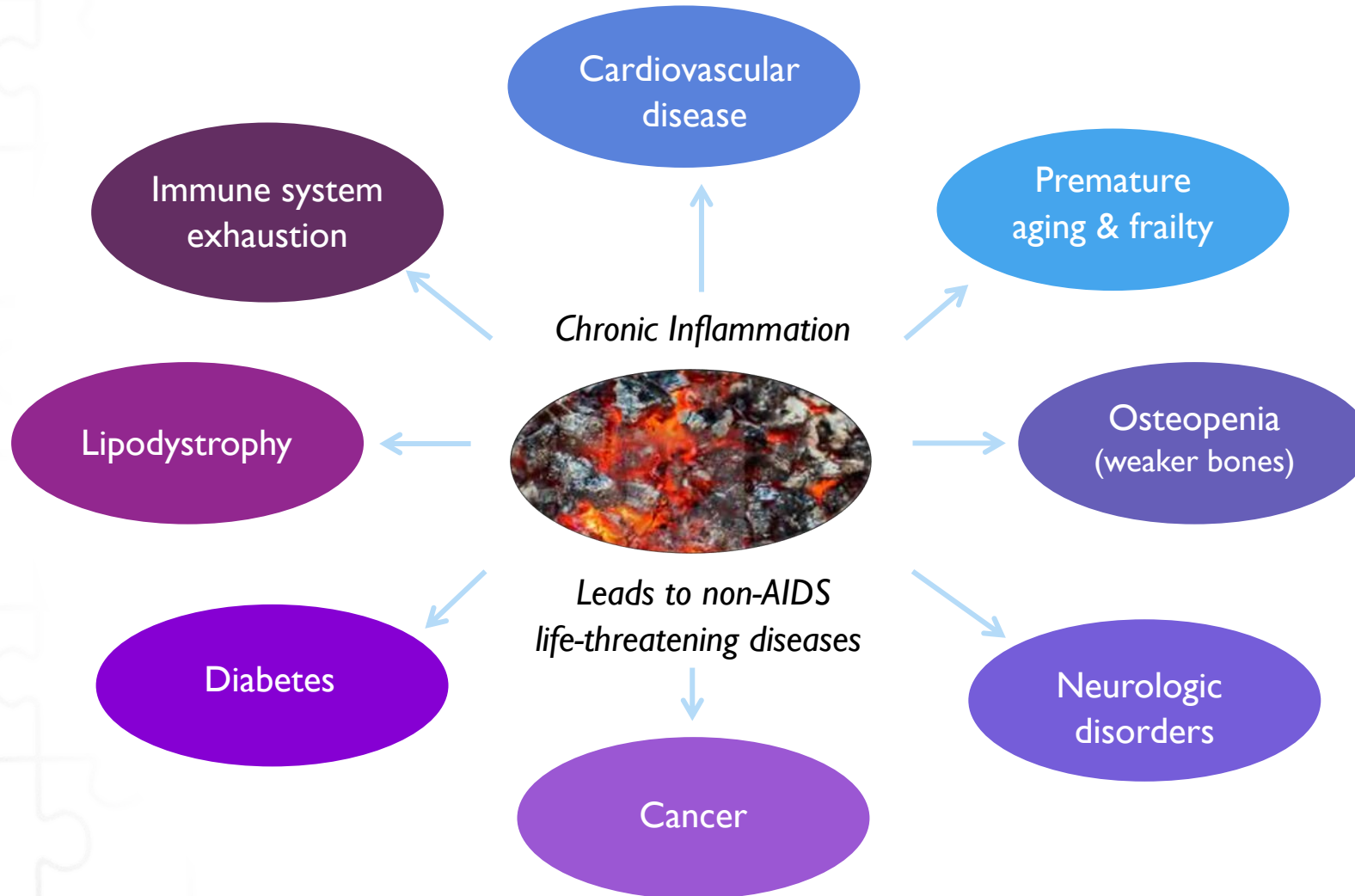
Reasons Why We Need Optimized Treatments and a Cure for HIV Infection

- **It is likely not economically nor logistically feasible to deliver daily antiretroviral therapy (ART) to >38 million people with HIV for their entire lives**
- **Challenges of adherence, retention in care, and negotiating the HIV “care continuum”**
- **Drug resistance, cumulative toxicities, and stigma associated with daily ART**

Why Do We Need an HIV Cure?



Why Do We Need an HIV Cure?



What is **HIV stigma**?

HIV stigma is negative attitudes and beliefs about people with HIV. It is the prejudice that comes with labeling an individual as part of a group that is believed to be socially unacceptable.

- Here are a few examples:
 - Believing that only certain groups of people can get HIV
 - Making moral judgments about people who take steps to prevent HIV transmission
 - Feeling that people deserve to get HIV because of their choices



HIV STIGMA AND DISCRIMINATION

What is **HIV Criminalization**?



- the overly broad use of criminal law to penalize alleged, perceived or potential HIV exposure
- or alleged nondisclosure of a known HIV-positive status prior to sexual contact (including acts that do not risk HIV transmission)
- or nonintentional HIV transmission
- sentencing can involve decades in prison or required sex offender registration, even when *no HIV transmission occurred*

**Nearly 200 cases
prosecuted in the US
since 2008**

“Evidence also indicates that penalties associated with HIV specific statutes are unevenly imposed on the basis of race and sex.” Communities of color, particularly women of color, are singled out for harsh penalties and long prison sentences.

- Yang & Underhill. 2018. New England Journal of Medicine



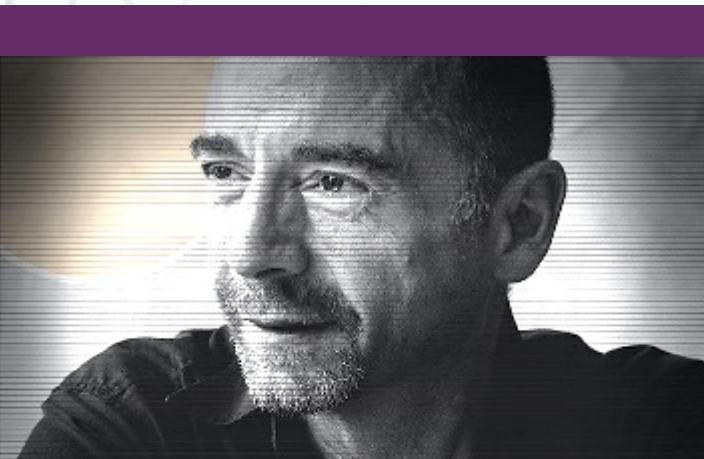
**Why do we think a cure for
HIV is possible?**





Introduction

Why We Believe a Cure Might be Possible

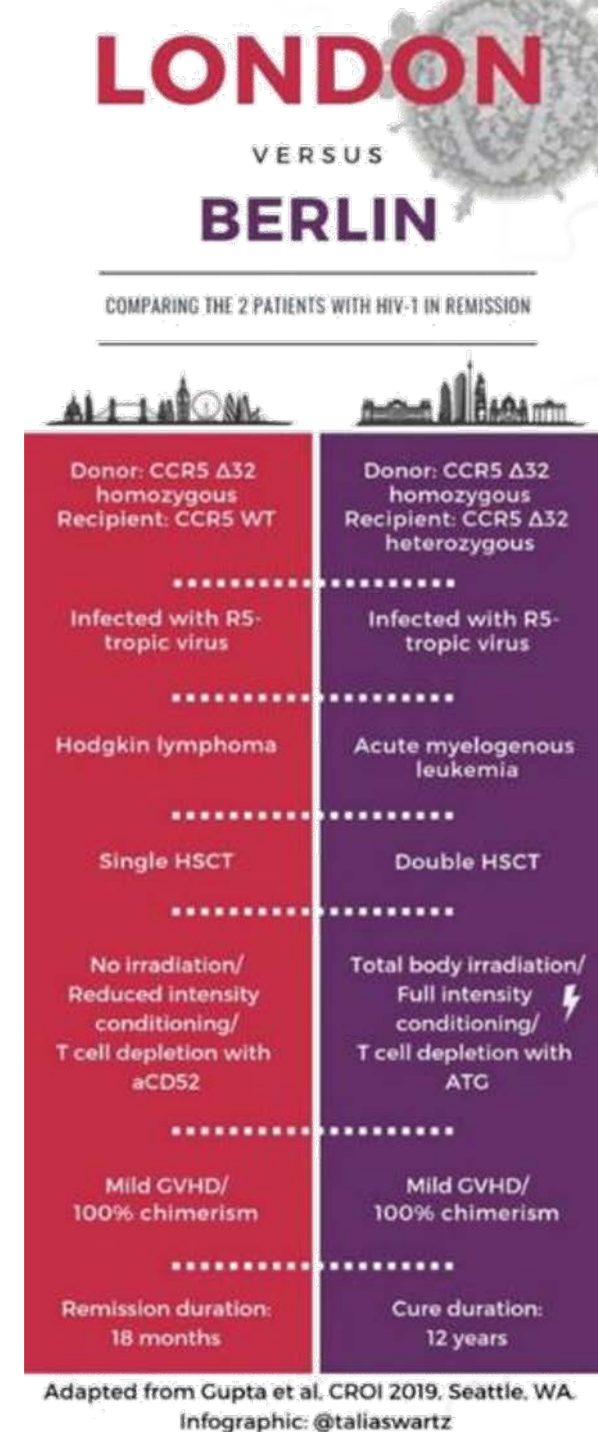


Timothy Ray Brown
“The Berlin Patient”

March 11, 1966 – September 29, 2020



Adam Castillejo
“The London Patient”

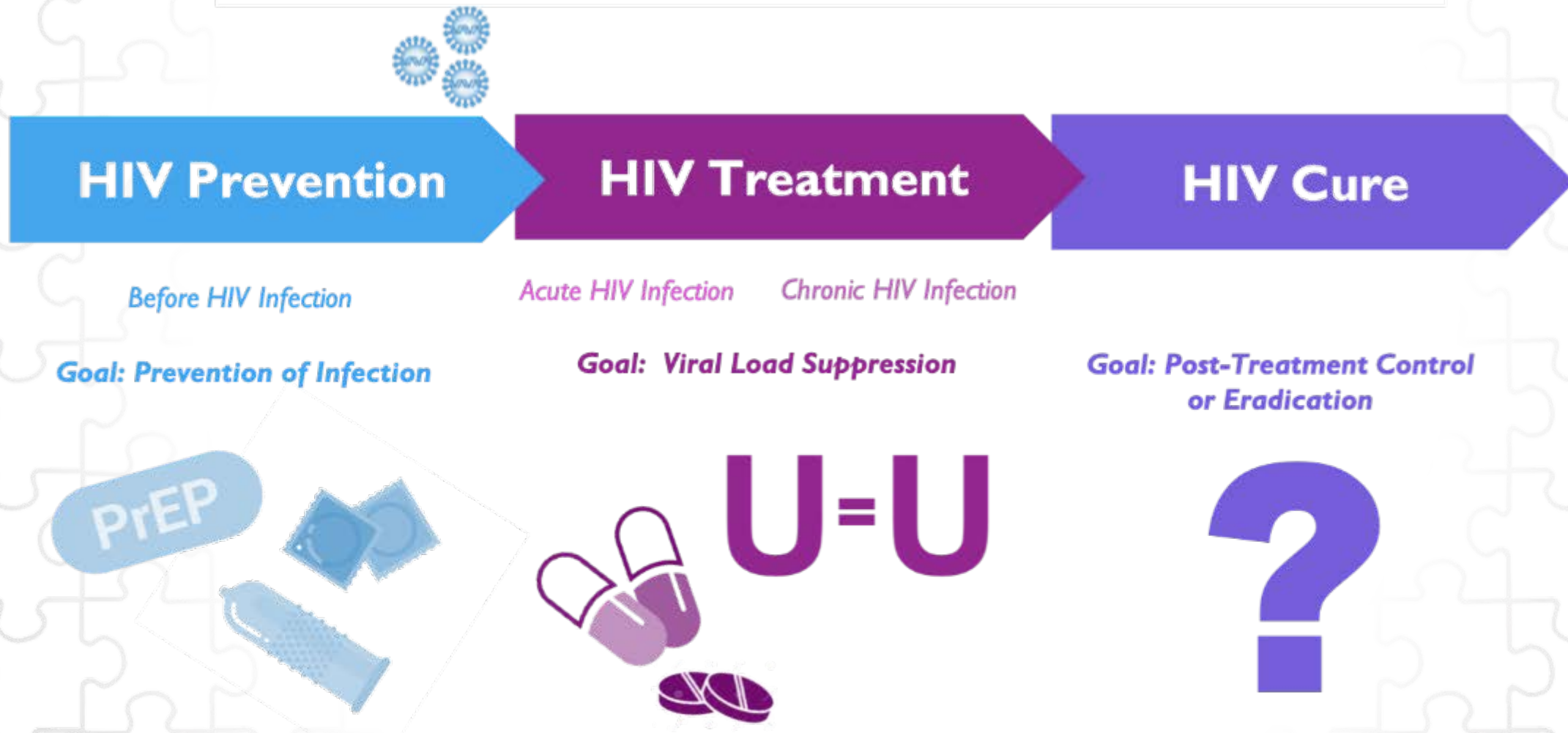


What has been the pathway to an HIV cure?

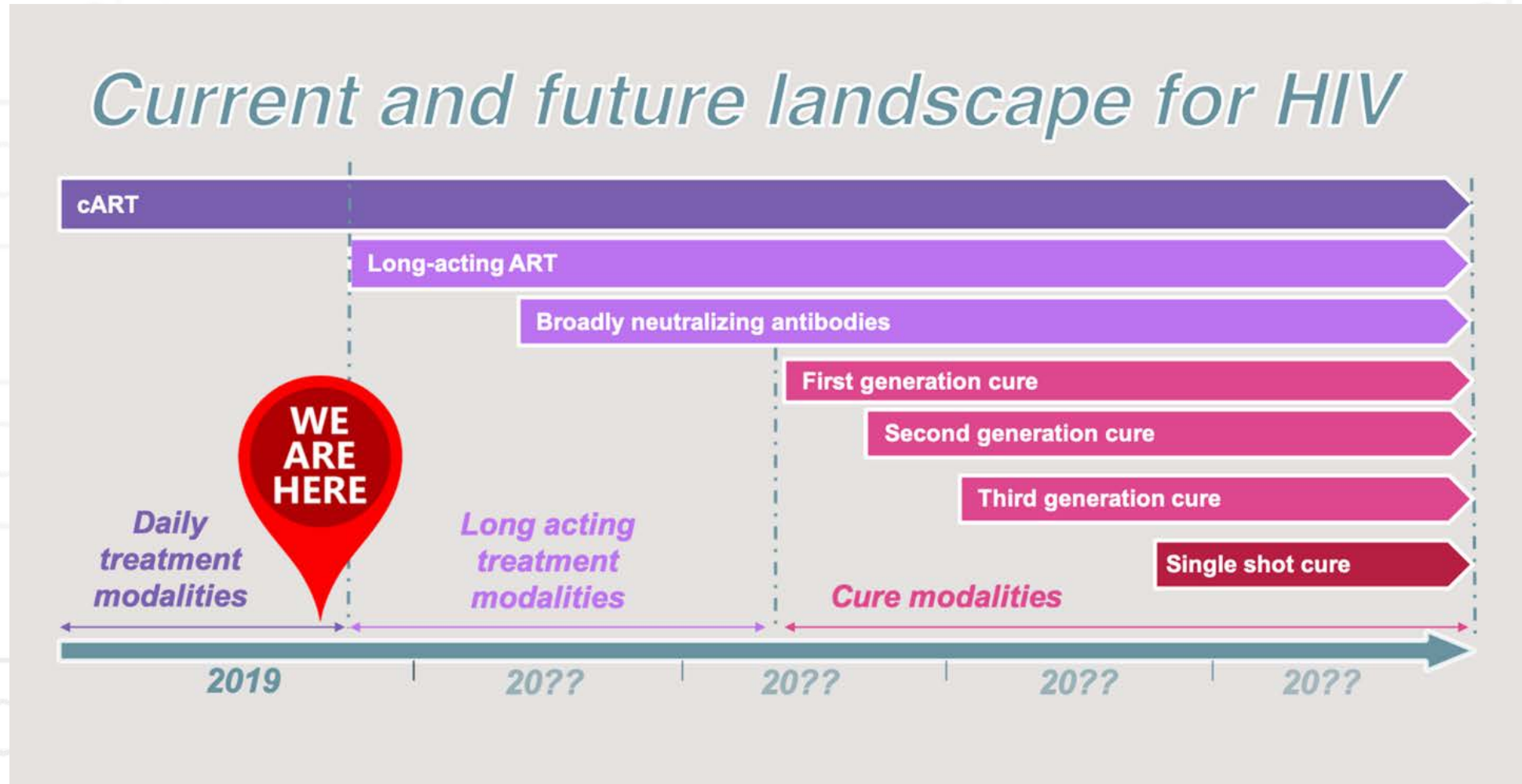


Background to HIV Cure-Related Research

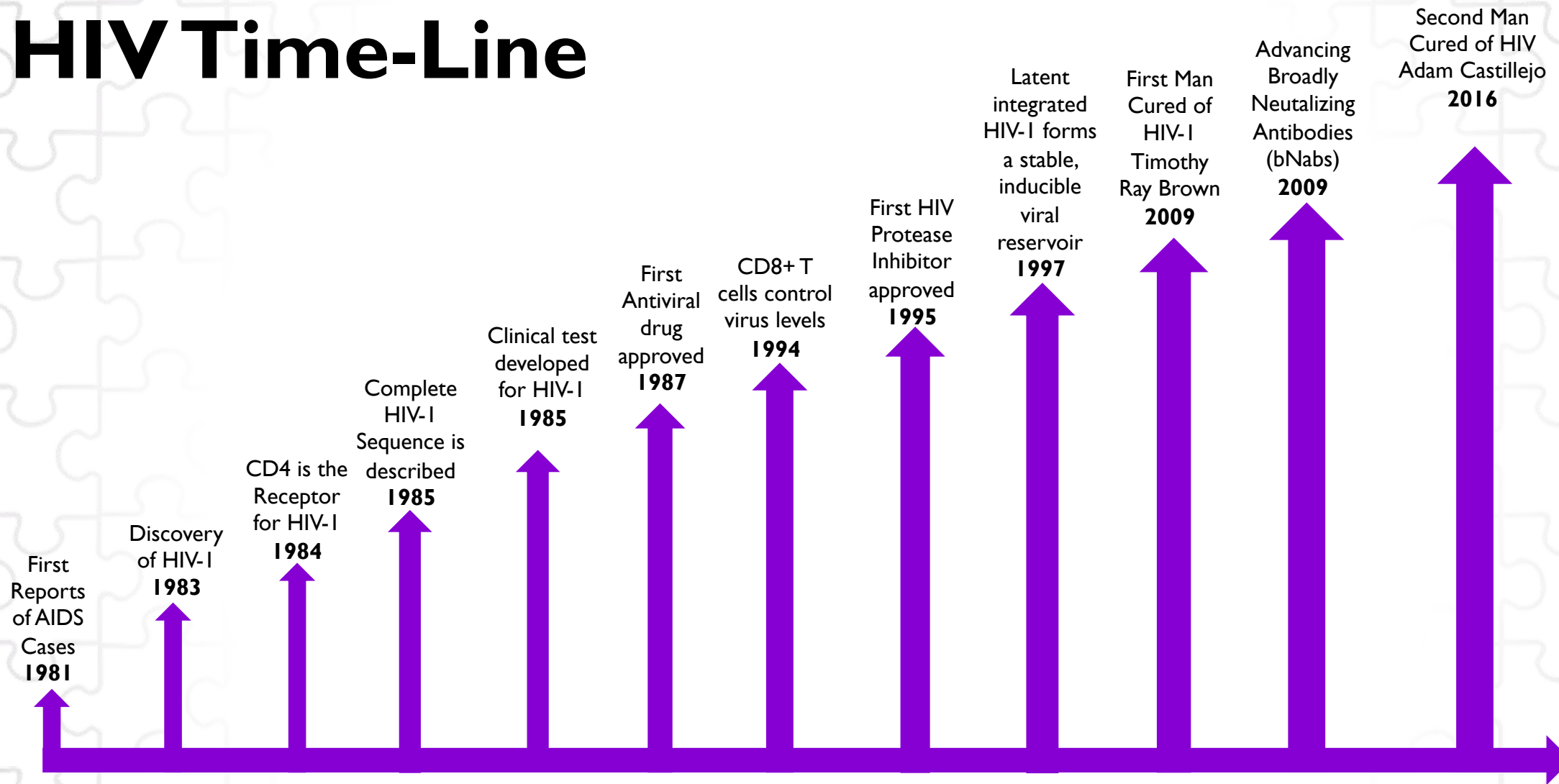
A Continuum



Evolution of HIV Cure Research



HIV Time-Line



Introduction



Evolving HIV Treatment Paradigm

Long Acting Injectables ?

The Integrase Era

Single-Tablet Regimens

Triple-Drug Therapy

ZDV/3TC

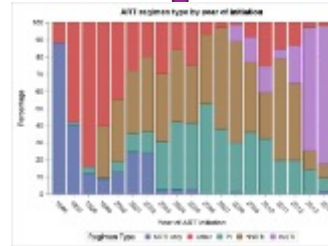
ZDV monotherapy

HIV-1 discovered

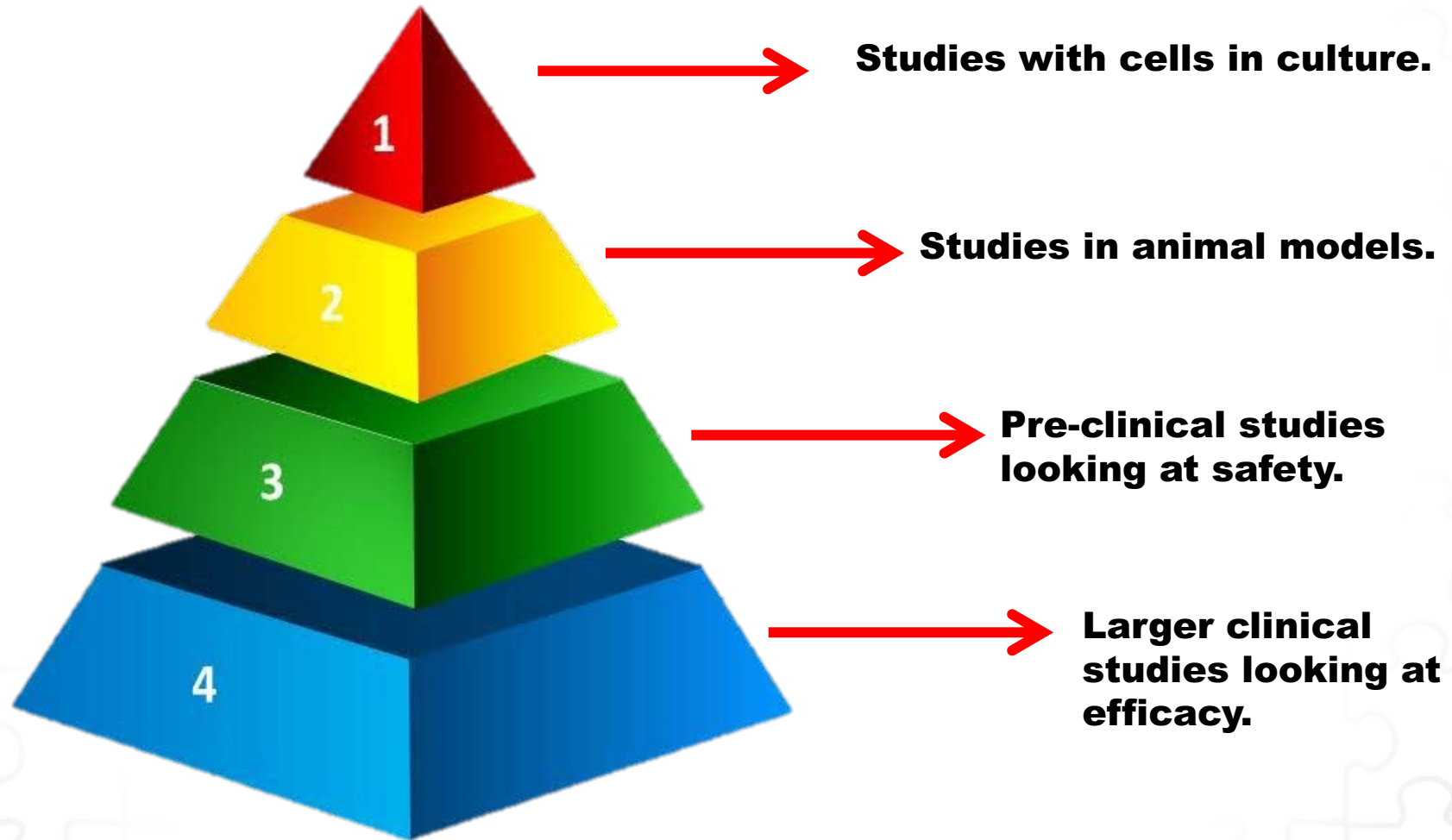
Cure?

ART-free durable control?

3TC = lamivudine
ZDV = zidovudine



Stages of Clinical Research



HIV Cure-Related Research

Bench Science

Understanding
Persistence &
Immune control

- Viral subtype
- Genetics
- Tissues
- Intervention Mechanism
- Analysis of preliminary work

Intervention Trials

Animal & Human
Studies



*Single or
Combination
Interventions*

Early
ART

Latency
modifying
agents

Immune
Therapies

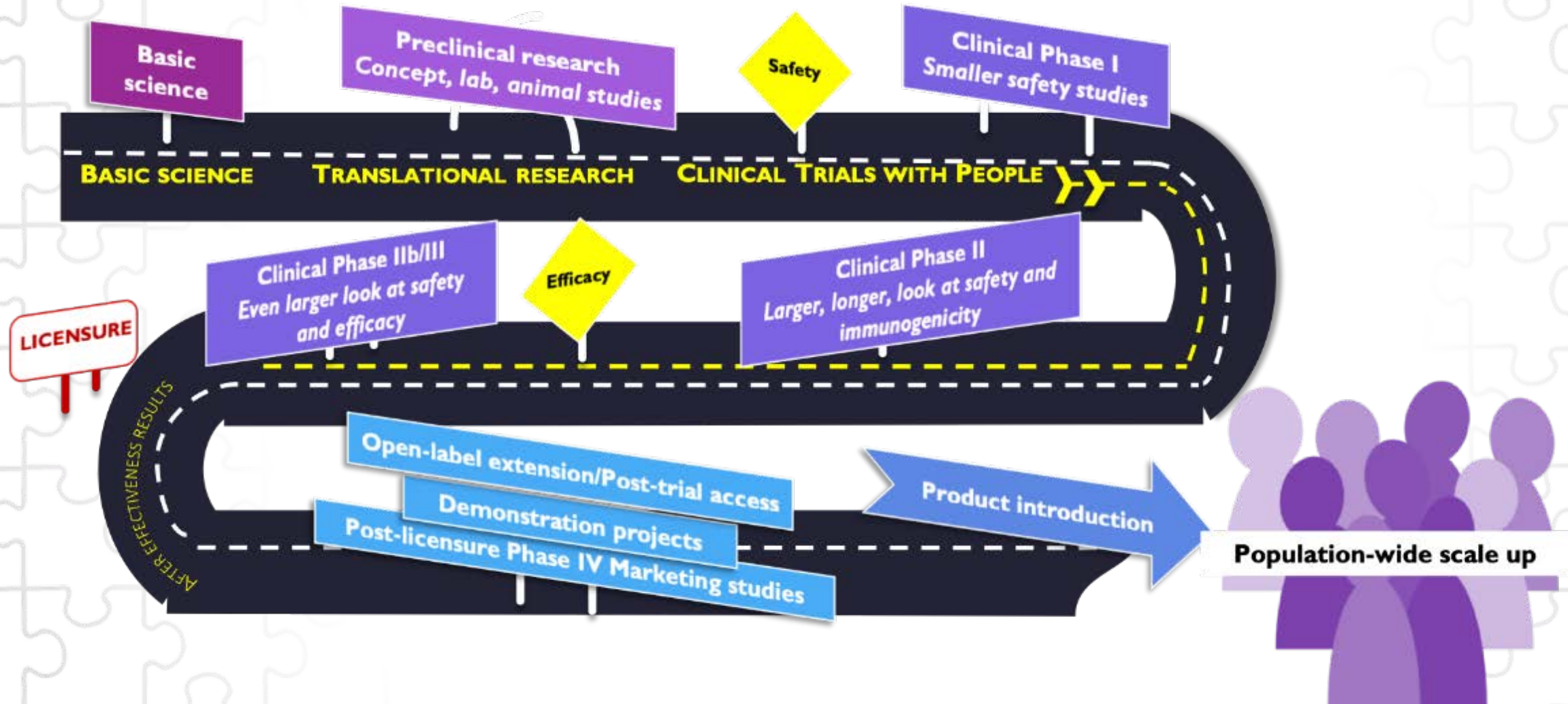
Cell &
Gene
Therapies

Ethics & Social-Behavioral Sciences

- Decision-making
- Perceptions of risks and benefits
- Attitudes about research
- Individual and societal impact



Overview of Research Process



Global Investment in HIV Cure R & D (2019)



approximately **US \$323.9 million**



The image features a purple rectangular banner with the text "Why is it difficult to cure HIV?". Above and below the banner are horizontal bands with a repeating pattern of interlocking puzzle pieces. Within the purple banner, there are four groups of puzzle pieces: two on the left and two on the right. Each group consists of one solid white puzzle piece and one white-outlined puzzle piece. The text is centered in the banner in a bold, white, sans-serif font.

Why is it difficult to cure HIV?

Why is HIV so hard to cure?

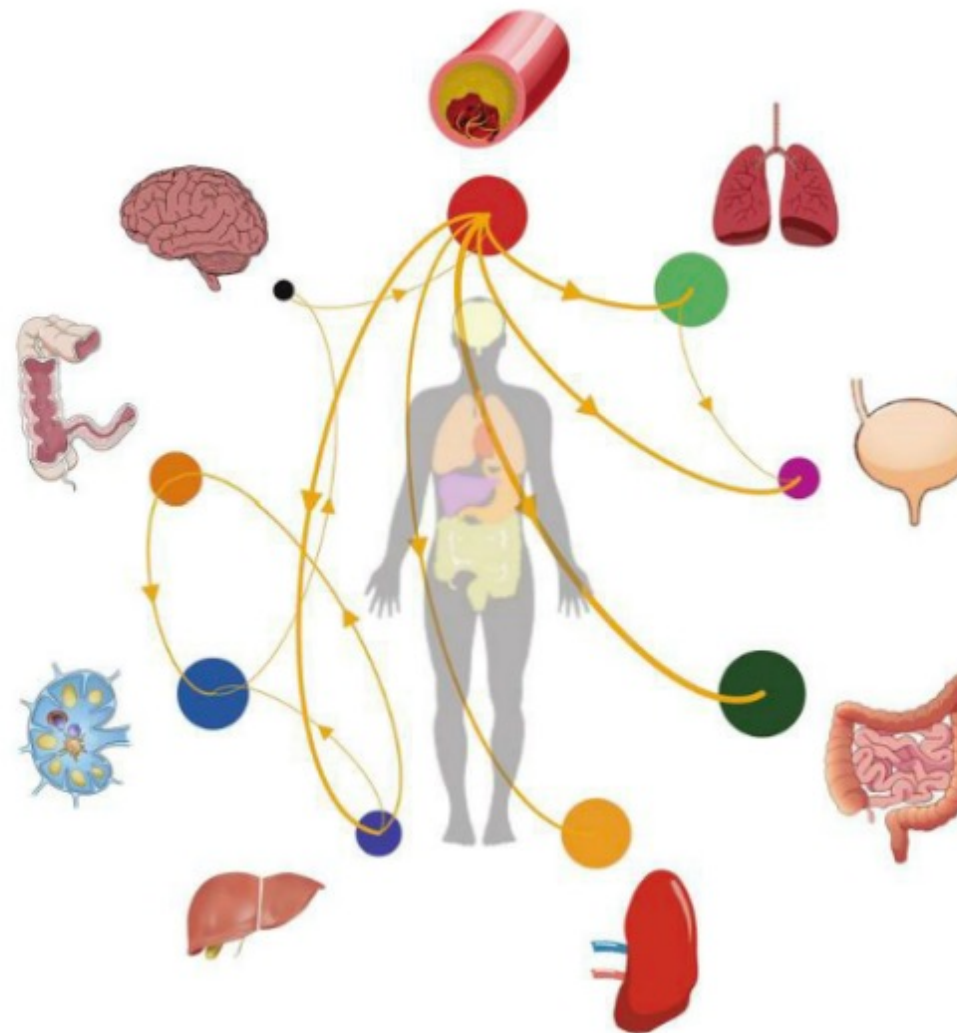


So few cells harbor HIV in people on antiviral medications and these cells appear normal to our immune system.



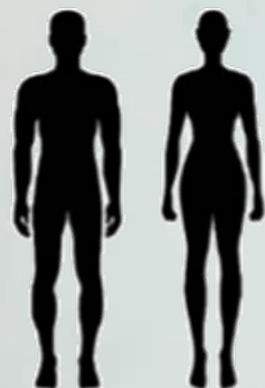
Where is the HIV Reservoir?

- Brain
- Lymph nodes
- Peripheral blood
- Gut
- Bone marrow
- Genital tract

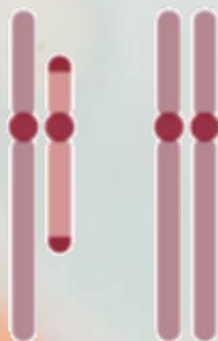




Sex Differences in HIV



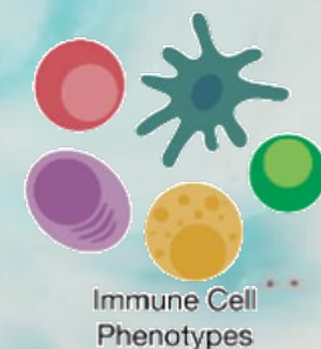
Anatomic



Genetic

Anatomic and hormonal differences

**Genetic differences
(e.g. X chromosomes)**



Immune Cell Phenotypes



Epigenetics



Microbiome

Immune system differences

Different epigenetic landscapes
(environments that surrounds genes)

Different microbiomes
(e.g. bacteria in the body)

Scully, Curr HIV/AIDS Rep, 2018



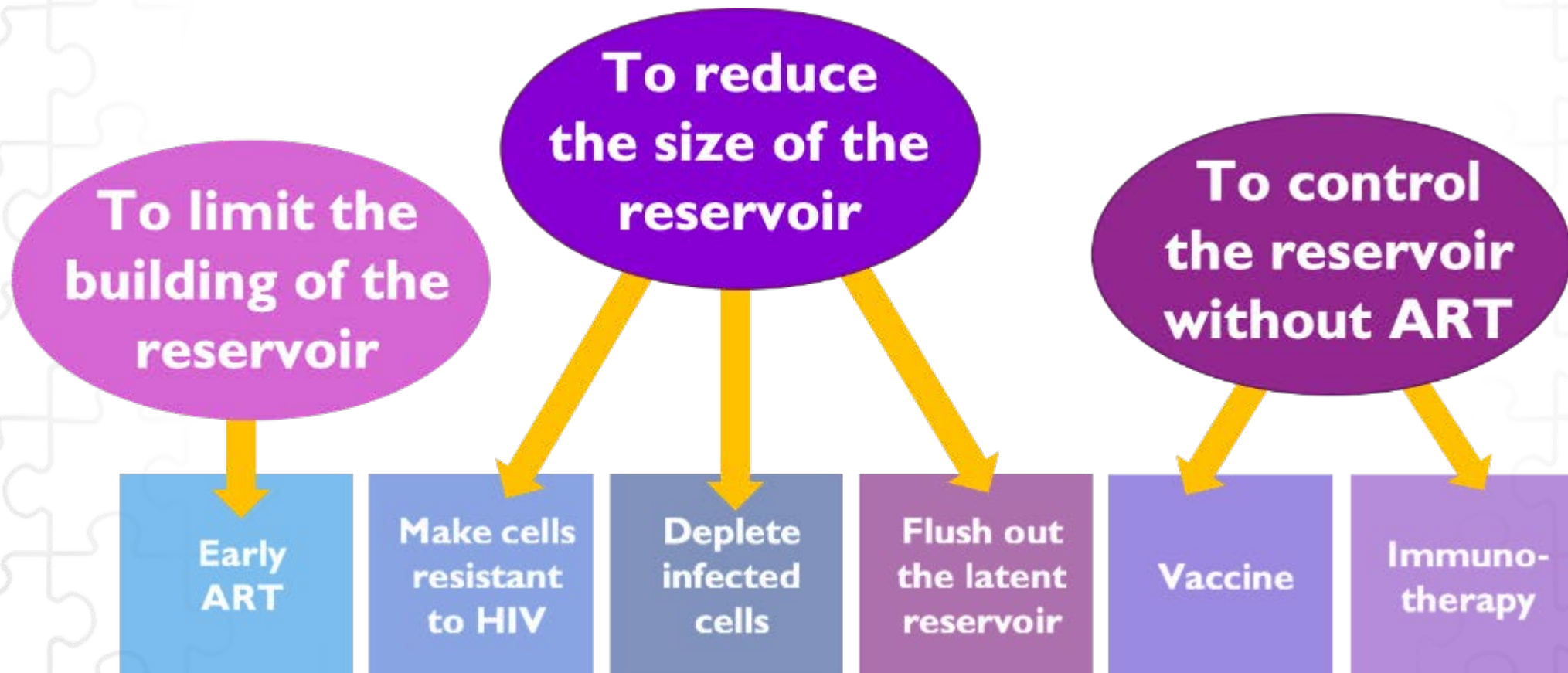
CUREiculum

Slide Credit: Ndung'u T. HIV Cure Research in Women. Community Cure Workshop. Saturday July 21, 2018.

**What pathways are
currently being explored?**



HIV Cure-Related Research Strategies Under Investigation



Strategies Towards HIV Cure



R. Brad Jones



Latency reversal– reactivate latent HIV with drugs and kill with immune system



Gene therapy to delete HIV out of cells



Gene therapy to make cells resistant to HIV



Vaccines / Immunotherapies – enhance immune responses to control virus



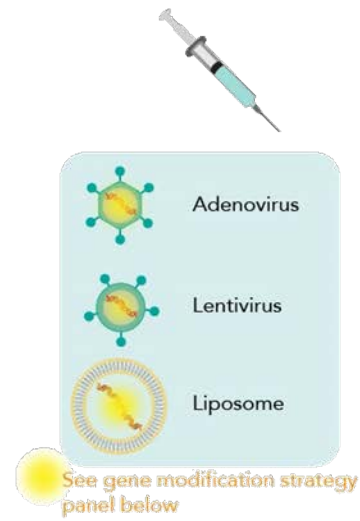
‘Block and lock’ – permanently silence HIV expression (force into deeper latency)



Cell & Gene Approaches

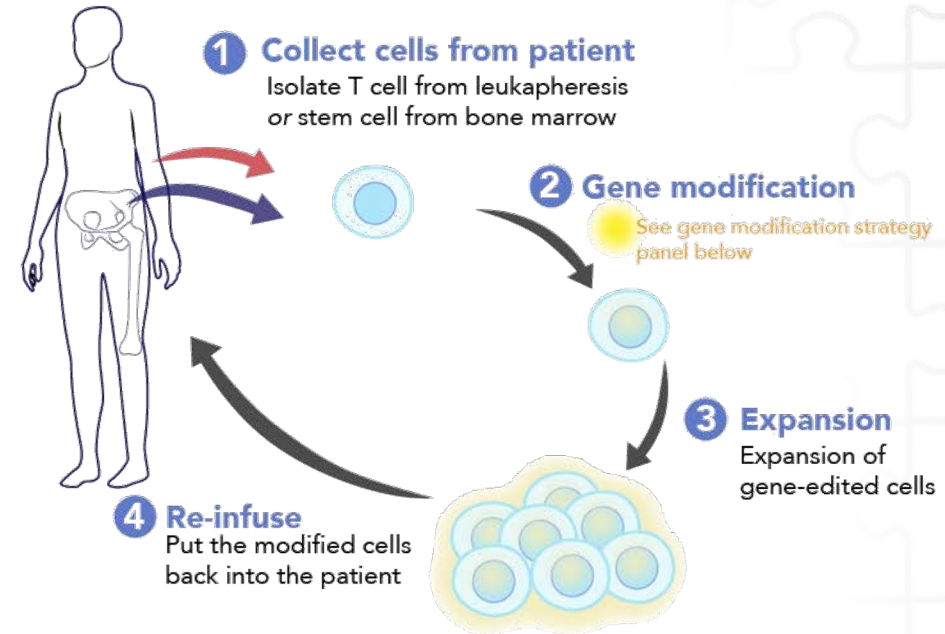
In vivo gene therapy

Vectors are used to carry anti-HIV genes to the target cells *in situ*



Ex vivo gene therapy

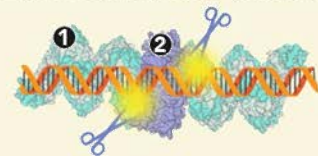
Isolation of desired cell types from the patient, followed by gene modification and reinfusion



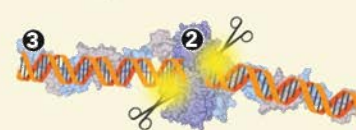
Gene modification strategy

Nucleases and CRISPR/Cas9 are like molecular scissors

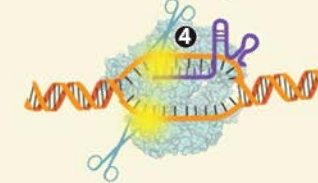
Transcription Activator-like Effector Nucleases (TALENs)



Zinc Finger Nuclease



CRISPR-Cas9 complexes



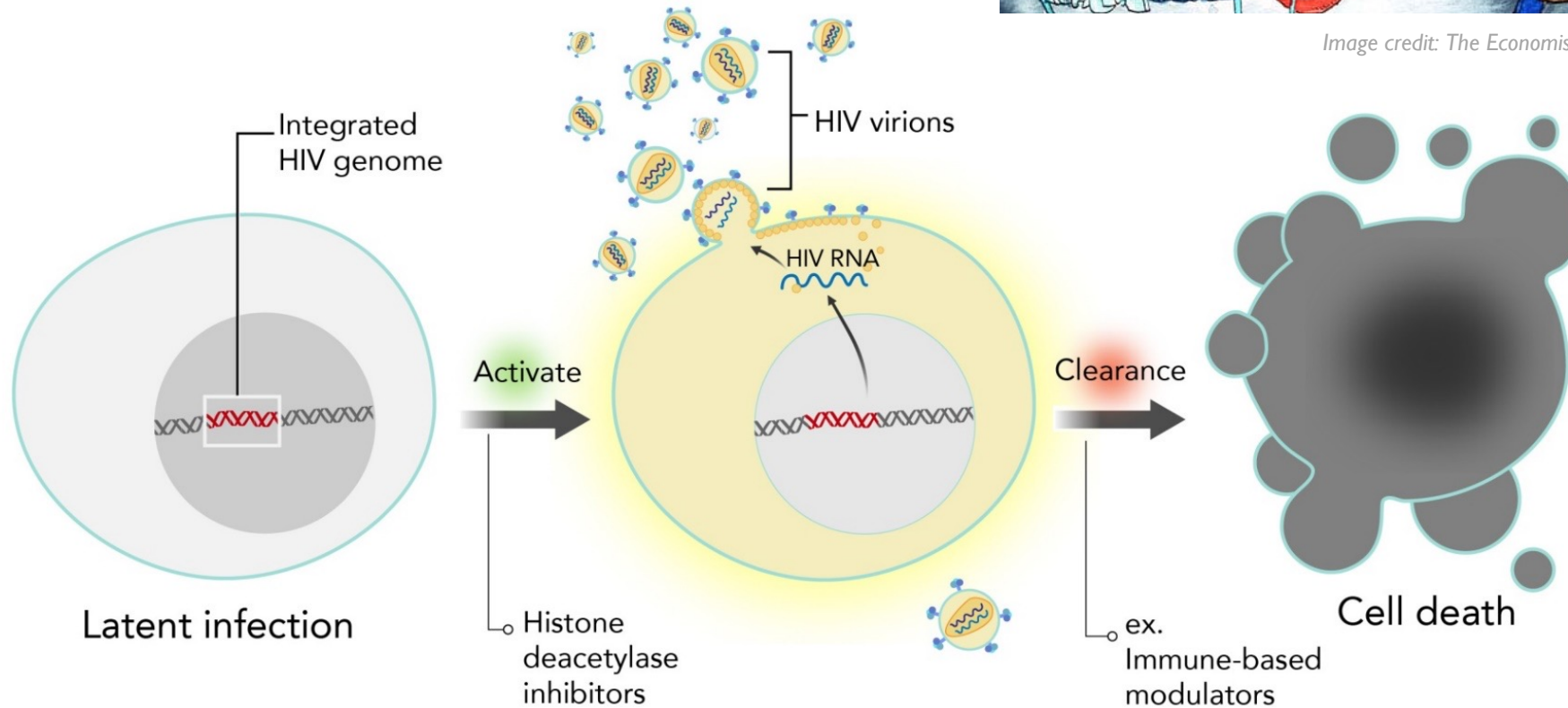
- 1** TAL-effectors
- 2** Nuclease
- 3** Zinc Fingers
- 4** Cas9



Latency Reversing Agents



Image credit: The Economist, July 11



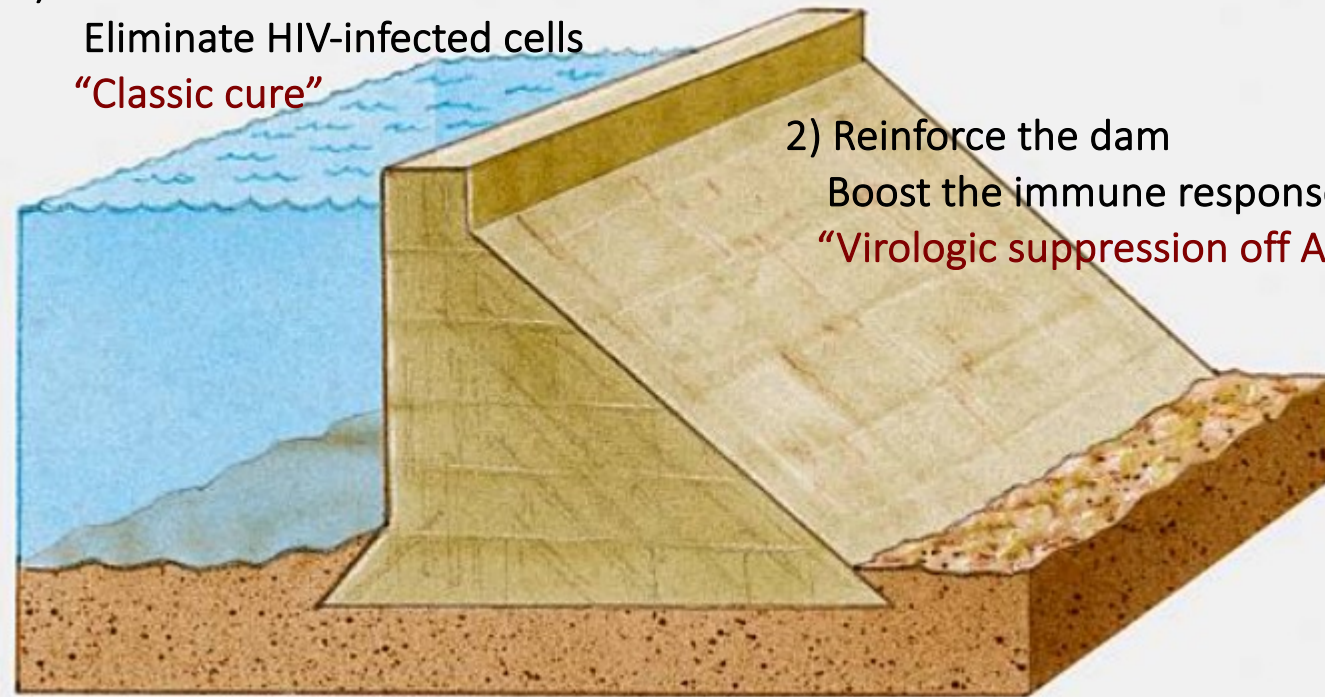
How Can We Prevent HIV From Rebounding Off of Therapy?



R. Brad Jones



- 1) Drain the HIV reservoir
Eliminate HIV-infected cells
“Classic cure”



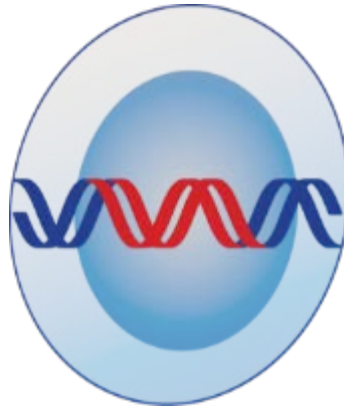
- 2) Reinforce the dam
Boost the immune response to HIV
“Virologic suppression off ART/remission”



The “Block and Lock” Approach



Block & Lock



Transcription
inhibitor



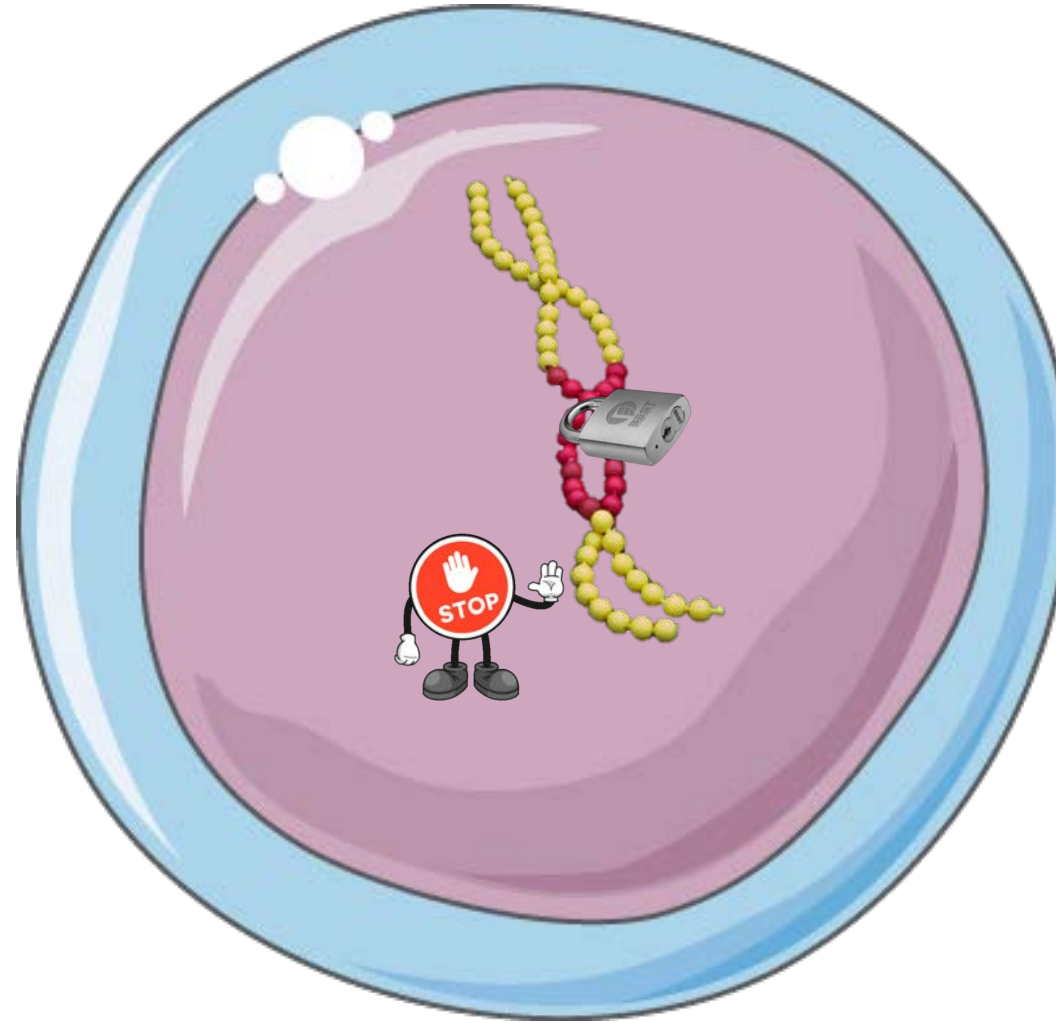
**Sleeping beauty keeps on sleeping
She never wakes up for the prince**

¹Kessing, Cell Report 2017; ²Ahlenstiel, Mol Ther Nucleic Acid 2015



Block and Lock

Block the reading
of the HIV DNA



Lock the HIV
DNA from ever
being read

<https://www.labroots.com/trending/health-and-medicine/7121/scientists-discover-block-and-lock-drug-cure-hiv>

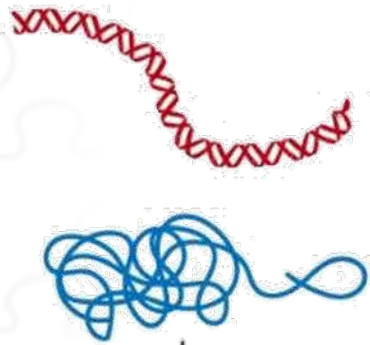


CUREiculum

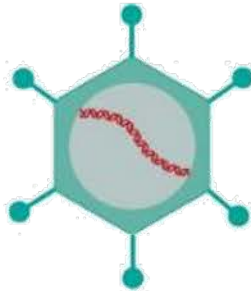
<https://kirby.unsw.edu.au/news/block-lock-pathway-hiv-remission>

Immune-Based Strategies

1. DNA and RNA vaccines



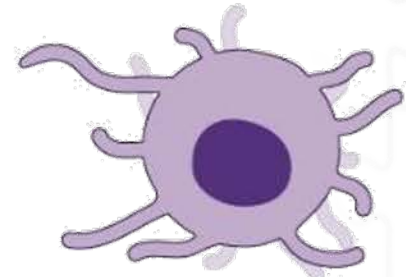
2. Viral vector vaccines



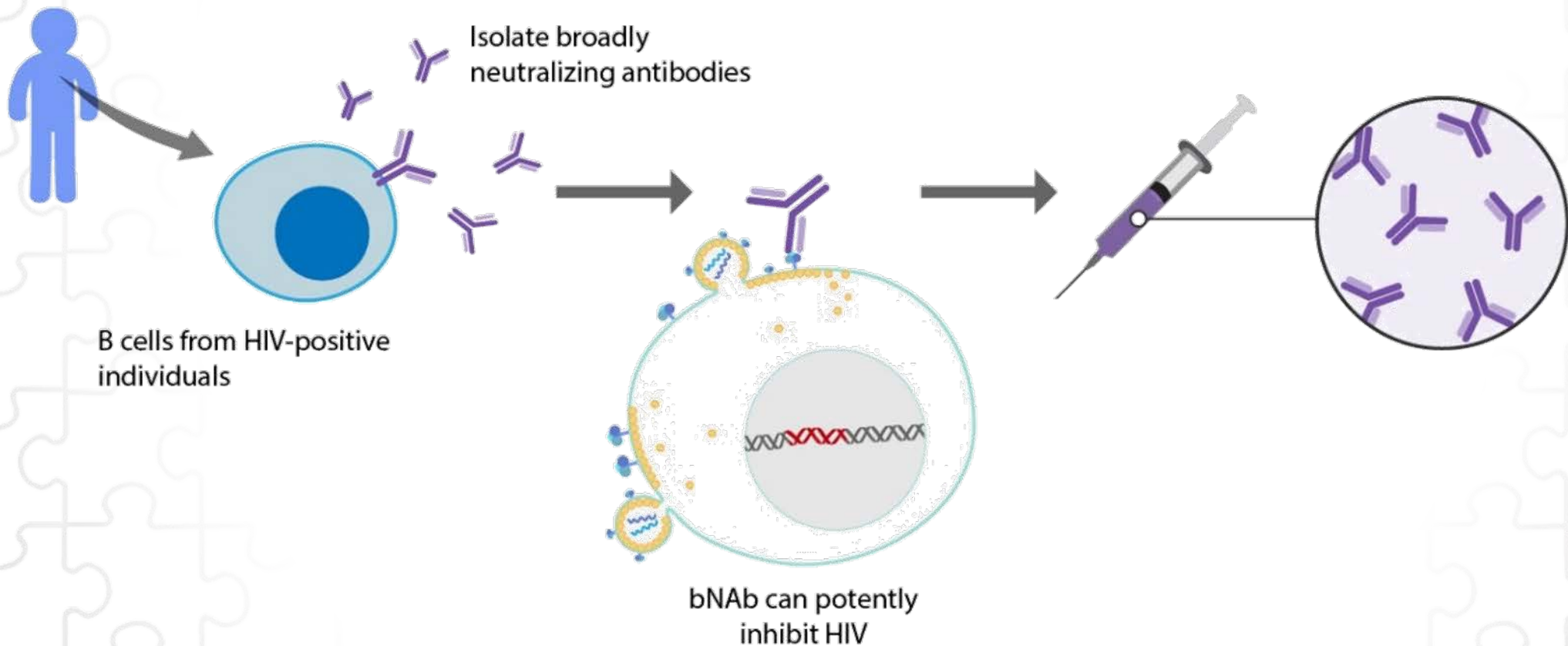
3. Protein or peptide vaccines



3. Dendritic cell vaccines

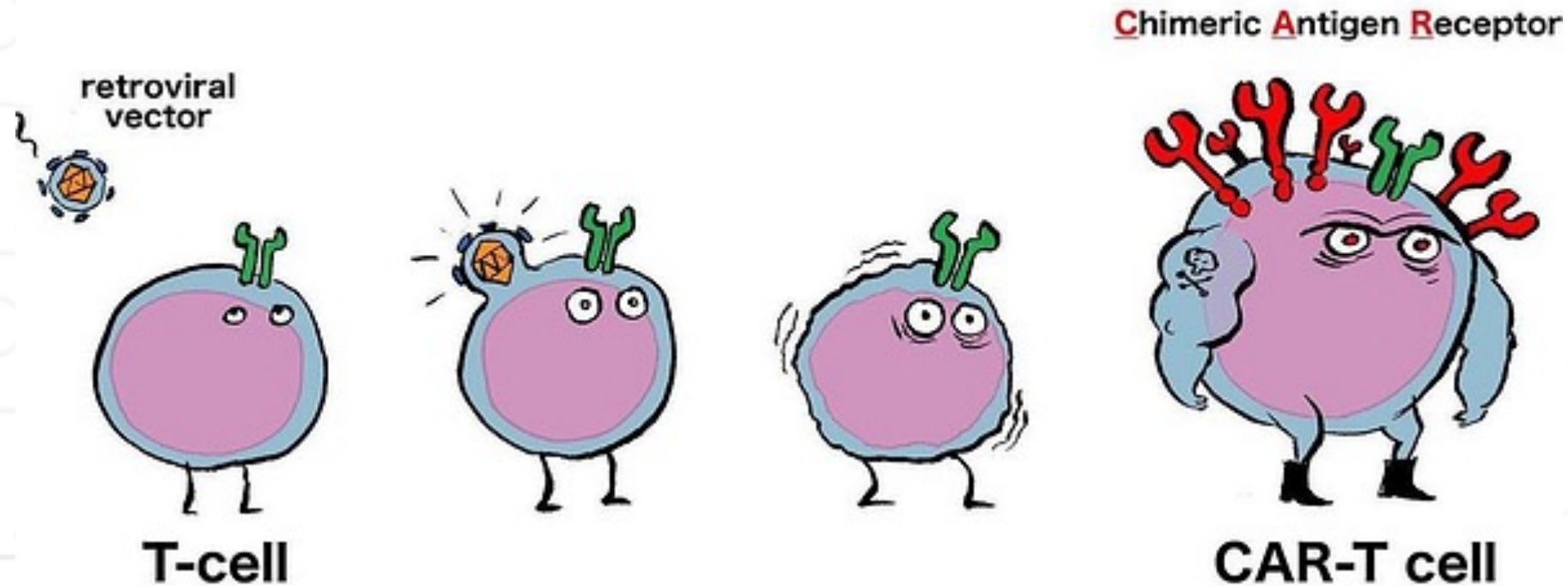


Broadly Neutralizing Antibodies



Chimeric Antigen T cells (CAR-T cell)

Generating super-soldiers the production of CAR-T cells



facebook.com/pedromics

https://blog.seracare.com/ngs/aacr-2019-day-one-highlights-next-generation-car-t-cells?utm_medium=social&utm_source=facebook



CUREiculum

Antiretroviral Treatment Interruptions (ATIs) to evaluate cure interventions

See separate ATI module for further details

*temporarily interrupting
or pausing ART in
someone who has HIV*



Image credit: Michael Louella

- **Other terms:**
 - Structured treatment interruptions (STI)
 - Intensively Monitored Antiretroviral Pause (IMAP)
- **Why pause ART?**
 - We cannot easily measure the HIV reservoir
 - We need to “jump start” the immune system



Ethical Challenges to HIV Cure-Related Research

See separate Ethics module for further details



- Language of HIV cure-related research
- Participation of people living with HIV
 - Informed consent
 - Background standard of care and U = U
 - Biological and social context of HIV cure-related research
 - Risks and benefit
 - Representation in research
- ATIs and partner protections *(see separate ATI module)*
- Scalability of interventions
- Access and affordability
- Structural inequities



Useful Video Links

- **Game Changers: Who & What is Behind an HIV Cure-Directed Study**

<https://player.vimeo.com/video/341333676?autoplay=0&badge=0&byline=0&portrait=0&title=0&api=1&wmode=transparent&fullscreen=1>

- **Flower Lesson For HIV Cure:**

https://www.youtube.com/watch?v=IVLbIsEn_AA&t=18s

- **Who Has Been Cured of HIV?**

<https://www.youtube.com/watch?v=BxBGyrYoacU>

- **HIV Criminalization: Masking Fear And Discrimination**

<https://www.youtube.com/watch?v=SgVWjleDBSaQ>

- **HIV: Basic Function Of The Immune System**

<https://www.youtube.com/watch?v=YUNVGCQVe2g>

- **HIV Infection Stages, Pathology And Treatment**

<https://www.youtube.com/watch?v=horX8xLVpCg>

- **HIV Infection Mechanism – Dendritic Cells**

<https://www.youtube.com/watch?v=ZroXIBg8keA>

- **Understanding HIV Reservoirs**

<https://www.youtube.com/watch?v=XkQqE02gbVc>

- **Understanding Broadly Neutralizing Antibodies**

<https://www.youtube.com/watch?v=Dr7werW5Or4&t=26s>



Useful Video Links (cont'd)

- **Gene Editing explained**
https://www.youtube.com/watch?v=E8vi_PdGrKg
- **CAR-T Cells in cancer**
<https://www.youtube.com/watch?v=OadAW99s4Ik>
- **Live Cell Image T cells with Macrophages**
<https://www.youtube.com/watch?v=SkTIZxsVSGM>
- **How One Cell Becomes Two Through Mitosis**
https://www.youtube.com/watch?v=L6IGp_d7evo





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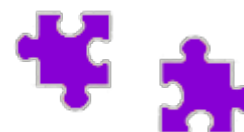
Michael Louella defeatHIV CAB

Lynda Dee AIDS Action Baltimore

Karine Dubé UNC Chapel Hill

We wish to thank **AIDS Treatment Activists Coalition**
for the funding to complete this module

Their caring support of the CUREiculum 2.0.
will make a difference in the lives of thousands.
of people living with HIV



Biomedical Co-Leads

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