



An HIV cure: how far are we, and how might we get there?

BC Telehealth Video Broadcast
September 19, 2019

Zabrina Brumme, PhD

Laboratory Director, BC Centre for Excellence in HIV/AIDS
Professor, Faculty of Health Sciences, Simon Fraser University



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Main Message

There is currently no cure for HIV.

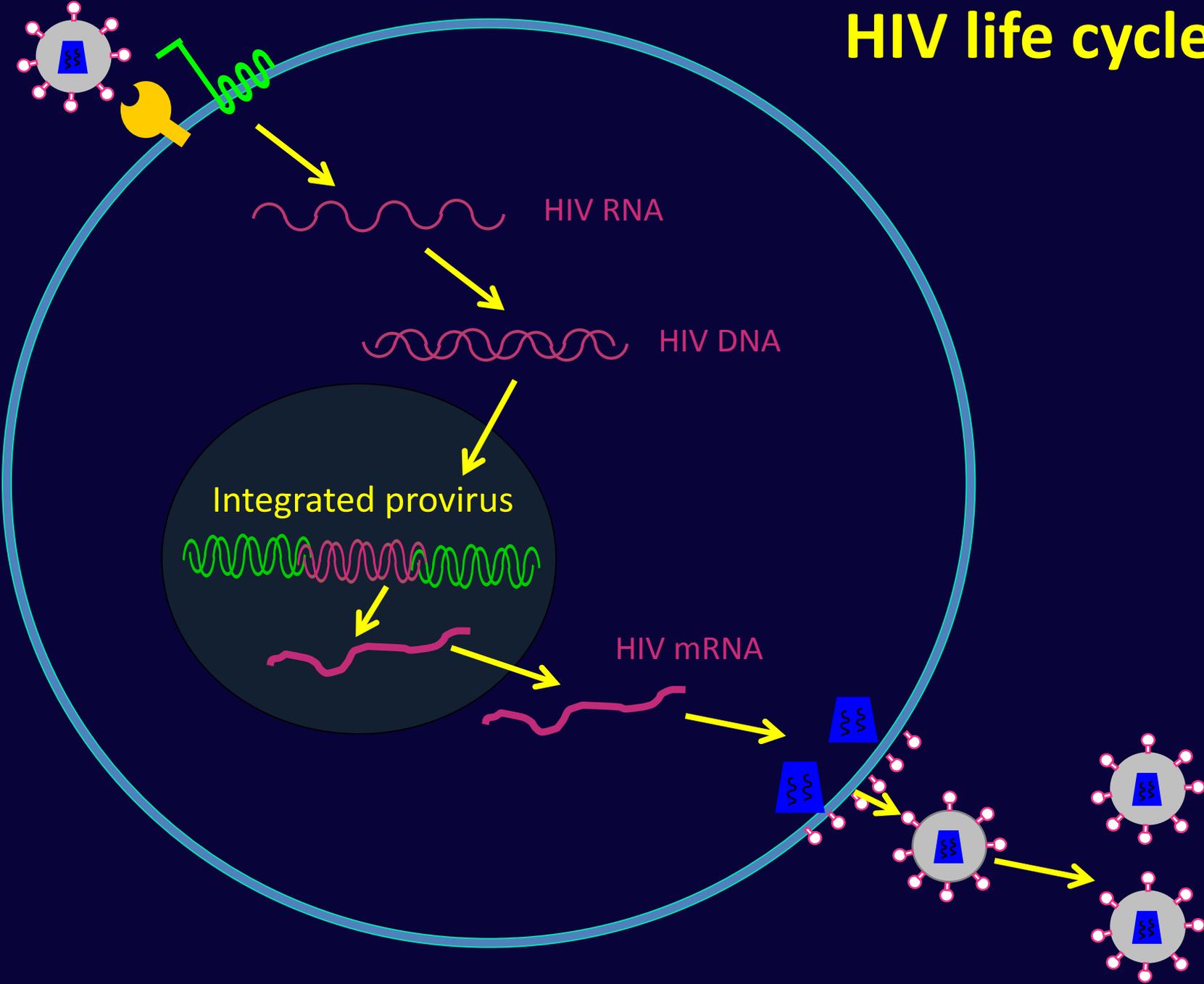
But scientists, doctors and community members are working together towards this goal.

Overview

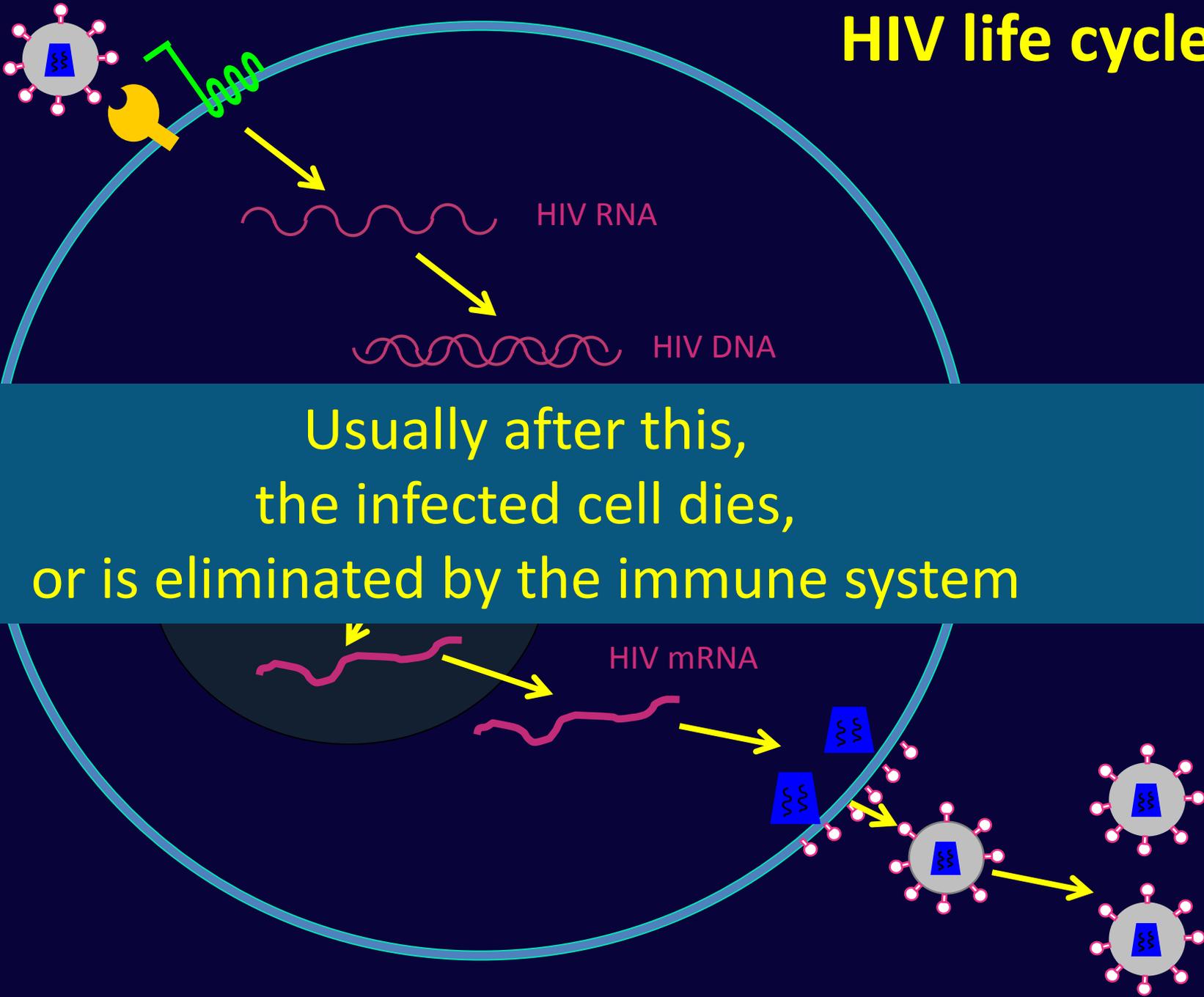
PART 1: HIV latency 101: why current therapies don't cure

PART 2: How we are trying to cure HIV

HIV life cycle

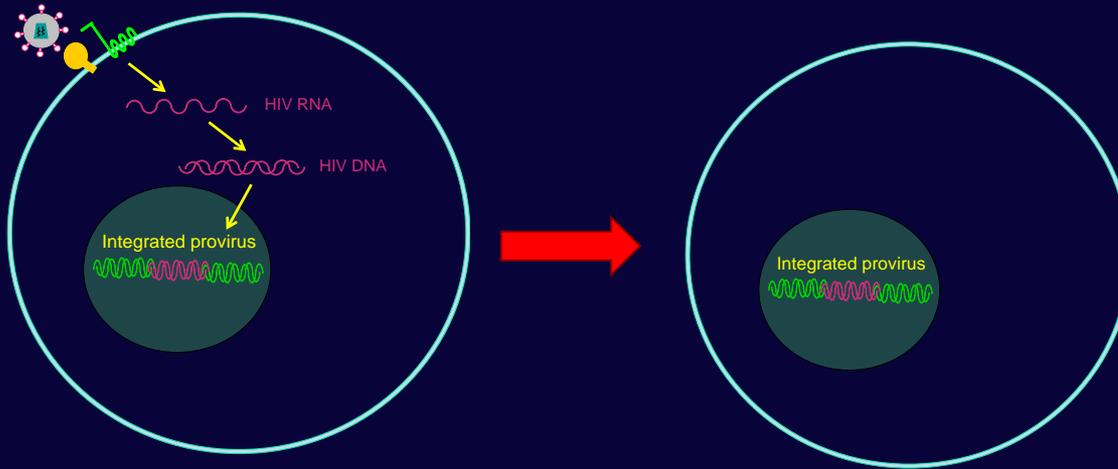


HIV life cycle

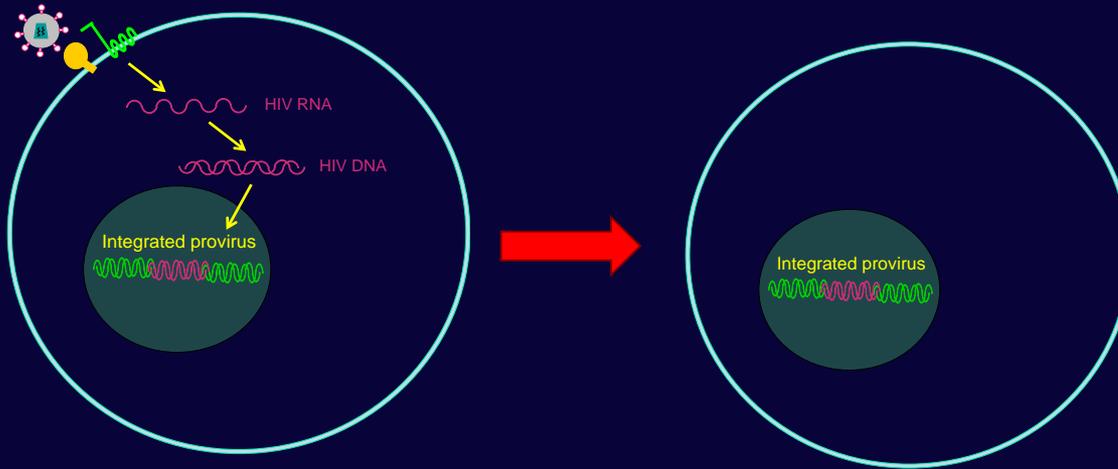


Usually after this,
the infected cell dies,
or is eliminated by the immune system

But... HIV can also lie dormant



But... HIV can also lie dormant

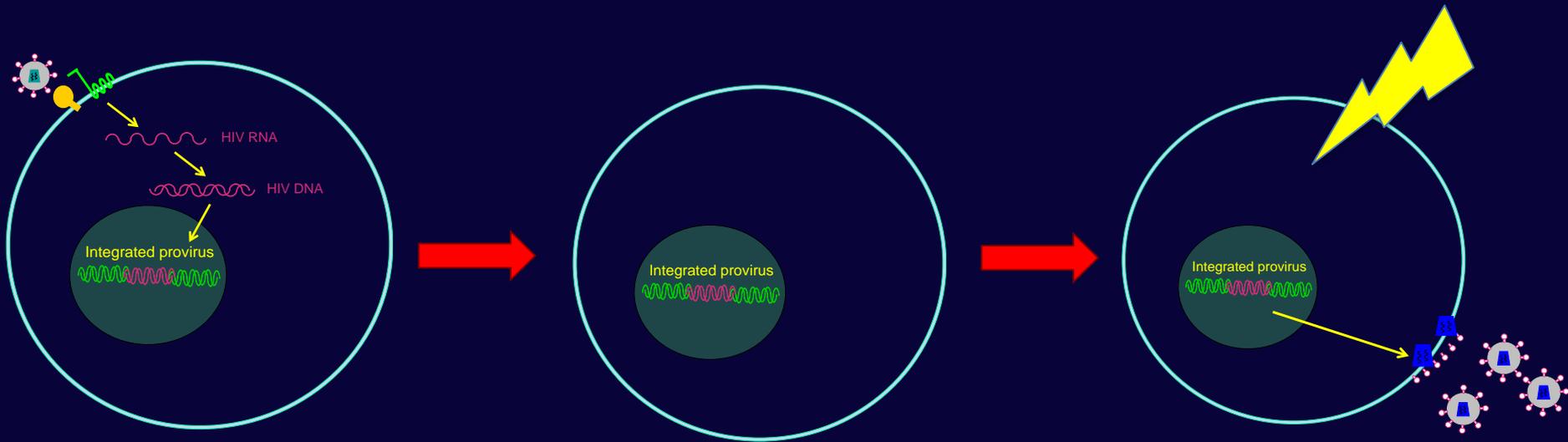


These cells are called “latently-infected cells” or “viral reservoirs”

Latently-infected cells are the main barrier to cure:

- > cART does not eliminate them
- > they are “invisible” to the immune system
- > they (or their descendants) can persist for years or decades

But... HIV can also lie dormant

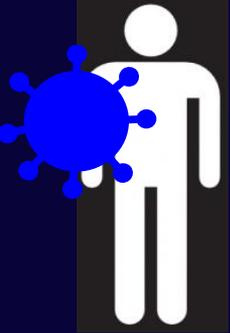


.... But they can reactivate at any time to produce infectious HIV

It is for this reason that cART needs to be maintained for life

HIV replication within an individual, over time

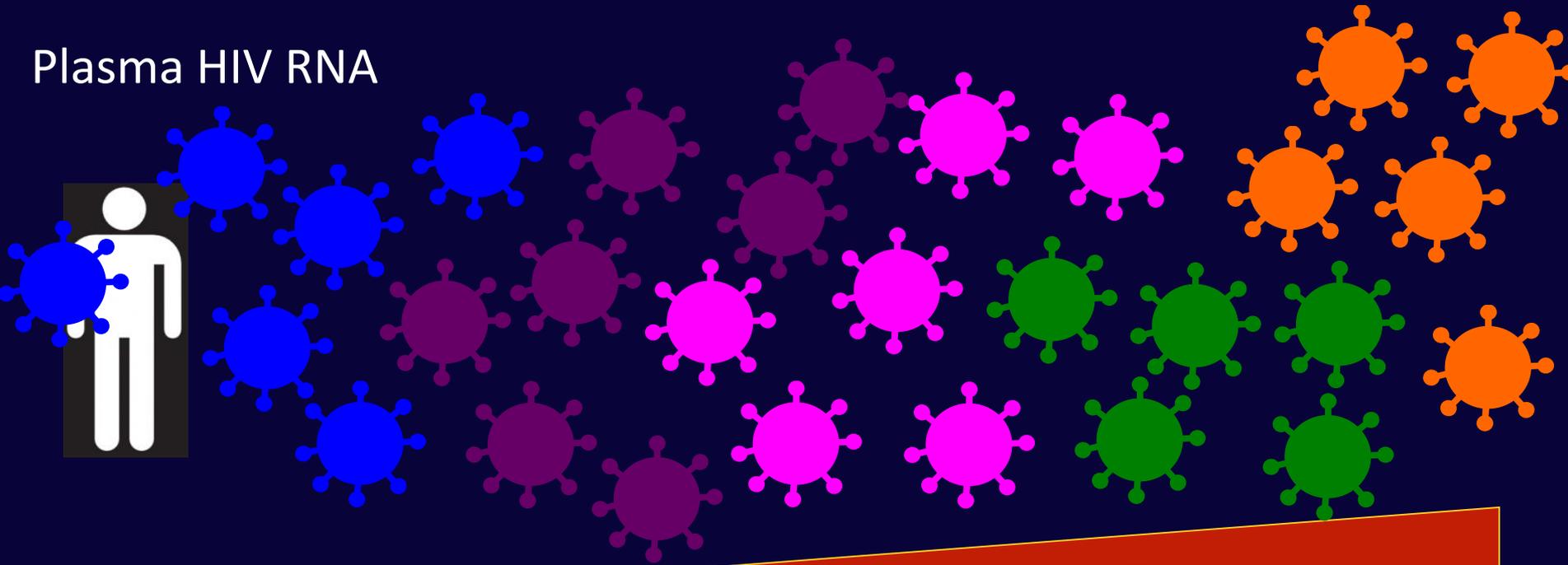
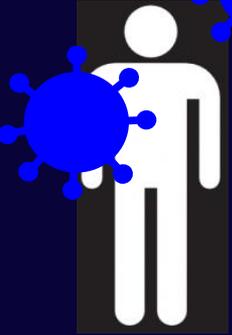
Plasma HIV RNA



Time since infection

HIV replication within an individual, over time

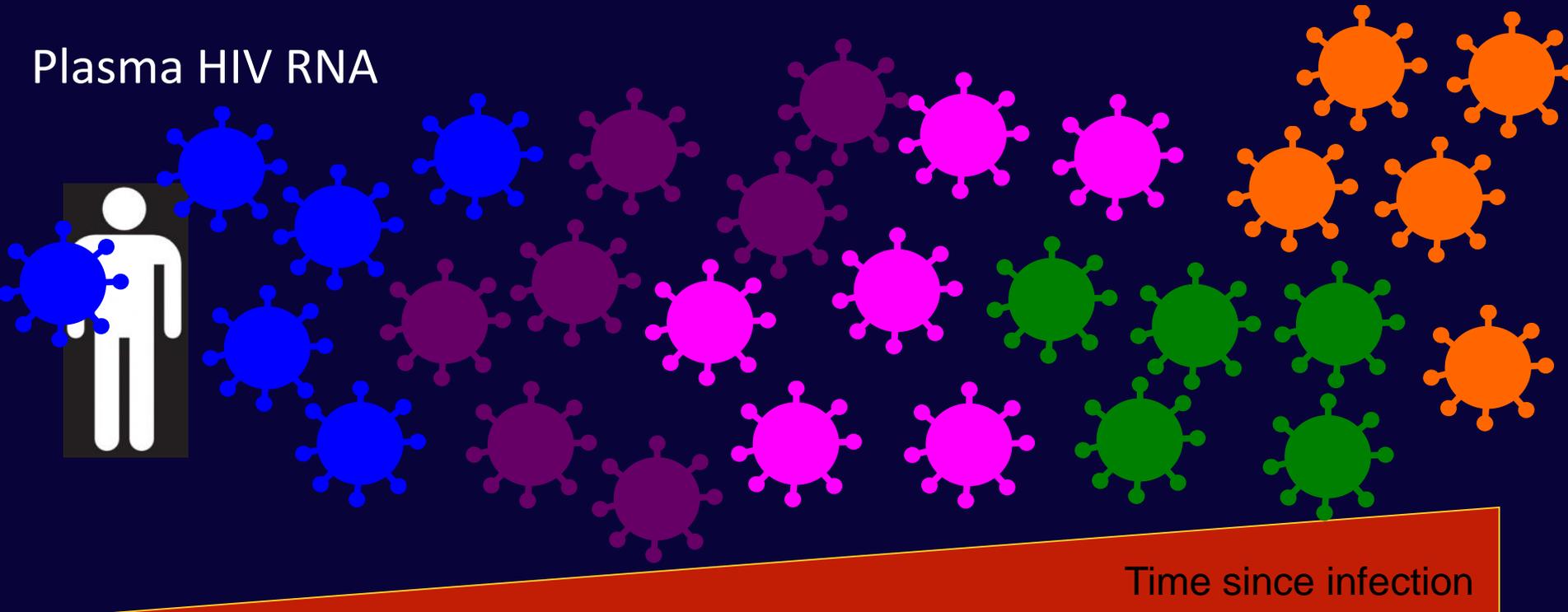
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Time since infection

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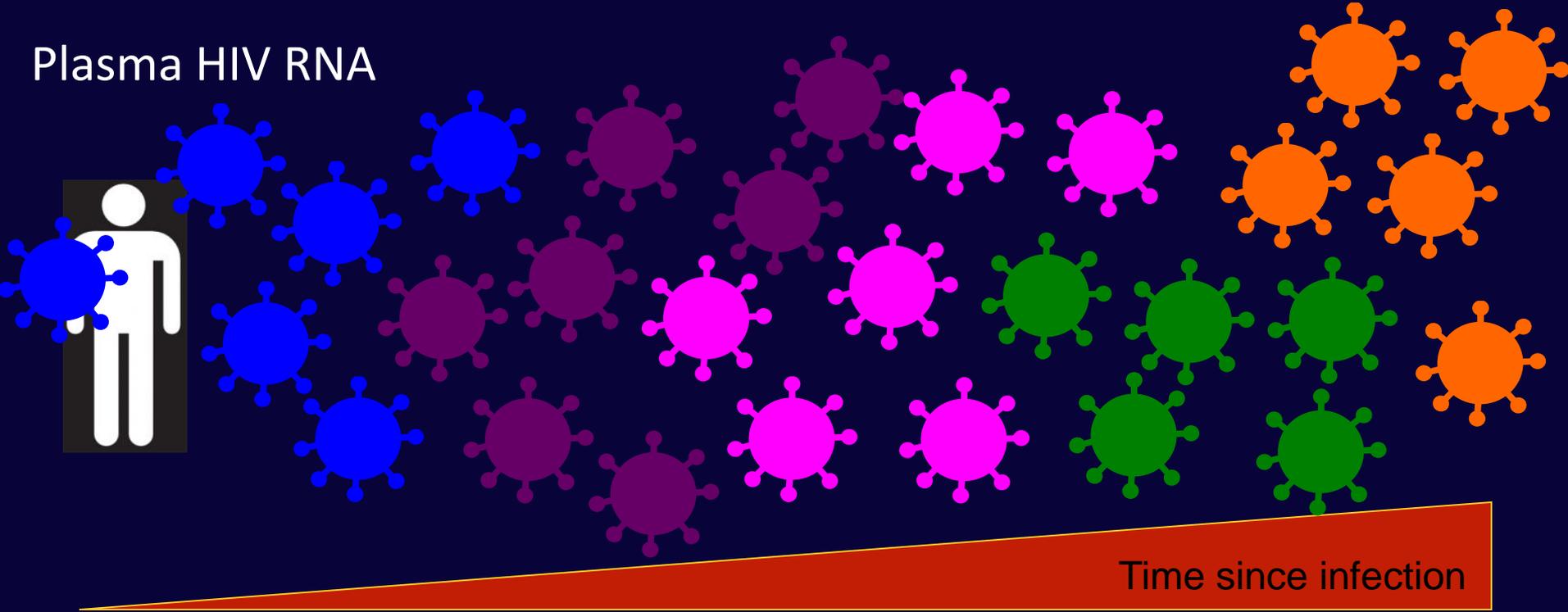


Latent ("dormant") reservoir

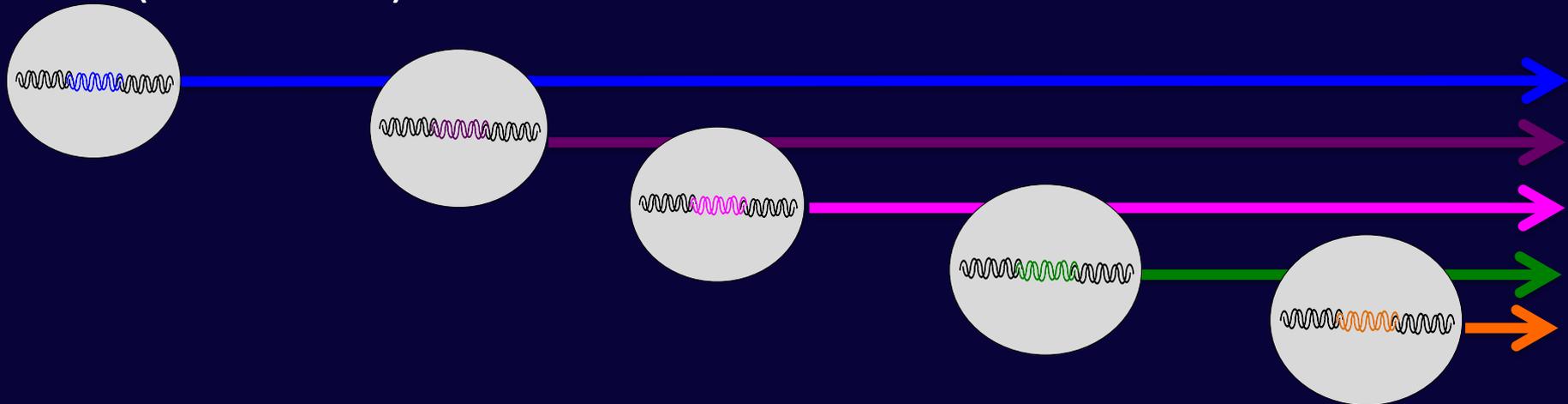


HIV replication within an individual, over time

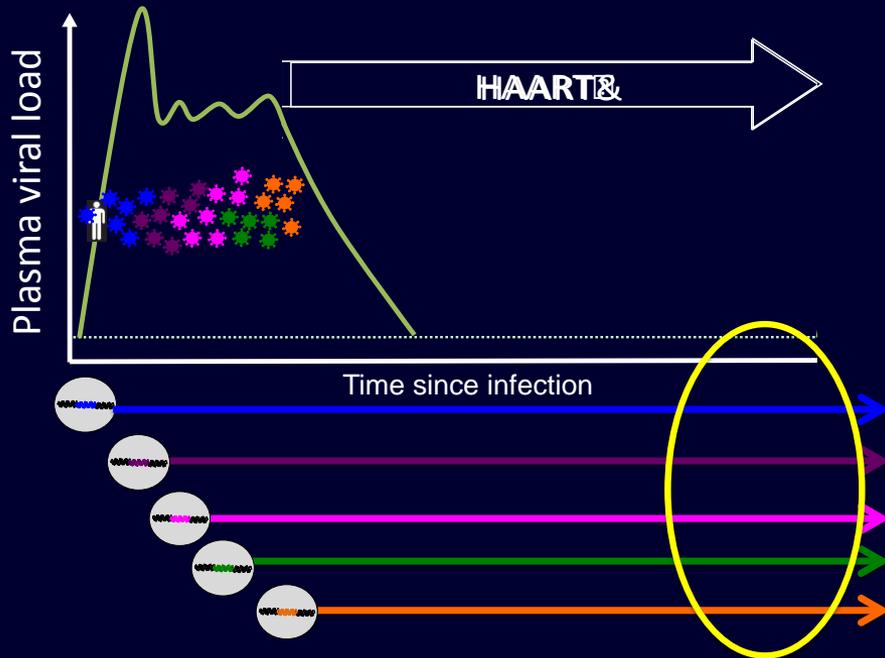
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Latent ("dormant") reservoir

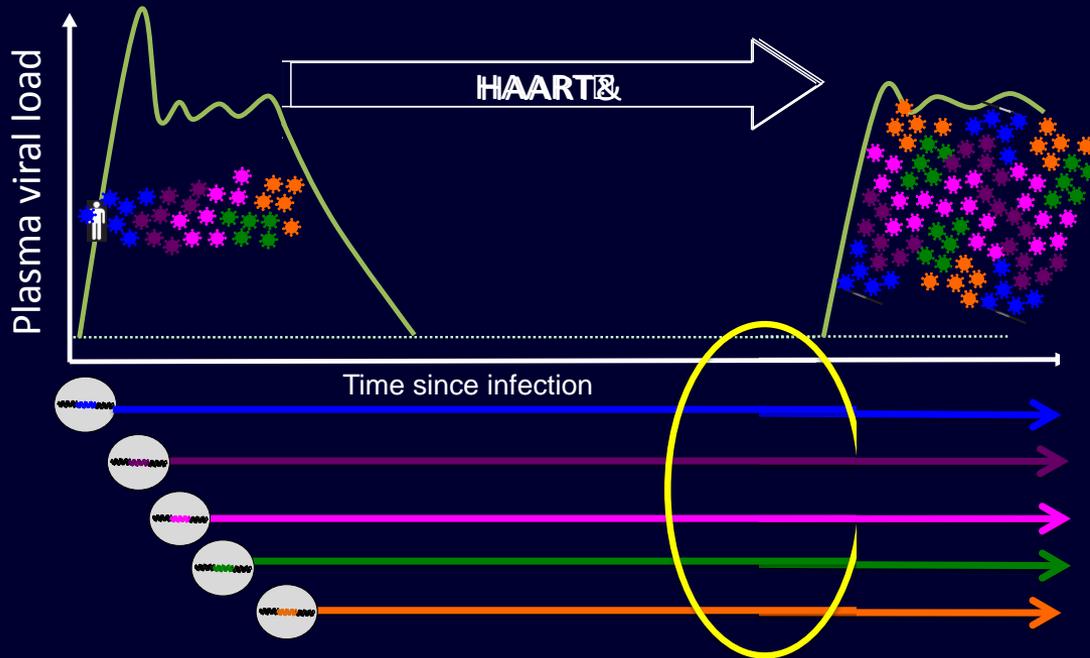


And, these “dormant” HIV lineages persist, even during long-term therapy



**And, these “dormant” HIV lineages persist,
even during long-term therapy**

*... and will reactivate as soon as therapy is
discontinued*



Overview

PART 1: HIV latency 101: why current therapies don't cure

PART 2: How we are trying (and so far, not succeeding) to cure HIV

First, clarifying some definitions

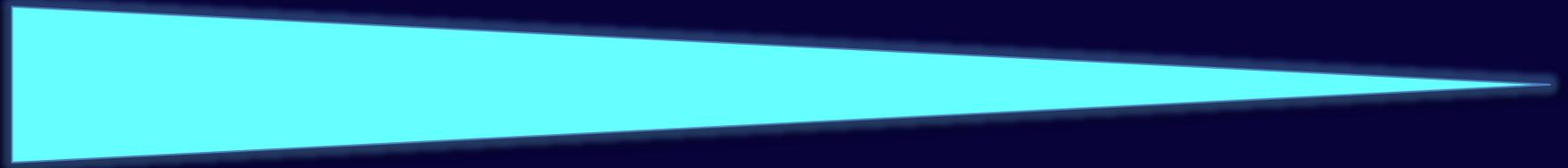
Sterilizing cure (or just plain “cure”)

A cure in the traditional sense, *i.e.* a state where someone is completely free of (infectious) HIV.

Sustained HIV remission (“functional cure”):

A state where a person can discontinue ART without the risk of viral rebound. A functional cure may not require elimination of every HIV particle from the body.

Now, enumerating our successes



Living with HIV

37 million

Now, enumerating our successes

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HIV remission

N ~ 100+

(largely) achieved via
early cART initiation

- VL suppressed
- No therapy
- Need VL monitoring
- Transmission risk?

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HIV cure

N=2

(the Berlin patient and now
the London patient)
Achieved via stem cell
transplant from
CCR5 Δ 32/ Δ 32 donor

- No HIV replication
- No therapy
- No VL monitoring
- No transmission risk
- ***But: N=2 and neither safe nor scalable***

HIV cure by bone marrow transplantation using donor cells that are naturally genetically “resistant” to HIV

Case 1: Berlin Patient Reported in 2009



Timothy Ray Brown, known by many researchers as "the Berlin patient," is the only person to have been cured of an HIV infection. ERIC RISBERG/AP PHOTO

How did the 'Berlin patient' rid himself of HIV?

Hutter et al, NEJM 2009, PMID: 19213682
Gupta et al, Nature 2019, PMID: 30836379

<https://www.sciencemag.org/news/2014/09/how-did-berlin-patient-rid-himself-hiv>

<https://www.newyorker.com/news/daily-comment/the-london-patient-and-a-plan-to-end-the-hiv-epidemic-in-the-united-states>

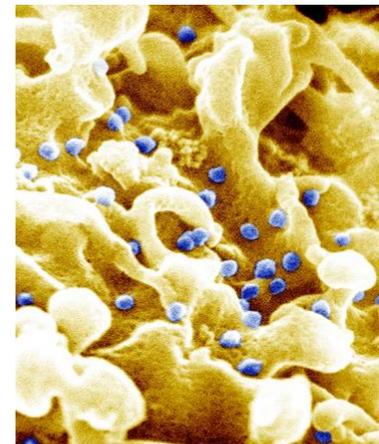
Case 2: London Patient Reported in March 2019

THE LONDON PATIENT AND A PLAN TO END THE H.I.V. EPIDEMIC IN THE UNITED STATES



By Jerome Groopman March 9, 2019

Stunning success in medicine can be born from abject failure. This week, researchers reported in the journal *Nature* what they hope will be a triumph: a man in London who had H.I.V. and may have been cured of the infection. This promising outcome is the direct result of earlier, unsuccessful attempts at a cure. The London Patient, as he is being called, first contracted H.I.V. and then later developed Hodgkin's lymphoma. The cancer was resistant to standard chemotherapy, so his doctors advised more intensive chemotherapy, along with a bone-marrow transplant.



Recent developments have increased the likelihood of eradicating H.I.V., but this progress may be sabotaged by the dismantling of the A.C.A.

Strategies to achieve HIV remission or cure

“Wake up” (reactivate) HIV reservoirs

Boost the Immune response to HIV

“Silence” (permanently deactivate) HIV reservoirs

Gene Therapy/Gene editing

Strategies to achieve HIV remission or cure

“Wake up” (reactivate) HIV reservoirs

Boost the Immune response to HIV

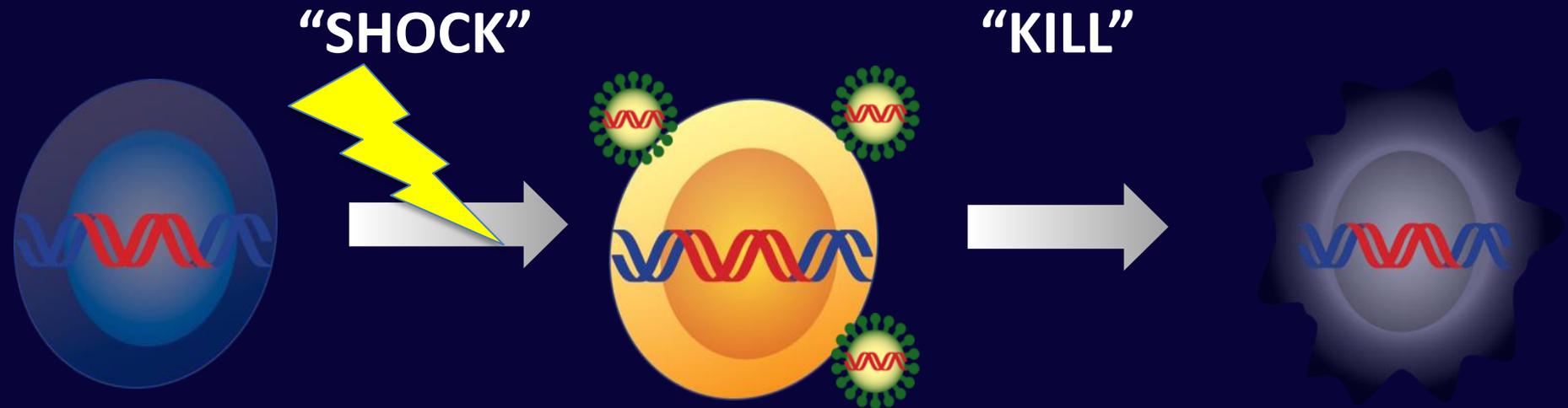
The “shock and kill” approach

The “Shock and Kill” Approach



Reactivate HIV reservoirs
using
latency reversing agents

The “Shock and Kill” Approach



Reactivate HIV reservoirs
using
latency reversing agents

Boost the immune system
to eliminate HIV

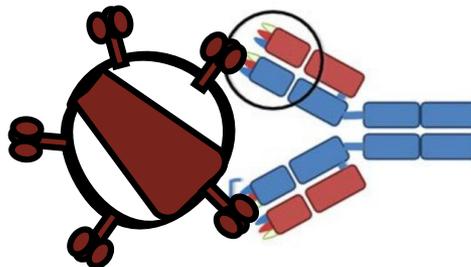
*Treatments would be administered multiple times in series;
cART is maintained throughout*

Where are we at with shock and kill?

Not very far, I am afraid.

A number of (small) clinical trials have been undertaken in humans, but so far none have been successful.

However, a recent study in monkeys using broadly neutralizing antibodies succeeded in inducing HIV remission in 50% of cases



Strategies to reduce/eliminate HIV reservoirs

“Wake up” (reactivate) HIV reservoirs

Boost the Immune response to HIV

“Silence” (permanently deactivate) HIV reservoirs

Gene Therapy/Gene editing

The “block and lock” approach

“Block and lock” to keep HIV reservoirs in a latent state permanently*



Clinical status:

Efficacy of leading compound, didehydro-Cortistatin A (dCA), has been demonstrated *in vitro* and in animal (mouse) models*.

No trials in humans yet.

*cannot be used to achieve a “sterilizing cure” – only remission or functional cure

Strategies to reduce/eliminate HIV reservoirs

“Wake up” (reactivate) HIV reservoirs

Boost the Immune response to HIV

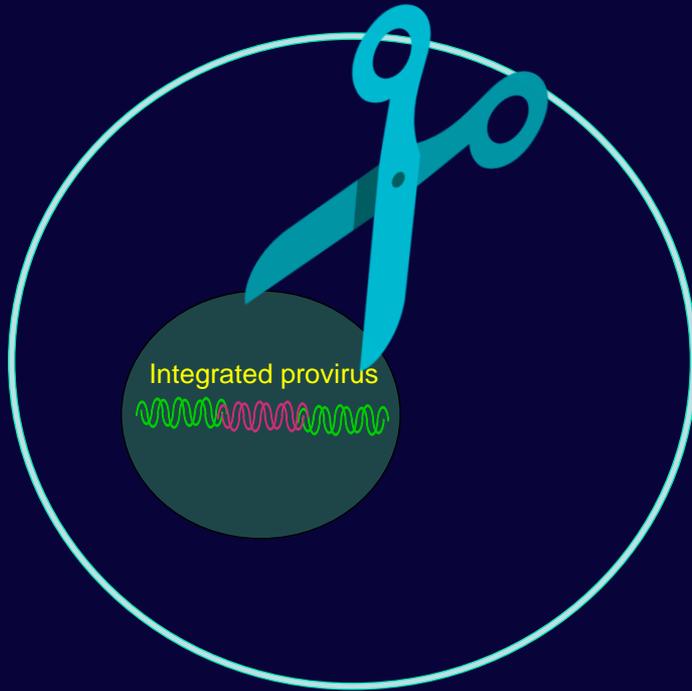
“Silence” (permanently deactivate) HIV reservoirs

Gene Therapy/Gene editing

Gene therapy to “cut out” HIV from latently-infected cells

CRISPR/Cas9

genome editing technique



Clinical status:

Proof of concept achieved *in vitro* and *in vivo* an experimental animal (mouse) model

Small human safety studies in the context of cancer therapy have been conceptually approved

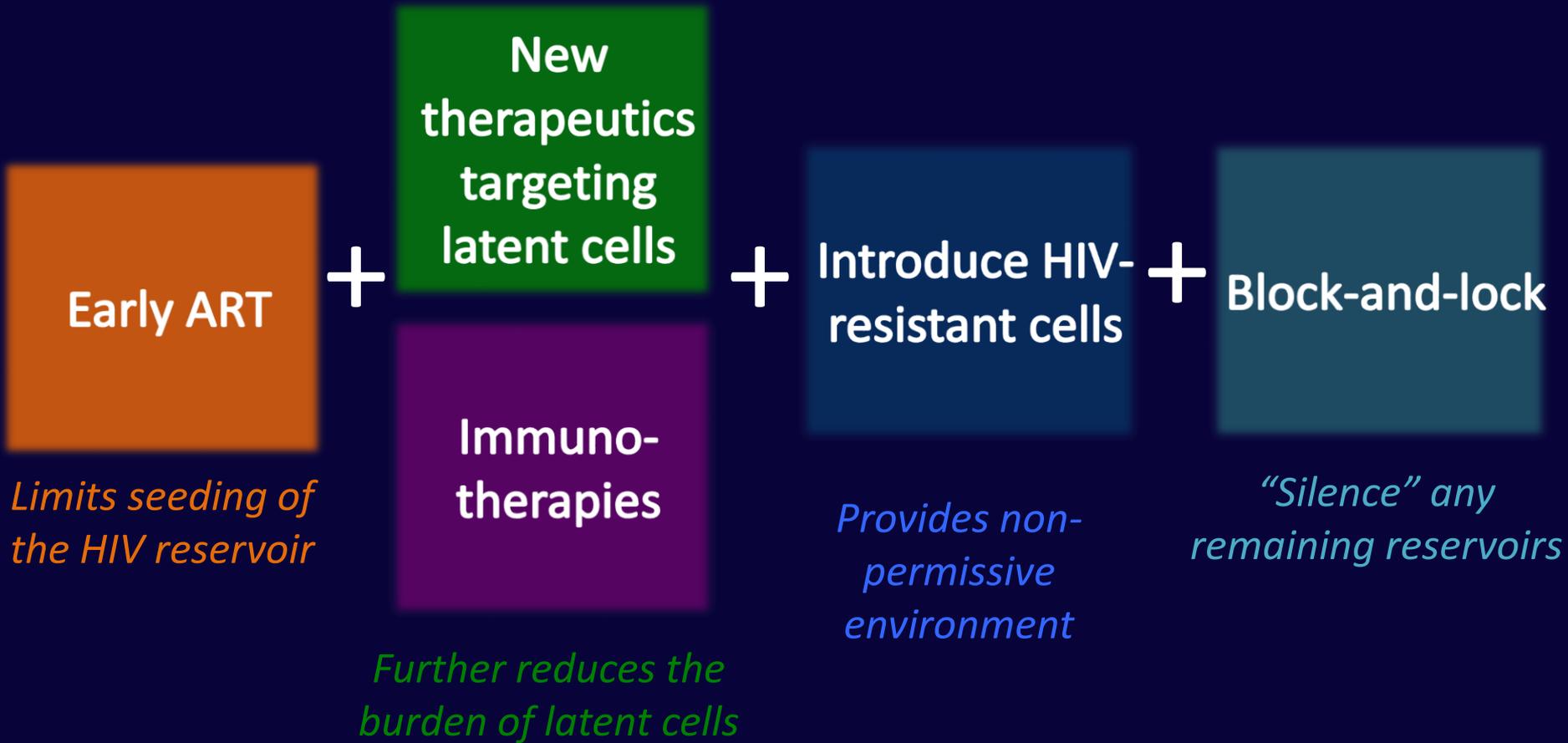
Gene therapy to render human cells resistant to HIV infection by inactivating the CCR5 gene



Clinical trials status:

2014 clinical trial succeeded in inactivating CCR5 in a minority (~5%) of immune cells *ex vivo* (outside the body), but this is not sufficient for cure

Combination approach to reducing the HIV reservoir



ART will still need to be maintained during these treatments

HIV cure research: where we're at

- A cure for HIV is not yet in sight, but many believe it is feasible
- An HIV cure is unlikely to be a single, one-size-fits-all approach – rather, combinations of methods and “personalized” strategies will likely be needed
- Interest, engagement and support of health care providers and community are essential



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**Thank-you for your attention,
and happy to take questions**



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