An update on HIV cure

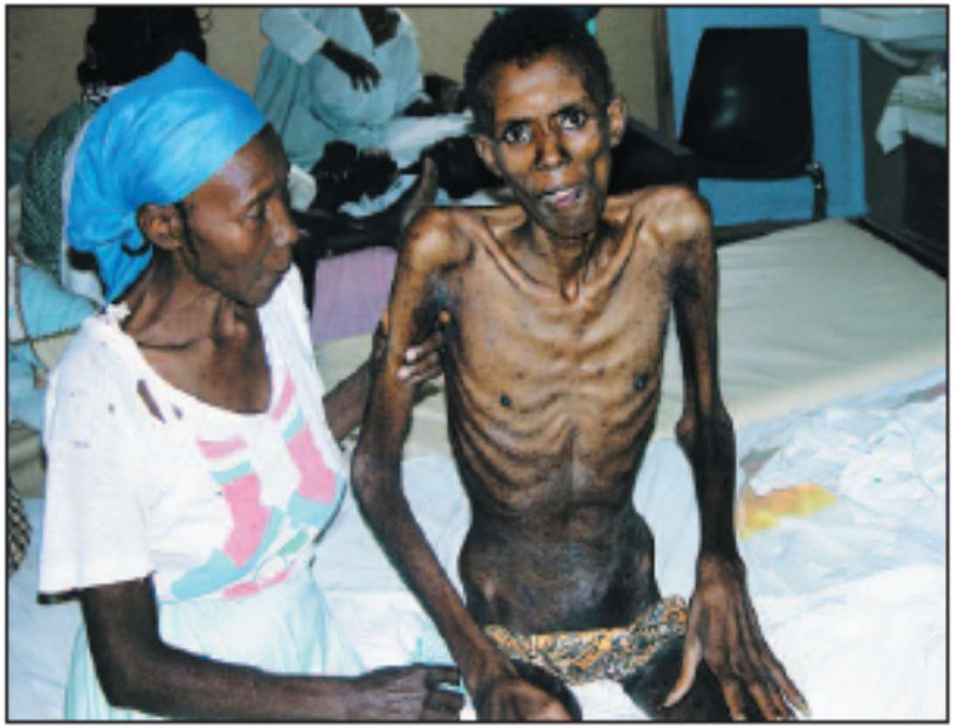
CHIVA

May 2022

Sarah Fidler

Imperial College London UK

Antiretroviral therapy works and is safe!!



Haitian Patient, before and after Receiving Free Treatment for HIV Infection and Tuberculosis.

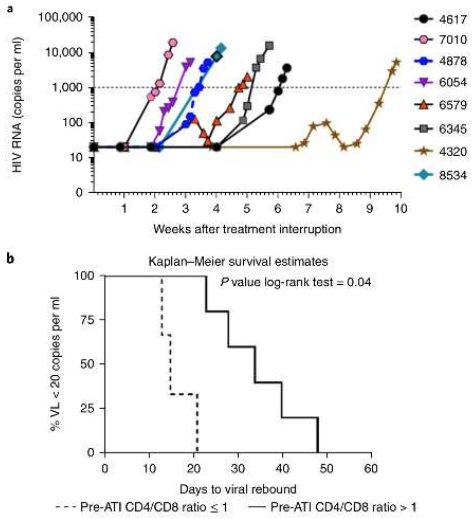
The photograph on the left was taken in March 2003, and that on the right in September 2003. Many impoverished patients in rural Haiti and Rwanda now receive comprehensive medical care through public–private partnerships.

ART alone cant cure HIV

ART has transformed the lives of people growing up and living with HIV

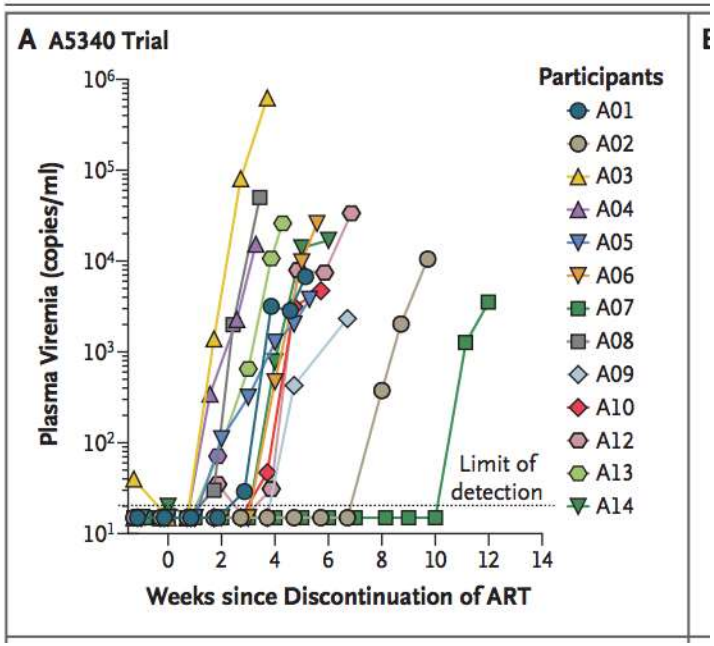
Most children born with HIV are now Young adults with rich healthy lives ahead

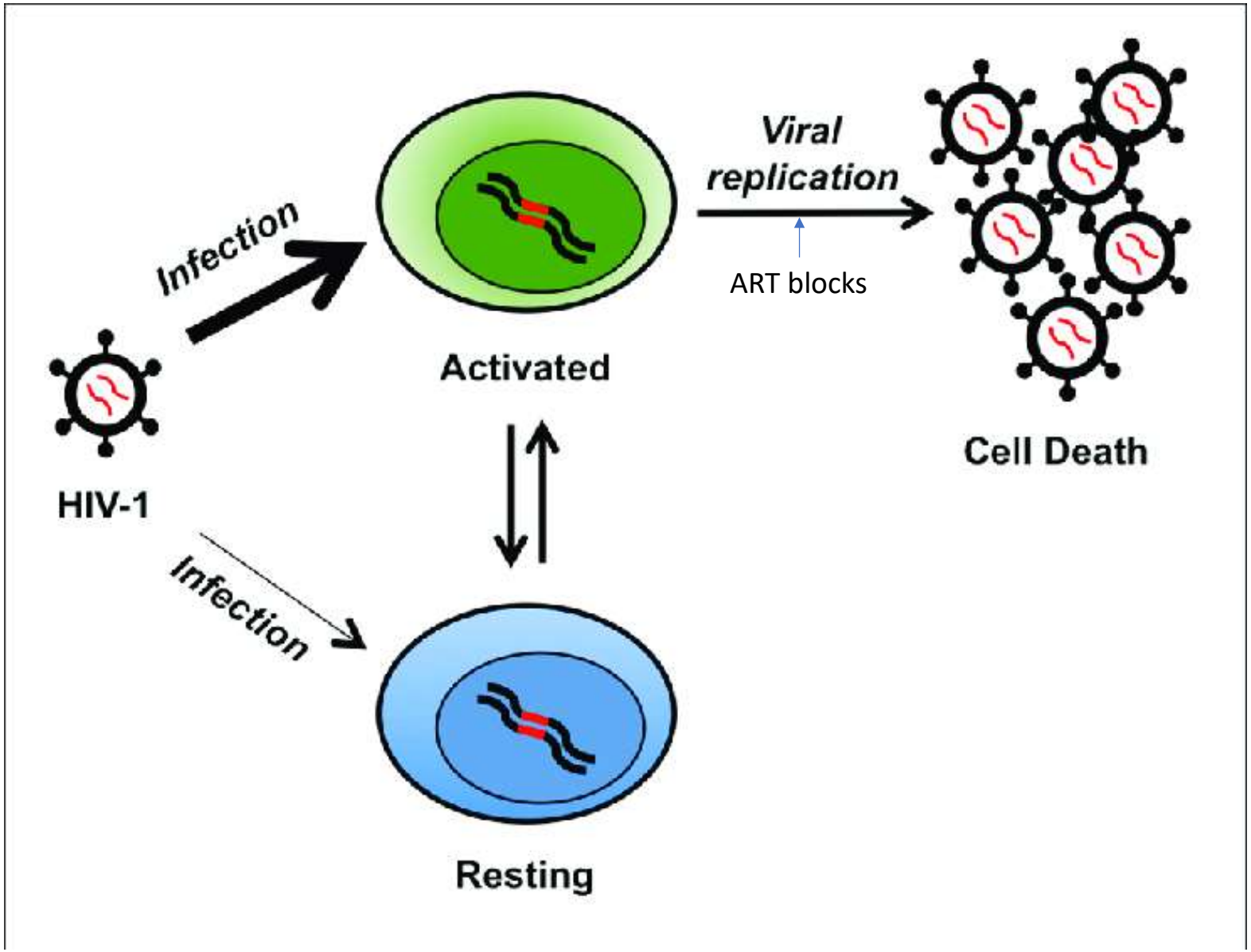
What happens when ART is stopped?
Even if started ART Very early, in acute infection



RV411 Study group Thailand
N = 8 individuals starting ART at Feibig I (first 2 weeks after infection)
On ART median 2.8 years
All experienced rapid viral rebound (>20 cpm x 2) by median 26 days following analytical treatment interruption
None controlled by week 24

Colby et al Nature Medicine 2018 24 923-926

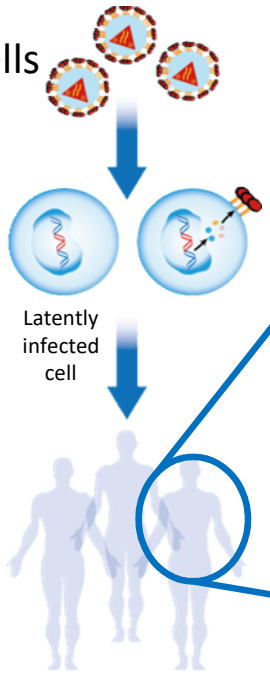



Infection
Activated
Viral
replication
ART blocks
Cell Death
HIV-1
Infection
Resting

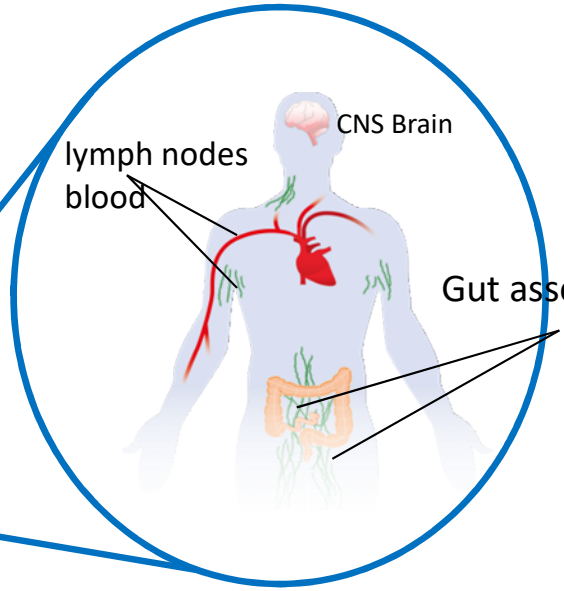
Why can’t ART alone cure HIV?

HIV infects CD4+ cells

Some CD4+ T-cells become resting memory cells; ‘reservoir’



HIV reservoirs



For PLWH on ART with undetectable viral load **1 : 1million** resting CD4 T-cells can be induced to produce virus

Assays to measure the HIV reservoir

Total HIV DNA

Intact HIV DNA

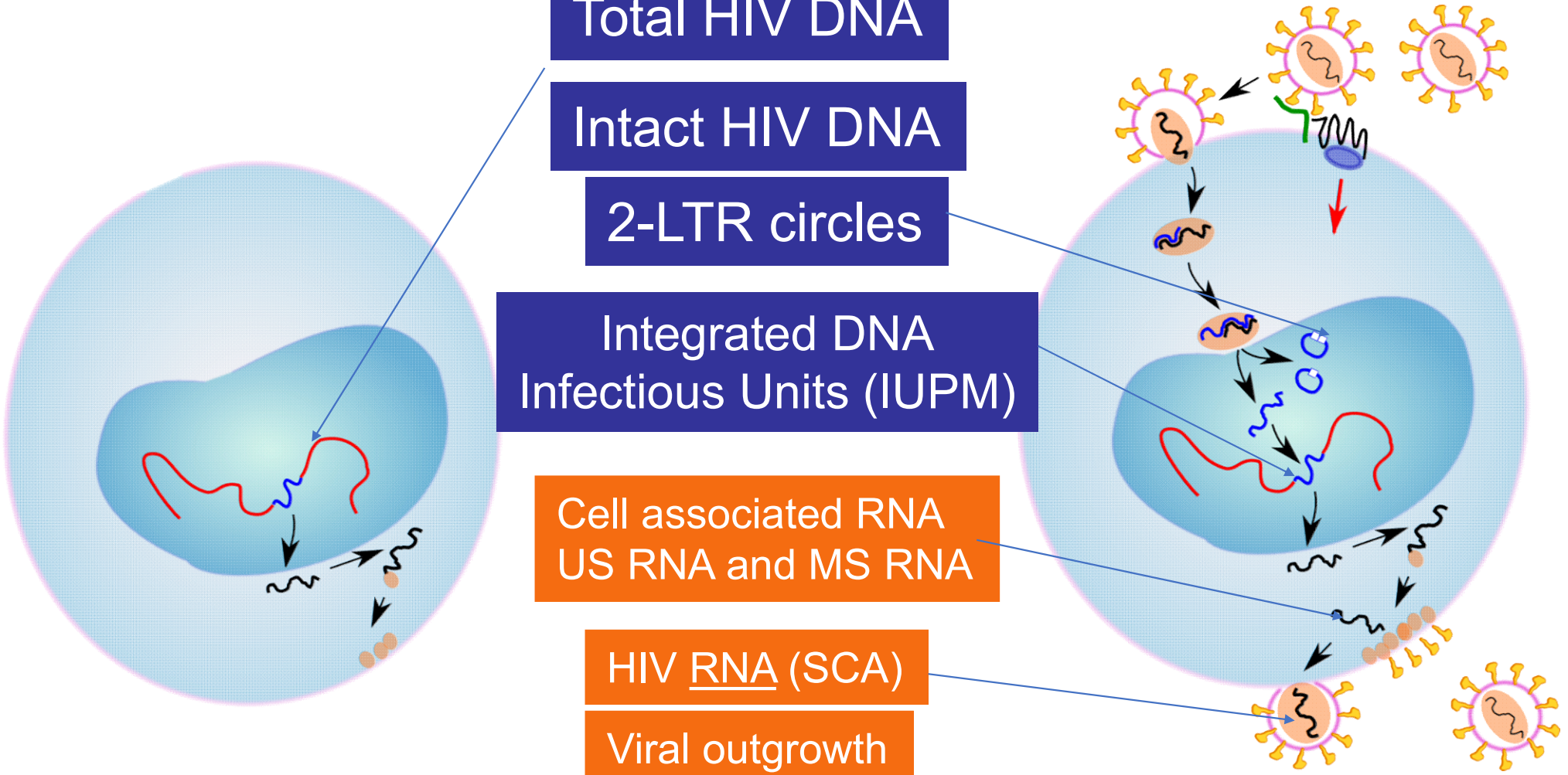
2-LTR circles

Integrated DNA
Infectious Units (IUPM)

Cell associated RNA
US RNA and MS RNA

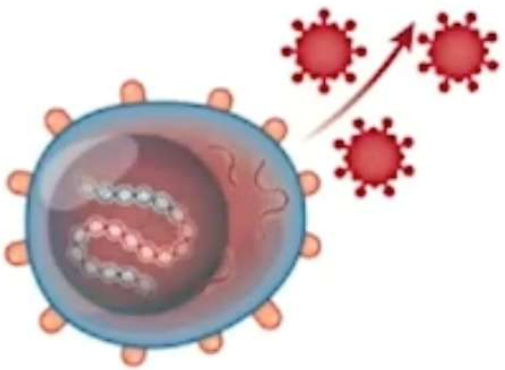
HIV RNA (SCA)

Viral outgrowth

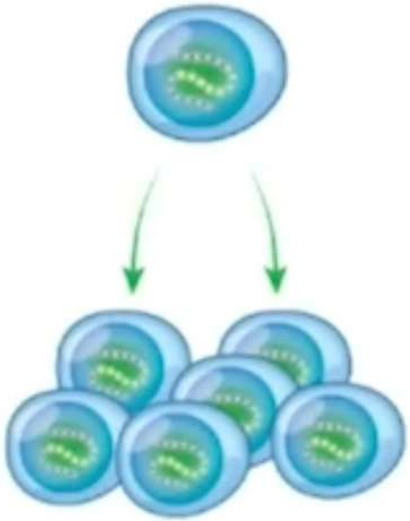


Newer concepts in HIV persistence and latency

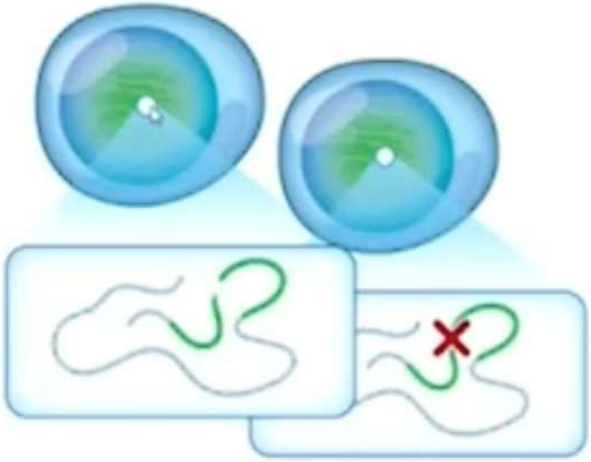
Productive Cell Survival



Proliferation

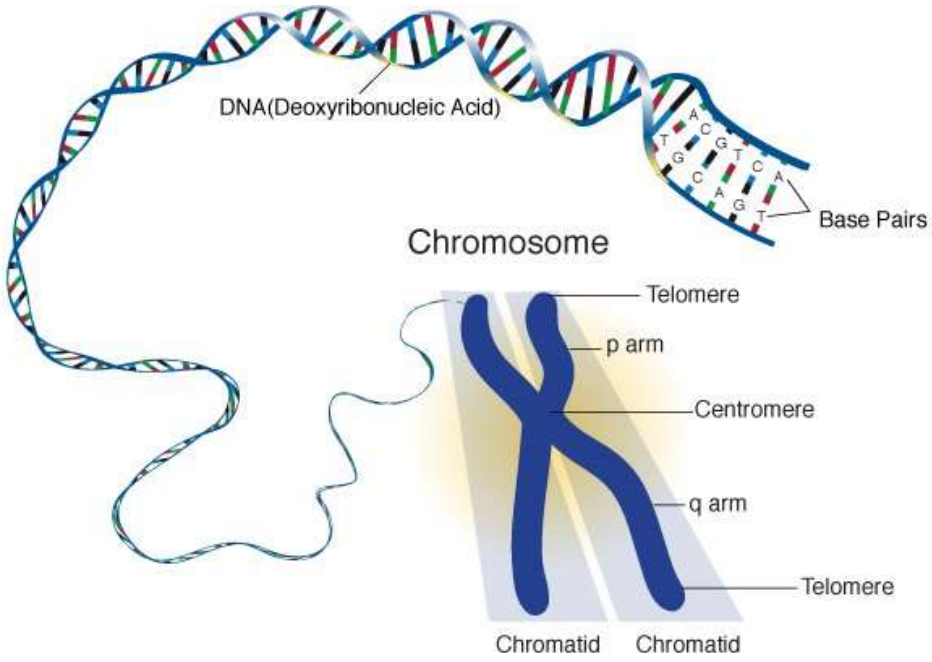


Defective vs. intact virus

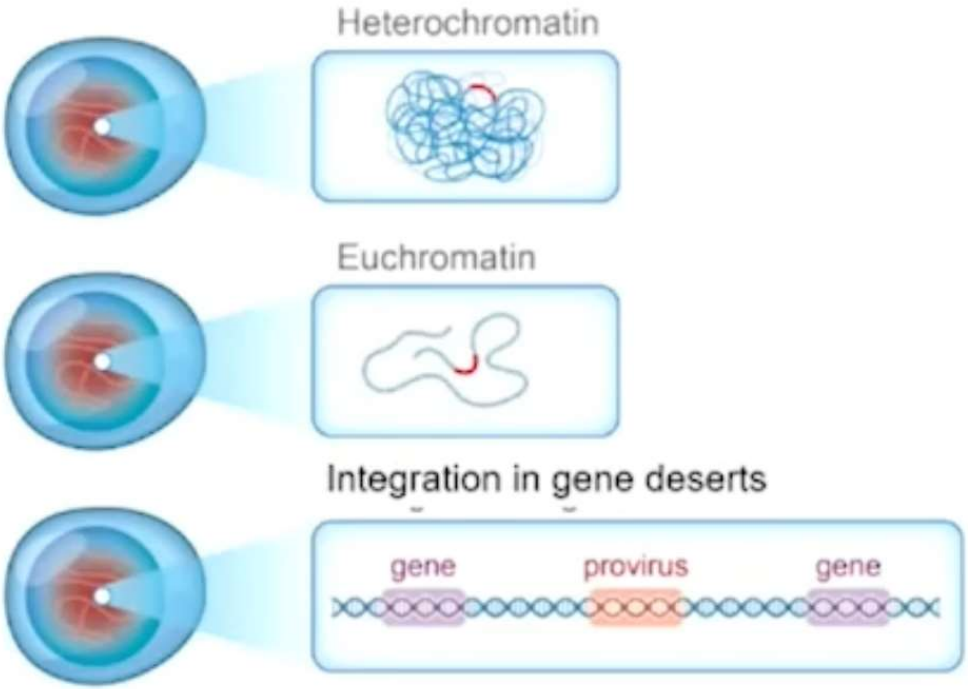


Courtesy of Sharon Lewin

Where HIV integrates on a chromosome matters



Position Matters: HIV integration sites



- Integration sites determine the likelihood of a virus being active or silent[1,2]
- New techniques determine integration site, sequence and transcription in the same cell (MIP-seq, PRIP-seq) [3,4]
- In a subset of elite controllers, intact virus is only found in gene deserts meaning limited or no HIV transcription[4]

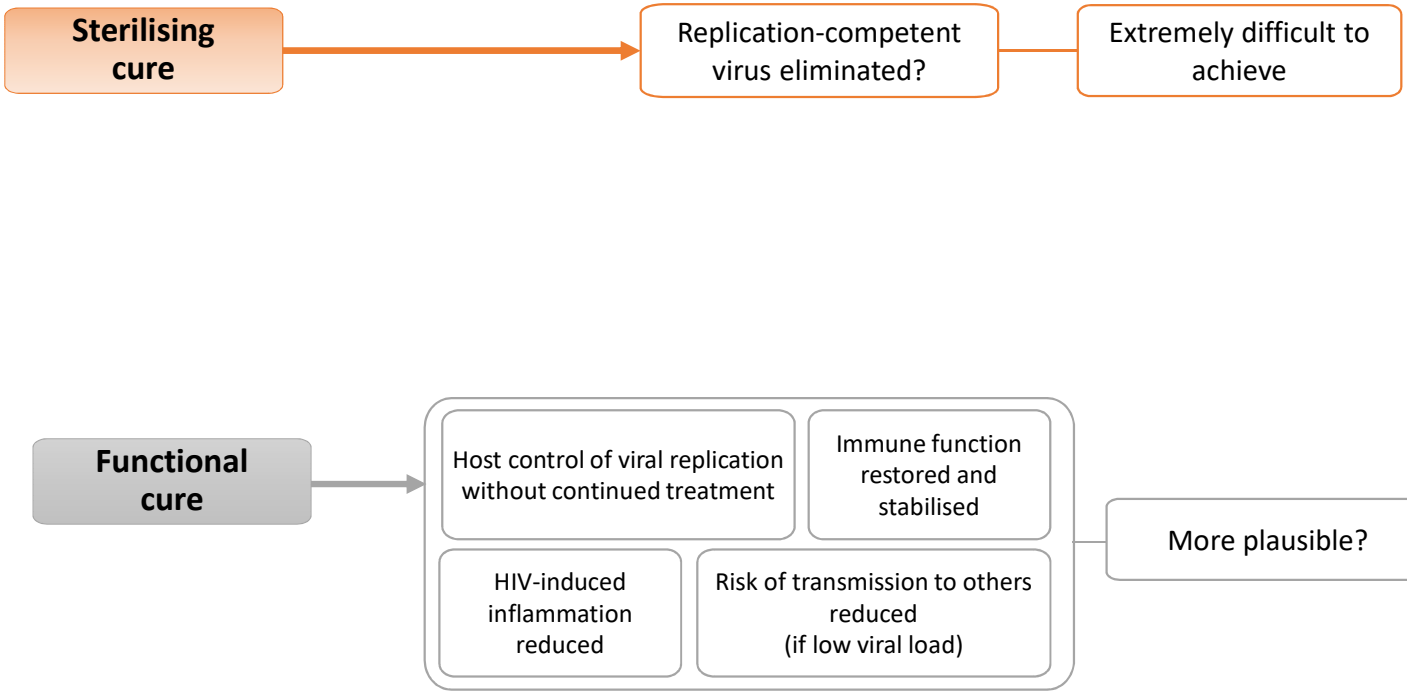
1 Jordan et al., EMBO J 2010; 2 Chen et al., Nat Struct Mol Biol 2017; 3 Einkauf et al., J Clin Inv 2019; 4 Yu et al., Nature 2020

Courtesy of Steve Deeks

Summary

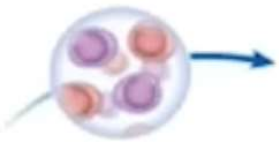
- HIV is a virus that inserts its genetic material into our DNA
- HIV can remain “latent” or asleep in the **HIV reservoir**
- Virus can survive in the “silent” HIV reservoir for many years.
- Even when people are on successful ART 1 in 1 million T-cells are reservoir cells
- Most of the virus that is inside the reservoir cells is “defective” this means it cant ever make new viruses.
- Virus “wakes up” or comes back in most people as soon as ART is stopped.
- The position that virus is integrated into our DNA matters and virus in special positions on the human gene may be less likely to ever wake up.

Two types of HIV "Cure"



The Many People Inspiring Cure Strategies

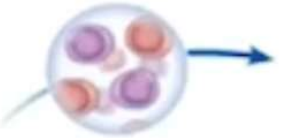
Immune-mediated Mechanisms?



Timothy Brown
Berlin
2009

VISCONTI
SPARTAC
CHAMP

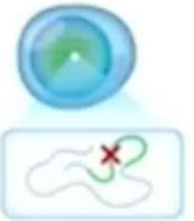
Post treatment
control (remission)
2010



Adam Castallejo
London
2019

Loreen Willenberg
San Francisco
2020

Esperanza
Argentina
2021



Hutter et al., N Engl J Med 2010; Gupta et al., Nature 2019; Gupta et al, Lancet HIV 2019; Jiang et al., Nature 2020; Turk et al., Ann Int Med 2021

Courtesy of Sharon Lewin

Summary of Stem cell transplantation

- This is not safe or scalable for everyone but there are an increasing number of people who have had this treatment and are cured of HIV
- Any HIV+ patient requiring BMT should receive d32 deletion donor wherever possible
- Better understanding of exact mechanisms may inform future less invasive interventions – we can learn from these cases
- **VERY rarely** some people are naturally “cured” of HIV

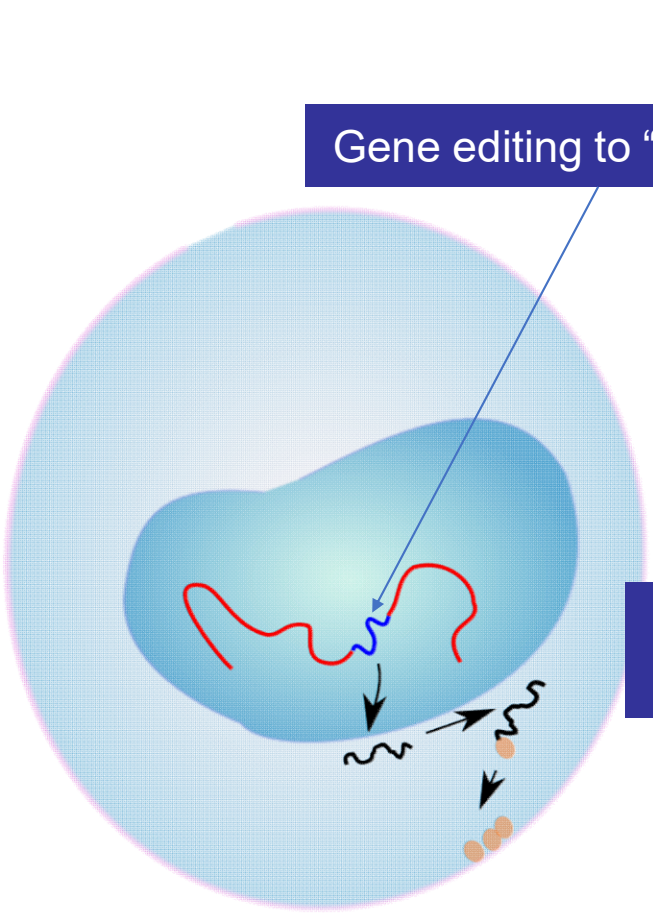
New ways to remove the HIV reservoir cells

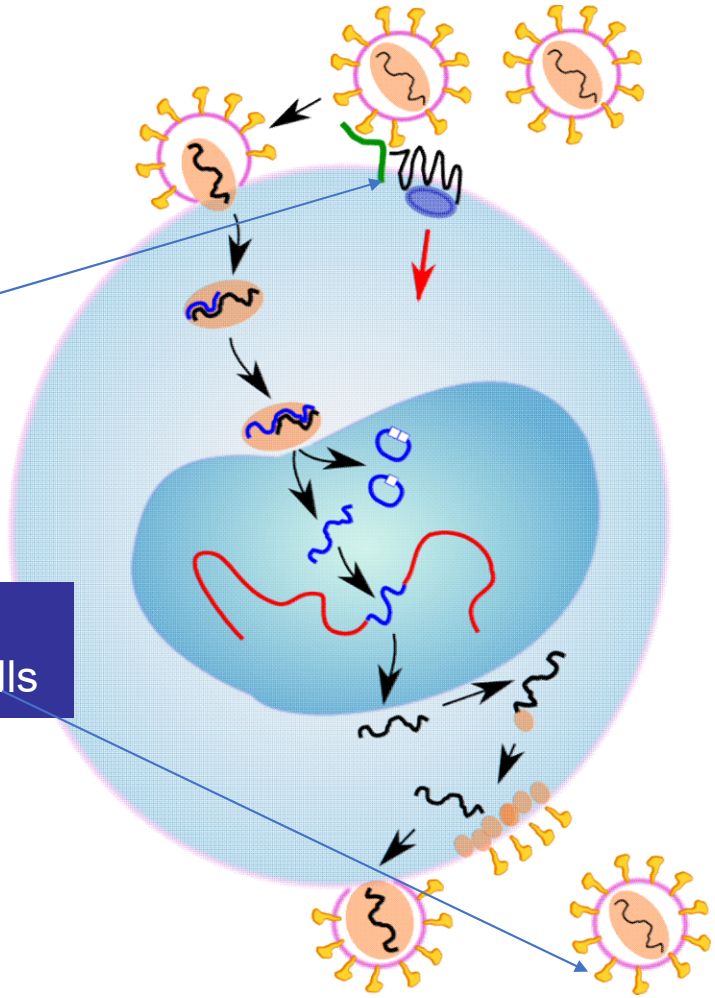
Gene editing to “chop out” HIV

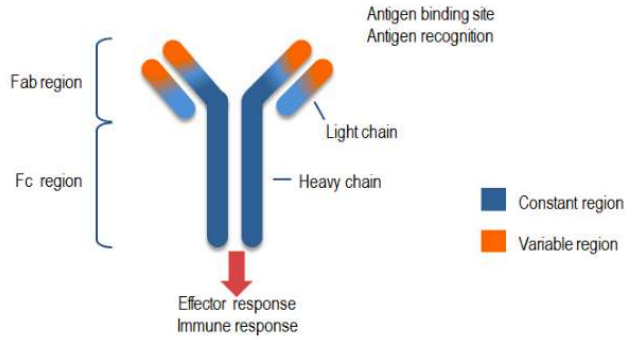
Gene editing to stop HIV entering new cells

Change immune cells to kill HIV reservoir CAR T-cells, Soluble TCR

Broadly neutralising antibodies
Block viruses and kill reservoir cells





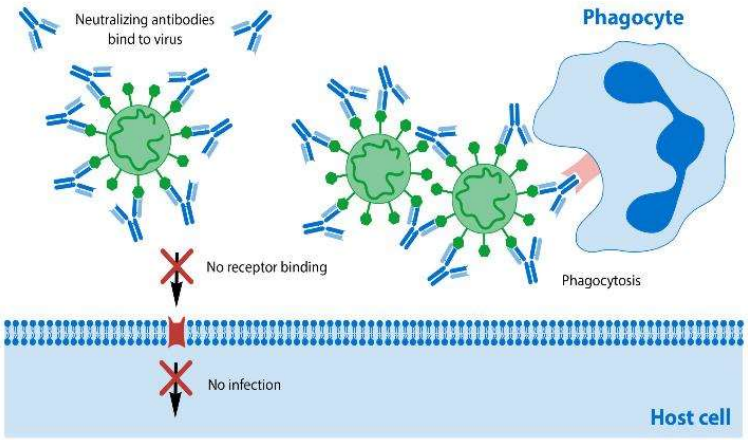


Immune modulation

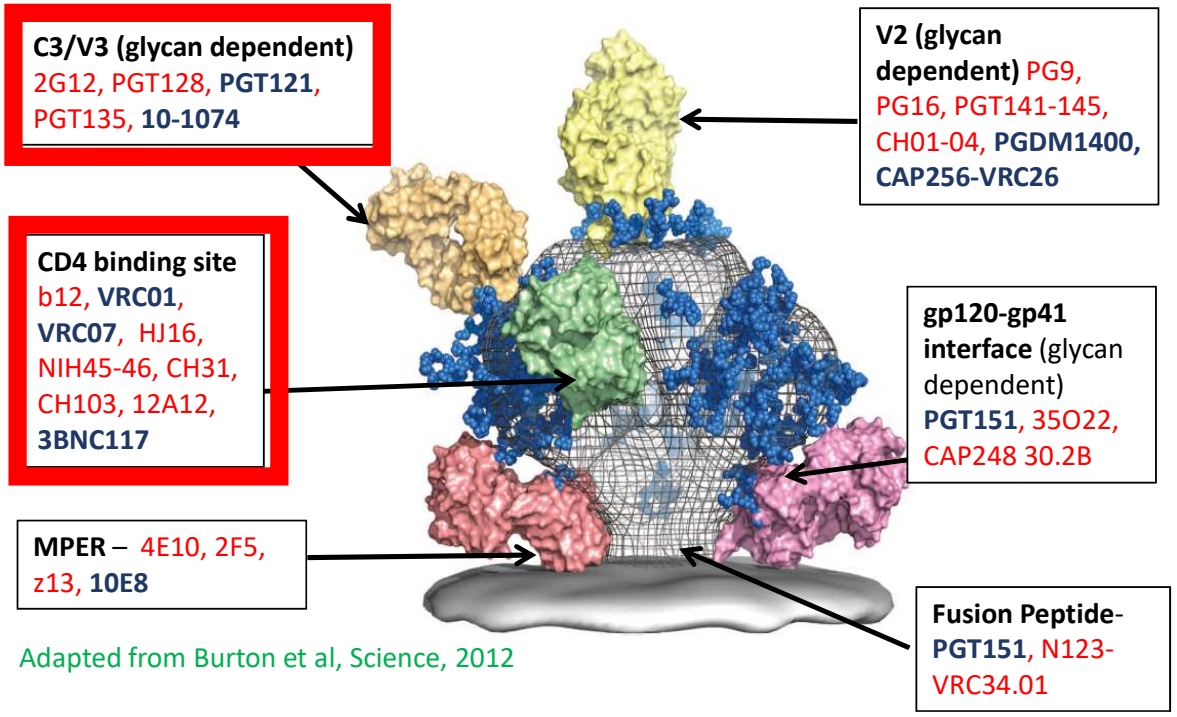
- Broadly Neutralising antibodies (bNabs)
- TLR7 or 9 Agonists
- Therapeutic vaccine
- CAR T-cells
- Soluble T-cell receptor drugs

How do bNAbs work in HIV?

- Direct antiviral action
- Elimination of latently infected HIV reservoir… towards a cure
  - Direct immune modulation via antibody interaction with innate and adaptive immune system may confer this additional aspect of therapy which is not delivered by current available antiretroviral therapy alone
  - bNAbs may be given with immune modulatory agents that lead to activation and viral transcription from the latent reservoir or immune “enhancers” that prime the immunomodulatory effects of the BNabs



bNAb binding on HIV envelope glycoprotein



Adapted from Burton et al, Science, 2012

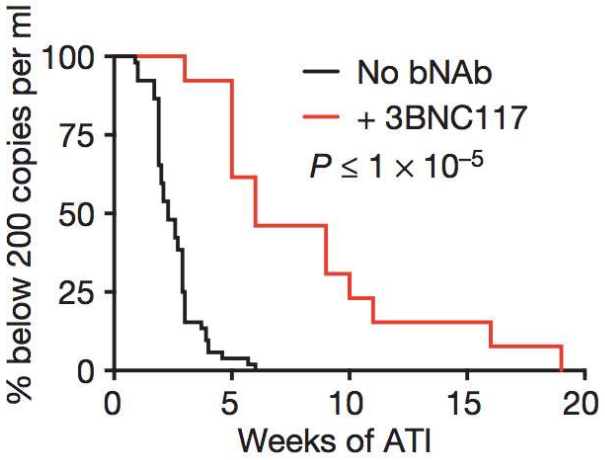
LETTER

doi:10.1038/nature18929

HIV-1 antibody 3BNC117 suppresses viral rebound in humans during treatment interruption

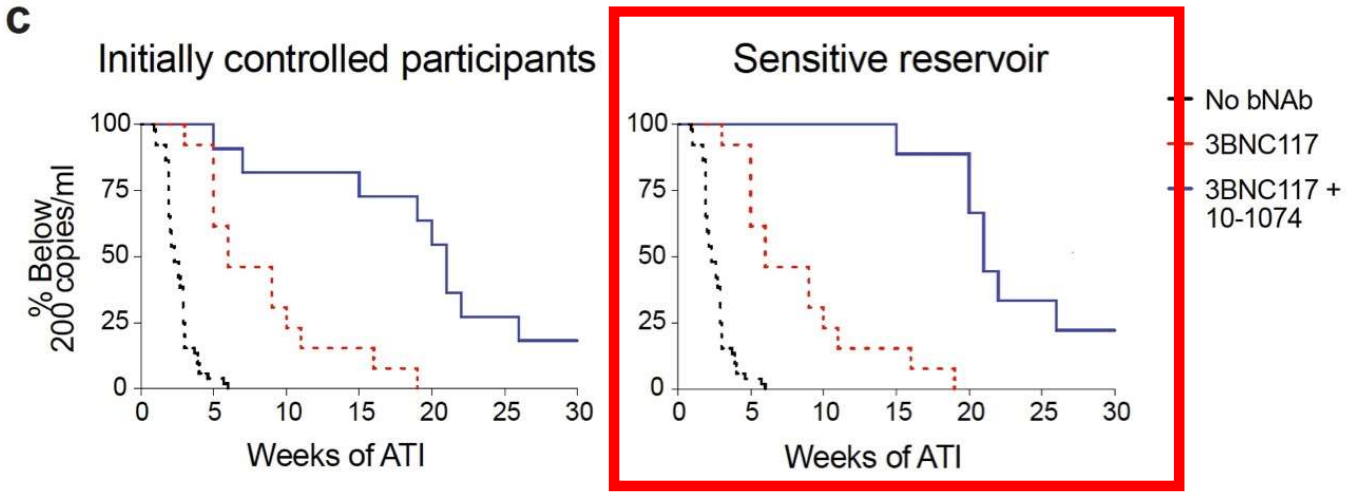
Johannes F. Scheid[1,2*], Joshua A. Horwitz[1*], Yotam Bar-On[1], Edward F. Kreider[3], Ching-Lan Lu[1], Julio C. C. Lorenzi[1], Anna Feldmann[4], Malte Braunschweig[1], Lilian Nogueira[1], Thiago Oliveira[1], Irina Shimeliovich[1], Roshni Patel[1], Leah Burke[5], Yehuda Z. Cohen[1], Sonya Hadrigan[1], Allison Settler[1], Maggi Witmer-Pack[1], Anthony P. West Jr[6], Boris Juelg[7], Tibor Keler[8], Thomas Hawthorne[8], Barry Zingman[9], Roy M. Gulick[5], Nico Pfeifer[4], Gerald H. Learn[3], Michael S. Seaman[10], Pamela J. Bjorkman[6], Florian Klein[1,11,12], Sarah J. Schlesinger[1], Bruce D. Walker[7,13], Beatrice H. Hahn[3], Michel C. Nussenzweig[1,14] & Marina Caskey[1]

July 2016



- N=13 with chronic HIV infection suppressed for >12 months
- Infusions of 3BNC117. TI 2 days later
- Up to 19 week delay in rebound vs historical controls (2.6 weeks)
- **Rebound occurred with escape variants or once antibody levels had dropped**

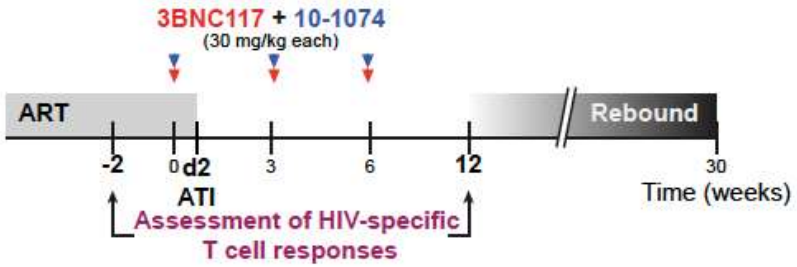
Two bNAbs confer control after stopping ART……

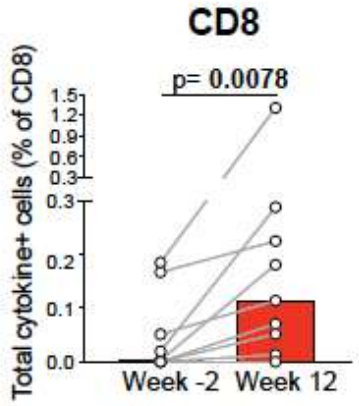


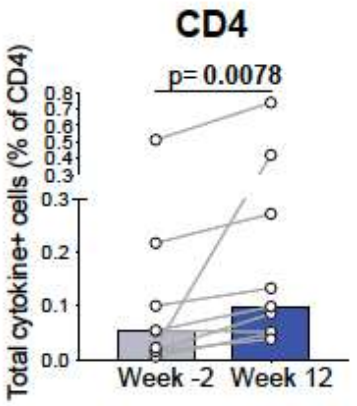
- Viral suppression for 5 to >30 weeks
- Median time to rebound 21 weeks vs 2.3 weeks for ART-only controls vs 6-10 weeks for single bNAb.
- Two never rebounded (? now one)
- Rebound in others due to resistance or as bNAb concentration dropped.

Combination anti-HIV-1 antibody therapy is associated with increased virus-specific T cell and humoral immunity

Evolution of Gag-specific T cell responses during suppressed viremia

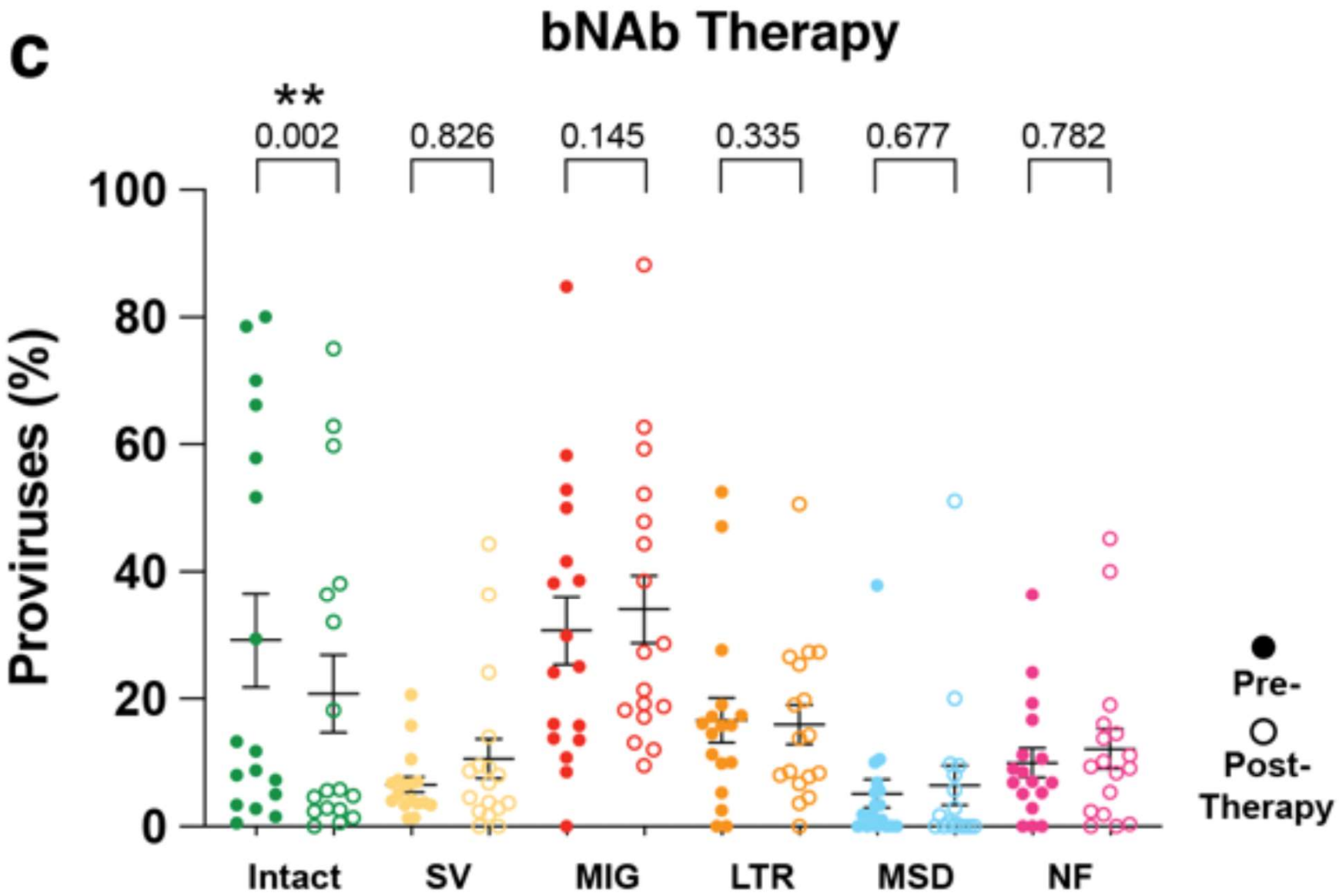






Niessl et al, *Nature Med.*, 2020

- bnAbs also enhance the clearance of HIV infected cells in vivo through engagement of Fcγ receptors (Lu et al, *Science*, 2016)


c
bNAb Therapy
**
0.002
0.826
0.145
0.335
0.677
0.782
Proviruses (%)
100
80
60
40
20
0
Intact
SV
MIG
LTR
MSD
NF
Pre-
Post-
Therapy

bNAb Safety data from clinical studies

- 30,000 doses amongst 3,000 HIV-negative individuals in AMP study reported only mild infusion related reactions
- Multiple clinical trials amongst PLWH using single agent bNAbs and in combination are ongoing with only mild reported side effects
- Serious adverse events are rare in PLWH but have been reported; a Phase 1 subcutaneous study of 10E8V-LS was recently stopped when 7/8 participants experienced erythema and induration at the injection site

The RIO Trial:

A randomised placebo controlled trial of ART plus dual long-acting HIV-specific broadly neutralising antibodies (bNAbs) vs ART plus placebo in treated Primary HIV Infection on viral control off ART

3BNC117-LS + 10-1074-LS

bNAbs in acute infection: clinical trials planned/underway

Name	Intervention	Population	Status	ATI
RV398 (MHRP - Ake)	- VRC01 > ART - VRC01 + ART	Acute infection	Enrolled / analysis ongoing	no
A5388 (ACTG – Crowell/Hsu)	- VRC07-523LS + PGT121BIJ414LS + ART	Acute infection	Planned 2021	yes
RHVIERA (Pasteur – Saez-Cirion)	- 3BNC117-LS + 10-1074-LS + ART	Acute infection	Planned 2021	yes
RIO (Imperial/Oxford – Fidler/Frater)	- 3BNC117-LS + 10-1074-LS during ATI - 3BNC117-LS + 10-1074-LS + ART following rebound	Treated during acute infection	Planned 2021	yes
A5389 (ACTG – Malvestutto/Riddler)	- VRC07-523LS + PGT121BIJ414LS + ART > waning bNAb - VRC07-523LS + PGT121BIJ414LS + ART > ART	Treated during acute infection	Planned 2021	yes

Summary of antibody studies

- Broadly neutralizing antibodies (bNAbs) can block virus and seem to stimulate the immune system to help control virus off ART
- Different bNAbs only work against some strains of virus so we will probably need to use them in combination and check first which antibodies work best for each persons virus
- bNAbs are safe and one injection can last up to 12 months
- bNAbs given with other types of treatment have the potential to induce a remission type cure HIV

Therapeutic T-cell HIV-1 vaccines and HIV reservoir

ERAMUNE 02	ART intensification (raltegravir or maraviroc) ± immunomodulation (DNA + HIV-rAd5 vaccine) did not significantly reduce the HIV DNA reservoir in blood or rectal tissue
RISVAC 03	MVA-B vaccination increased Gag- and Env-gp120-specific T-cell responses but had only marginal impact on VL rebound after cART interruption
ACTG A5197	rAd5 HIV-1 Gag vaccine showed positive correlation between Gag-specific cells and lower viral rebound during treatment interruption, although the effect decreased over time
NCT00659789	Vacc-4x, a p24Gag HIV-1 vaccine, lowered VL but did not affect the proportion of participants resuming cART before end of study or change in CD4 counts during treatment interruption
NCT00751595	HIV-1 Tat protein was safe, well tolerated and induced anti-Tat Abs in most patients. Vaccination promoted a durable and significant restoration of T, B, NK cells, and CD4+ and CD8+ central memory subsets. A significant reduction of blood proviral DNA was seen after Week 72
HVTN 090	rVSV vaccine recipients became seropositive for VSV after two vaccinations. Gag-specific T-cell responses were detected in 63% of participants by interferon-γ enzyme-linked immunospot at the highest dose postboost

AeLix002 more encouraging CROI 2021 Bea Mothe
ChAdprime MVA boost Tom Hanke

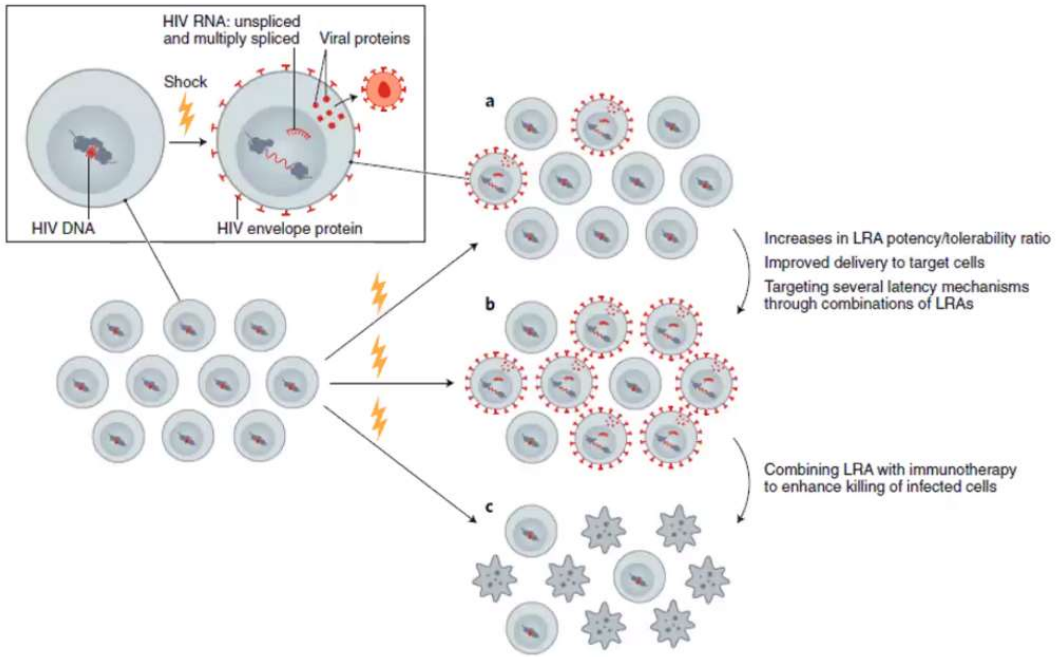
Combination approaches towards cure

Targeting the provirus

nature medicine REVIEW ARTICLE
https://doi.org/10.1038/s41591-021-01590-5

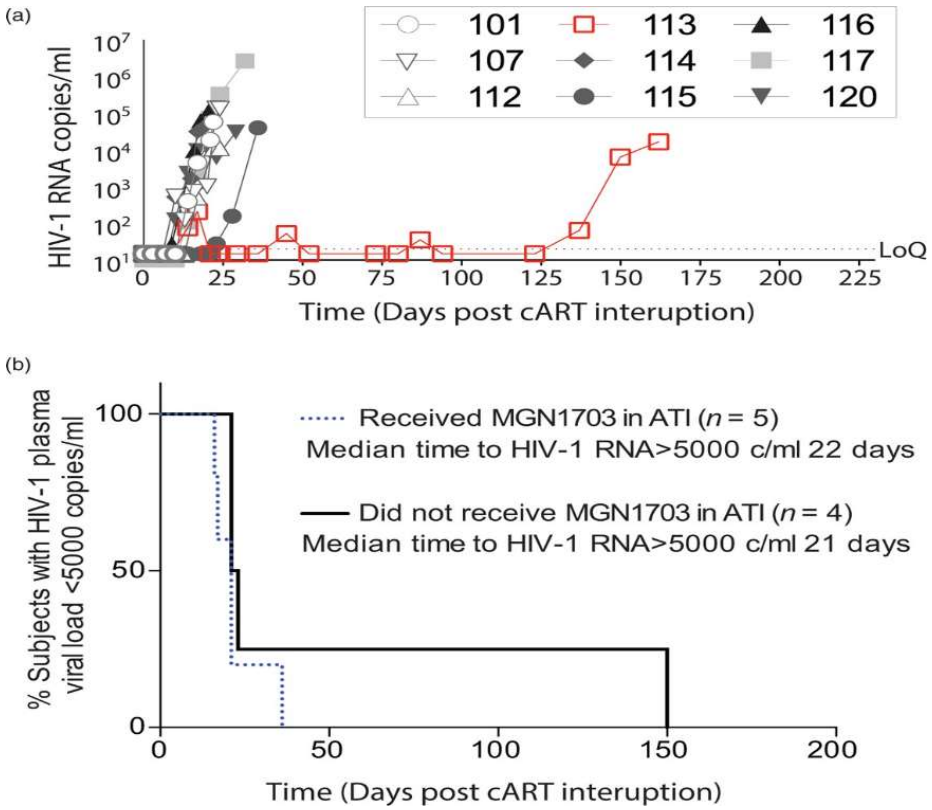
Research priorities for an HIV cure: International AIDS Society Global Scientific Strategy 2021

Steven G. Deeks[1,2], Nancie Archin[3], Paula Cannon[4], Simon Collins[4], R. Brad Jones[5], Marein A. W. P. de Jong[6], Olivier Lambotte[7], Rosanne Lamplough[8], Thumbi Ndung'u[9,10,11], Jeremy Sugarman[12], Caroline T. Tiemessen[13], Linos Vandekerckhove[14], Sharon R. Lewin[15,16,17] and The International AIDS Society (IAS) Global Scientific Strategy working group*



- Develop improved strategies to reverse latency
- Develop strategies to permanently silence the provirus
- Determine the impact of targeting the provirus at the time of initiation of ART
- Define the role of viral subtype on the effectiveness of interventions

TLR 9 agonist



- Toll-like receptor (TLR) agonists are potent enhancers of innate antiviral immunity and may also reverse HIV-1 latency.
- Vibhom et al AIDS 2019 n = 12 individuals 24 weeks treatment with TLR9 agonist (MGN1703; Lefitolimod) was safe and improved innate as well as HIV-1-specific adaptive immunity in HIV-1+ individuals
  - BUT ATI led to rapid viral rebound

RIVER
Research In Viral Eradication of HIV Reservoirs

A two-arm (proof of concept) randomised phase II trial

ART vs ART + Vorinostat + a prime boost HIV-1 Vaccine

Antiretroviral therapy alone versus antiretroviral therapy with a kick and kill approach, on measures of the HIV reservoir in participants with recent HIV infection (the RIVER trial): a phase 2, randomised trial

Sarah Fidler, Wolfgang Stöhr, Matt Pace, Lucy Dorrell, Andrew Lever, Sarah Pett, Sabine Kinloch-de Loes, Julie Fox, Amanda Clarke, Mark Nelson, John Thornhill, Maryam Khan, Axel Fun, Mikaila Bandara, Damian Kelly, Jakub Kopycinski, Tomáš Hanke, Hongbing Yang, Rachel Bennett, Margaret Johnson, Bonnie Howell, Richard Barnard, Guoxin Wu, Steve Kaye, Mark Wills, Abdel Babiker, John Frater, on behalf of the RIVER trial study group

Summary

Background Antiretroviral therapy (ART) cannot cure HIV infection because of a persistent reservoir of latently infected cells. Approaches that force HIV transcription from these cells, making them susceptible to killing—termed kick and kill regimens—have been explored as a strategy towards an HIV cure. RIVER is the first randomised trial to determine the effect of ART-only versus ART plus kick and kill on markers of the HIV reservoir.

Methods This phase 2, open-label, multicentre, randomised, controlled trial was undertaken at six clinical sites in the UK. Patients aged 18–60 years who were confirmed as HIV-positive within a maximum of the past 6 months and started ART within 1 month from confirmed diagnosis were randomly assigned by a computer generated randomisation list to receive ART-only (control) or ART plus the histone deacetylase inhibitor vorinostat (the kick) and replication-deficient viral vector T-cell inducing vaccines encoding conserved HIV sequences ChAdV63. HIVconsv-prime and MVA.HIVconsv-boost (the kill; ART + V + V; intervention). The primary endpoint was total HIV DNA isolated from peripheral blood CD4+ T cells at weeks 16 and 18 after randomisation. Analysis was by intention to

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See Online/Comment
https://doi.org/10.1016/S0140-6736(20)30264-6

Department of Infectious Disease, Imperial College London, London, UK
(Prof S Fidler PhD, M Khan BSc, J Thornhill PhD, S Kaye PhD);
NIHR Imperial Biomedical Research Centre, London, UK

Summary of Kick and Kill studies

- One RCT (RIVER) shown no effect of HDACi (Vorinostat) + T-cell vaccine vs ART alone on measures of HIV reservoirs
- Latency reversal using this HDACi maybe inadequate or T-cell vaccine epitopes may not recognize the correct viral sequences
- There are other ways to induce the kick and kill under investigation
- TLR9+ bNAb (TITAN)
- IL-15 + bNAbs or T-cell vaccines

Combination immunotherapy: clinical trials planned/underway

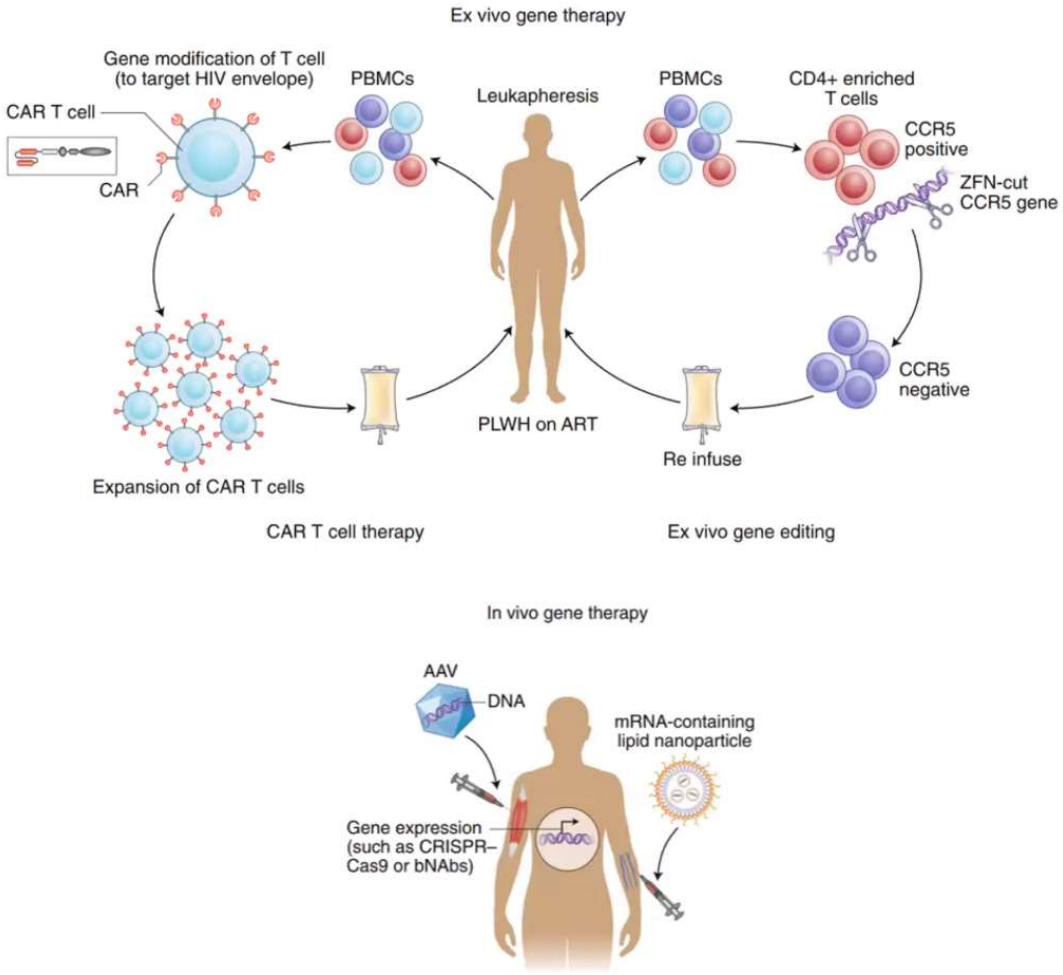
Name	Intervention		Population	Status	ATI
ROADMAP (Sogaard/Caskey/Fatkenheuer)	3BNC117	Romidepsin	Chronic	CROI2020	yes
eCLEAR (Sogaard/Fidler)	3BNC117	Romidepsin	Early infection (viremic)	Late follow up	yes
A5386 (ACTG –Wilkin/Caskey/Jones)	VRC07-523LS 10-1074	N-803	Chronic	Planned 2021	yes
U01 – RU/Penn/Cornell (Caskey/Wilkin/Tebas)	3BNC117-LS 10-1074-LS	N-803	Chronic	Planned 2021	yes
BEAT HIV2 (Monaner/Tebas)	3BNC117 10-1074	Type I IFN	Chronic	Ongoing	yes
TITAN (Sogaard/Lewin)	3BNC117 10-1074	TLR9	Chronic	Ongoing	yes
amfAR/UCSF (Deeks)	VRC07-523LS 10-1074	DNA/MVA TLR9	Treated during acute infection	Ongoing	yes
A5374 (ACTG – Riddler/Gay/Mellors)	3BNC117-LS* 10-1074-LS*	ChAd/MVA TLR7	Treated during acute infection	Planned 2021	yes

Gene and cell therapies

nature medicine REVIEW ARTICLE

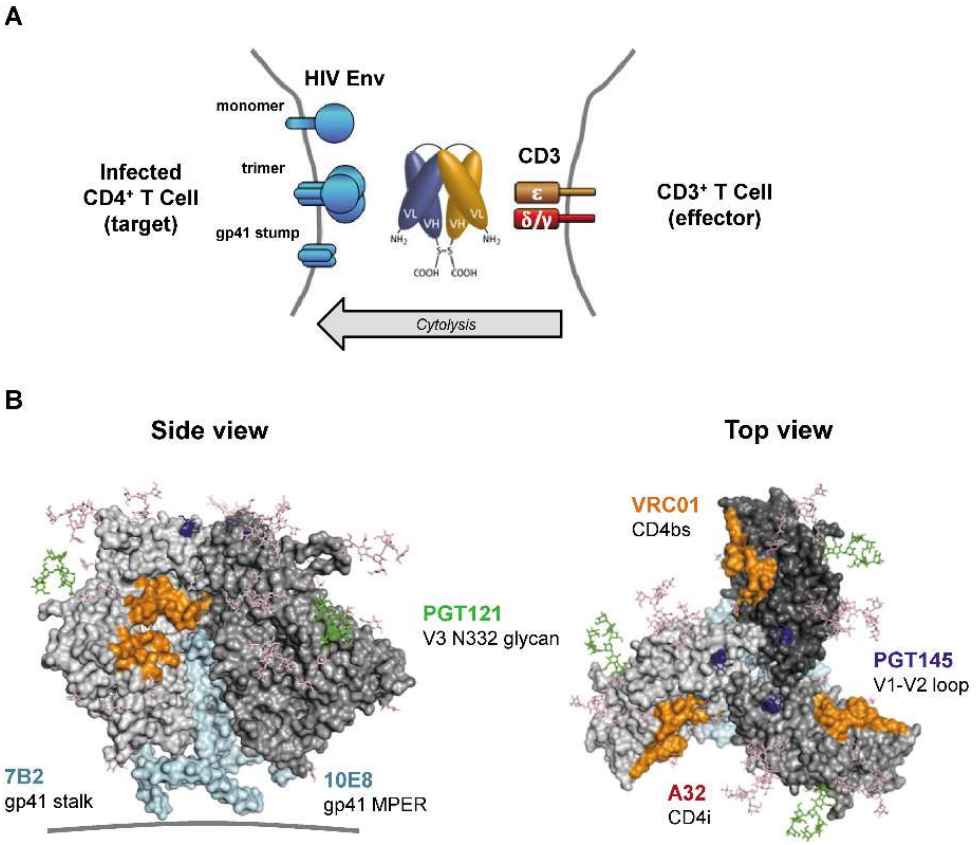
Research priorities for an HIV cure: International AIDS Society Global Scientific Strategy 2021

Steven G. Deeks[1,55], Nancie Archin[2], Paula Cannon[3], Simon Collins[4], R. Brad Jones[5], Marein A. W. P. de Jong[6], Olivier Lambotte[7], Rosanne Lamplough[8], Thumbi Ndung'u[9,10,11], Jeremy Sugarman[12], Caroline T. Tiemessen[13], Linos Vandekerckhove[14], Sharon R. Lewin[15,16,17] and The International AIDS Society (IAS) Global Scientific Strategy working group*

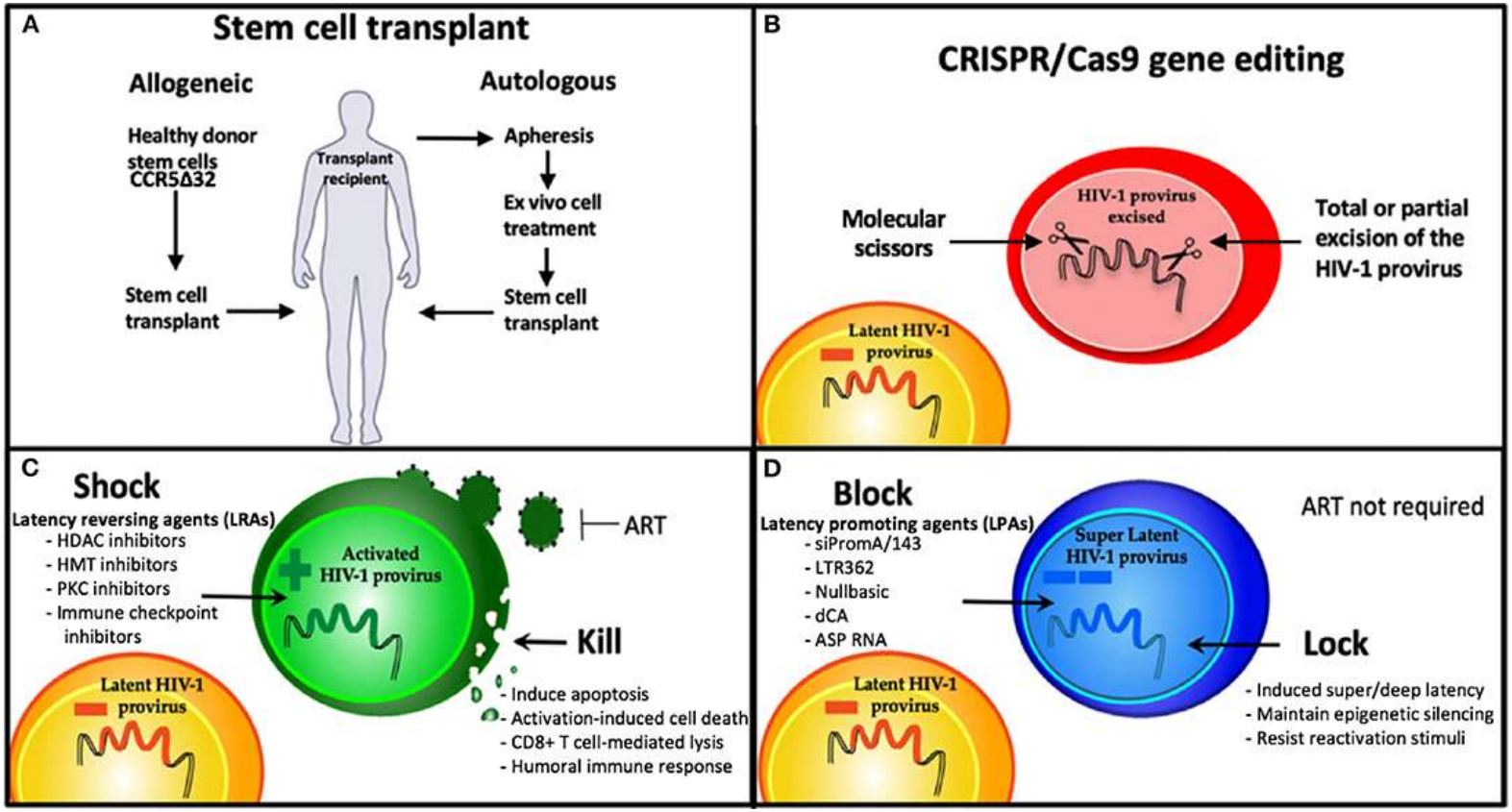


- Define the level of antigen expression needed to enable direct targeting (CAR-T cells)
- Develop gene-editing strategies that target the provirus
- Develop strategies for sustained production *in vivo* of antiviral antibodies
- Leverage advances in other biomedical fields

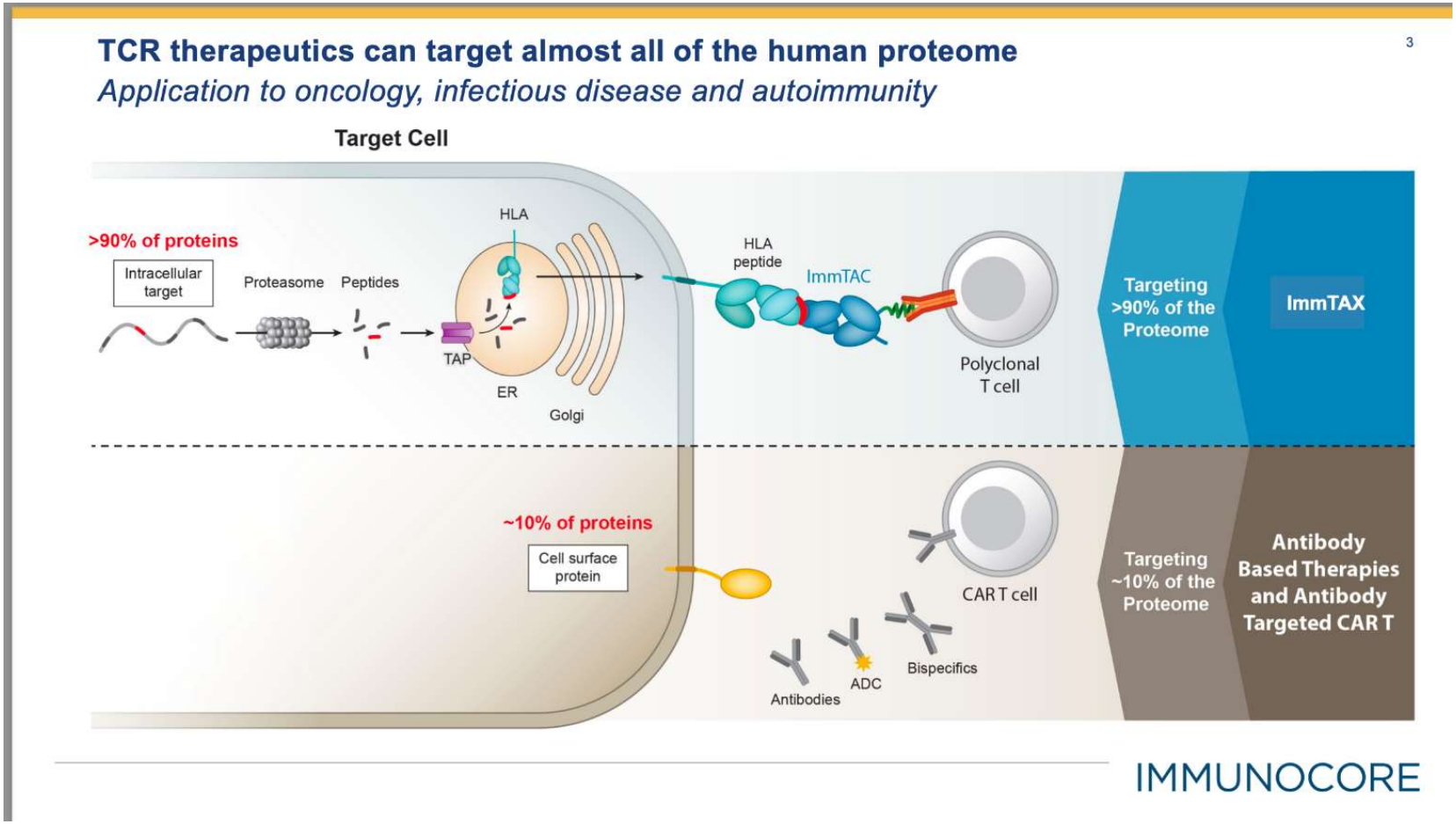
Dual Affinity re-targeting molecules DARTs



Gene editing

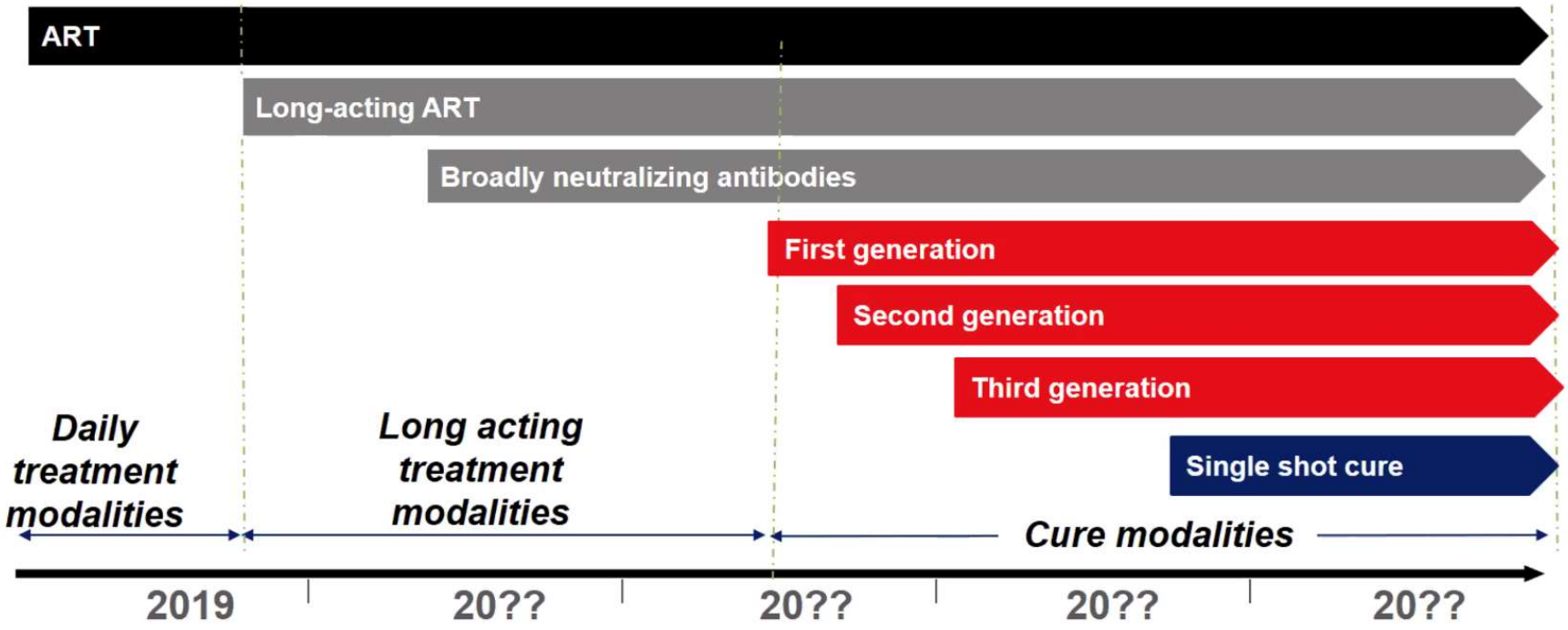


Soluble targeted T-cell receptor molecules



Cure: Iterative and incremental progress expected

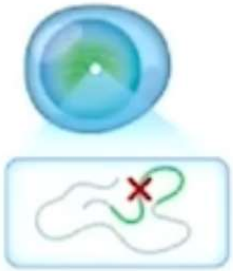
The first generation of cures are expected to complex and difficult-to-scale, as were the initial antiretroviral regimens



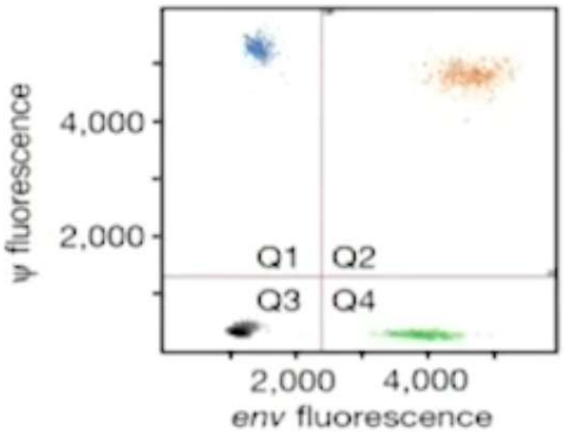
Future HIV cure perspectives

- ART still needed as the basis all treatment but on its own isn't enough to cure most people
- Rare cases of people who need BMT for blood cancers should receive donors that have genetic changes that clear HIV
- Newer therapies as well as ART work in completely different ways to help clear the HIV reservoir cells
- It seems likely a combination of immune based treatments will be needed to keep virus undetectable off ART

A large proportion of virus that persists is defective

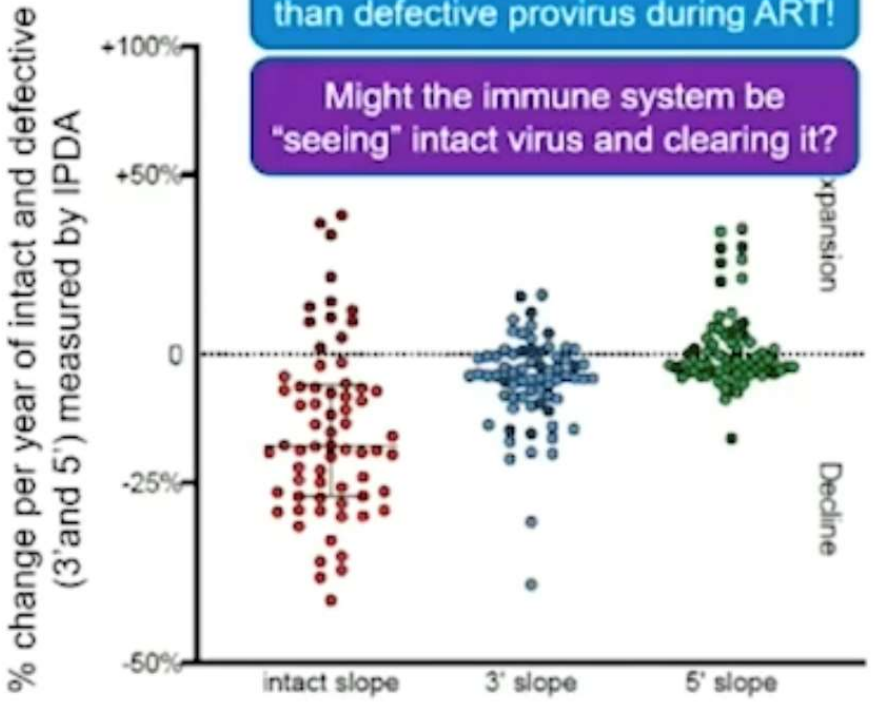


The intact proviral DNA assay (IPDA) can quantify **intact** and **defective** DNA using droplet digital PCR



Intact provirus decays *more rapidly* than defective provirus during ART!

Might the immune system be "seeing" intact virus and clearing it?



n=81, PWH on ART followed for a median of 7 years

Bruner et al., Nature 2019; Gaebler et al., J Exp Med 2019

Peluso et al., JCI Insight 2020 (See also: Gandhi et al., JID, 2021)