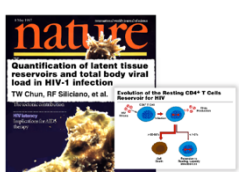
HIV cure from bench to bedside…..and to community

A short history of HIV cure research: from cure to remission to cure again



HIV latency identified

1997

2009

The Berlin patient

VISCONTI
SPARTAC
CHAMP

Post treatment control (remission)

2010

2013

Case reports of delayed viral rebound

Mississippi baby
Boston patients
San Francisco patient

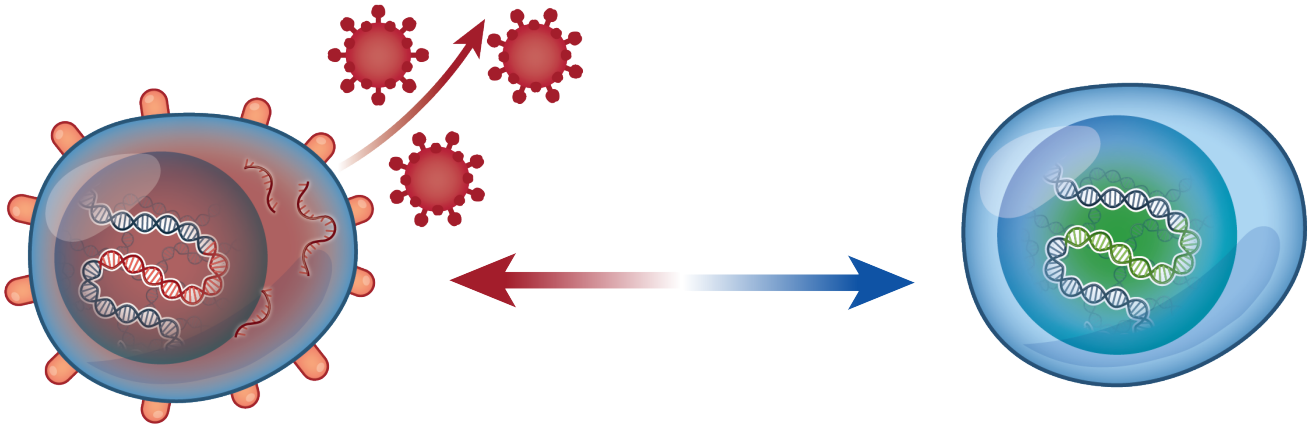
nature

The London patient

2019

Why and how does HIV persist on ART?

Two major forms of HIV infected cells

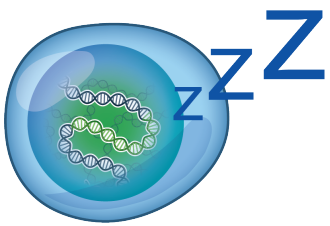


Productive infection
DNA positive
RNA positive
HIV protein positive
DEATH

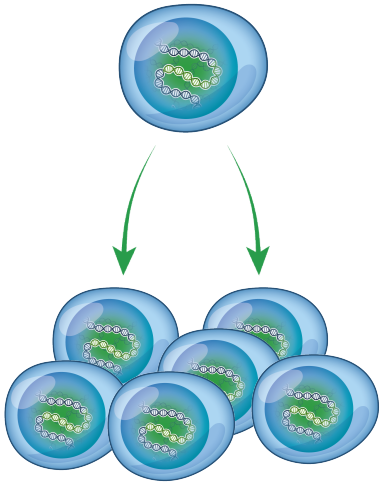
Latent infection
DNA positive
RNA negative
HIV protein negative
SURVIVAL

New concepts in HIV persistence and latency

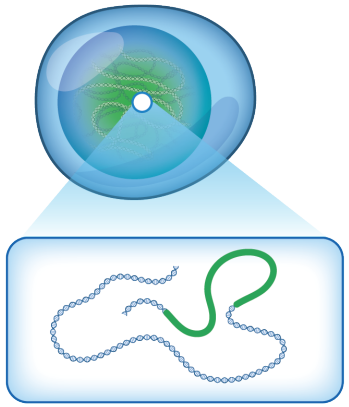
1.
Reservoir ‘activity’



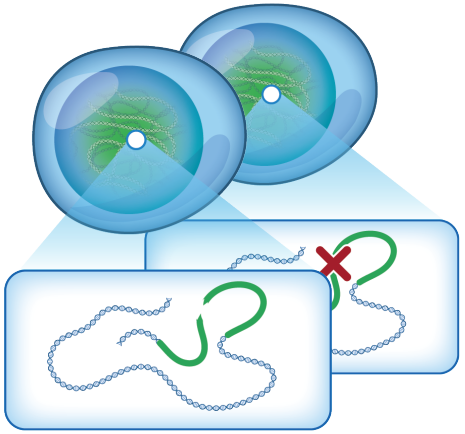
2.
Proliferation



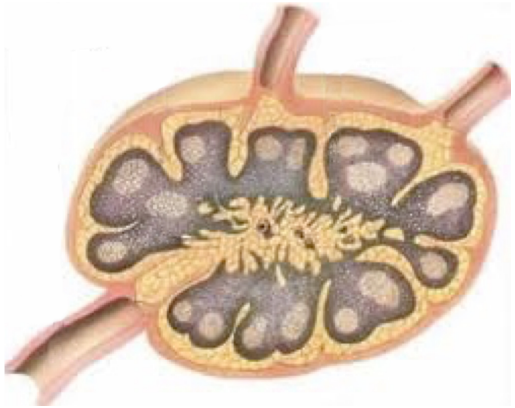
3.
Position matters

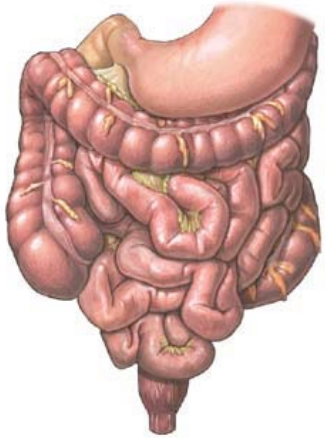


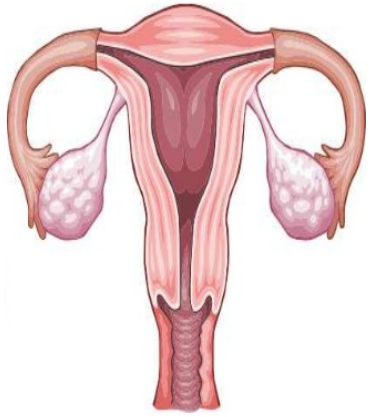
4.
Defective and
intact virus



Reservoir ‘activity’: importance of place







- Tissues (lymph node, the GI and female genital tract) have more infected cells but also are more likely to be RNA+ ie transcriptionally active[1-4]
- Enriched for specific T-cells that are more permissive to infection and persistence: Tissue Resident Memory (TRM) cells[5]

1 Estes et al., Nat Med 2018; 2 Banga et al., Nature Med 2018; 3 Khoury et al., J Infect Dis 2018; 4 Anderson et al., Infect Dis 2019; 5 Cantero Perez et al., Nature Comms 2019

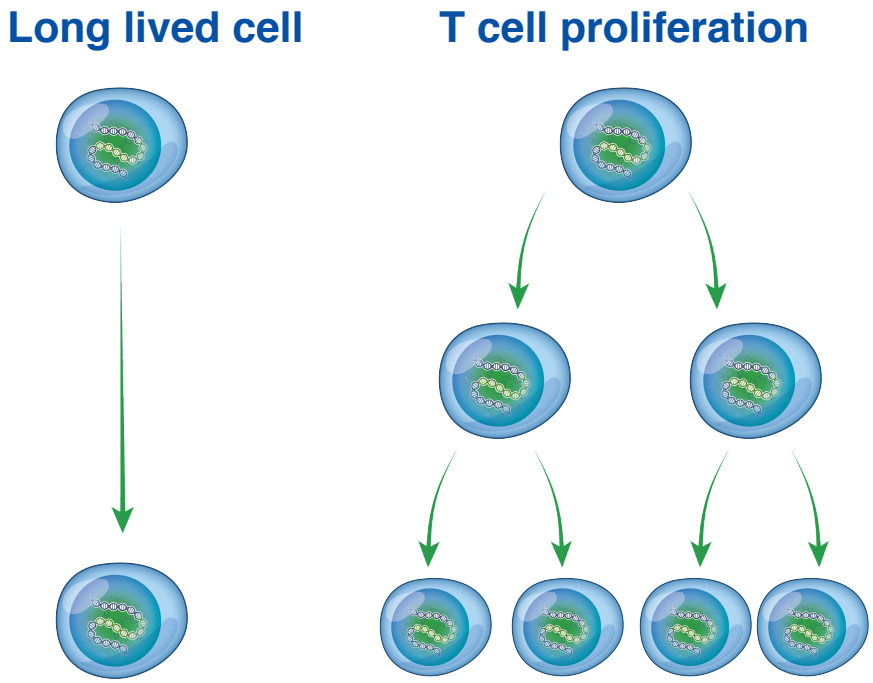
Reservoir activity: importance of time

- Proteins that control the circadian cycle (CLOCK and BMAL-1) can also activate HIV transcription by binding to the HIV-LTR[1]

- In people living with HIV (PLWH) on ART (n=17), HIV RNA expression varies with time of day consistent with a circadian cycle[2]

1 Chang et al., AIDS 2018; 2 Stern, Roche, Cockerham et al., IAS HIV Science Meeting, Mexico City 2019

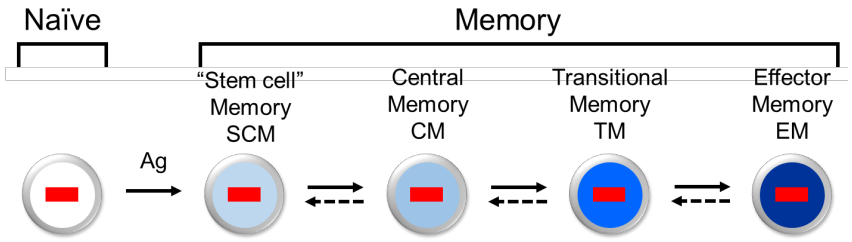
Proliferation: latently infected cells clonally expand



- Clonally expanded cells make up 50% of the reservoir[1-4]
- Clonally expanded cells can contain intact virus and contribute to plasma virus[5]
- Drivers for proliferation unknown
  - Homeostatic proliferation
  - Antigen specific expansion
  - Site of integration

1 Lorenzo, et al., Proc Natl Acad Sci USA 2016; 2 Huang et al., J Exp Med 2017; 3 Bui et al., Plos Path 2017; 4 Patro et al., Proc Natl Acad Sci USA 2019; 5 De Scheerder et al., Cell Host Microbe 2019

Proliferation: Differentiated T-cells have more clones

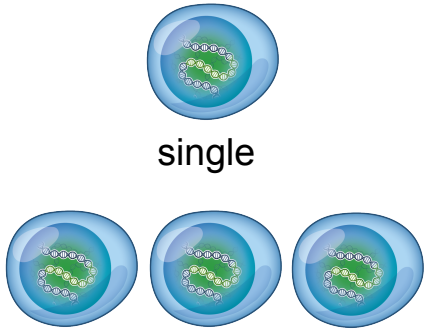


Simonetti et al., CROI 2020, abs 73
Mendoza et al., CROI 2020, abs 370LB

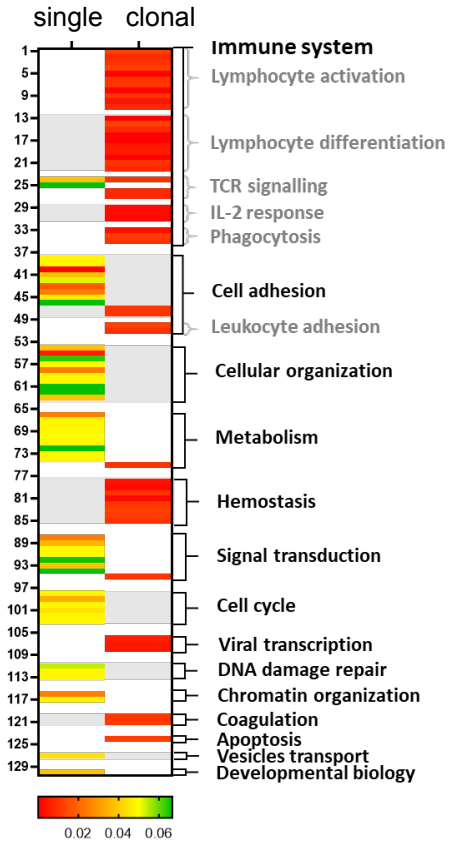
PLWH on ART for > 2 years received deuterated water and cell sorting into T-cell subsets

Bacchus-Souffan, Hunt, McCune, Deeks, Symons, Lewin et al (unpublished);

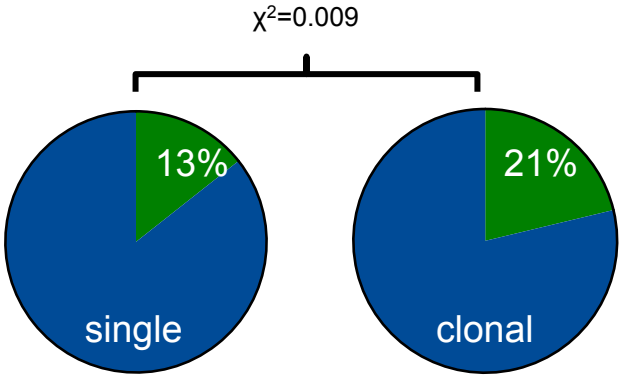
Position matters: HIV integration sites in clones are different and are associated with cancer



Gene Ontology biological function

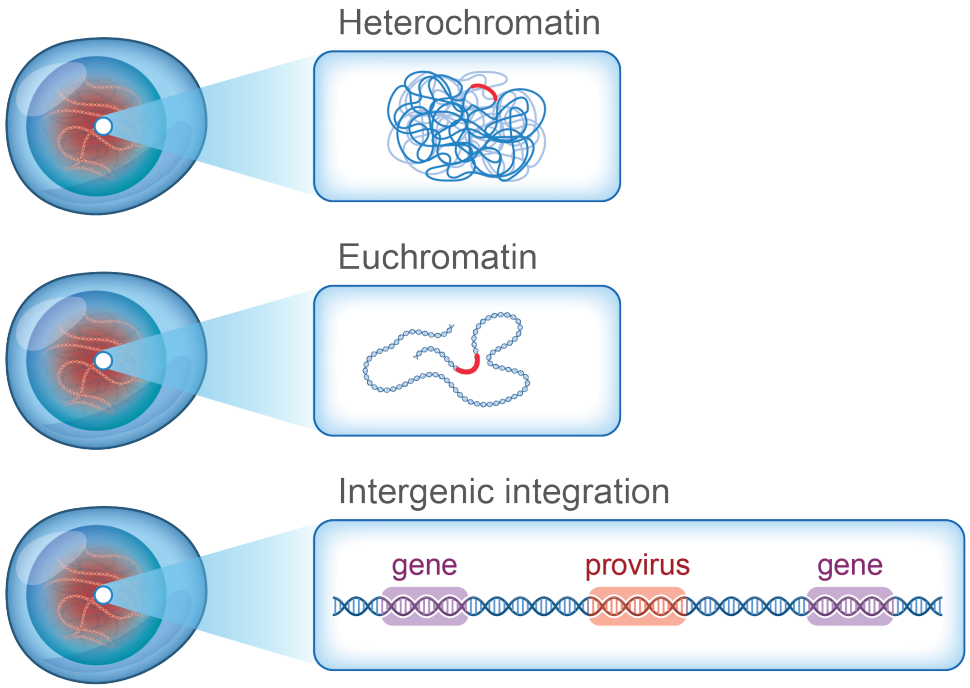


Percentage of genes associated with cancer



Symons et al, unpublished

Position matters: HIV integration is important for virus transcription…..allowing it to stay silent or activate

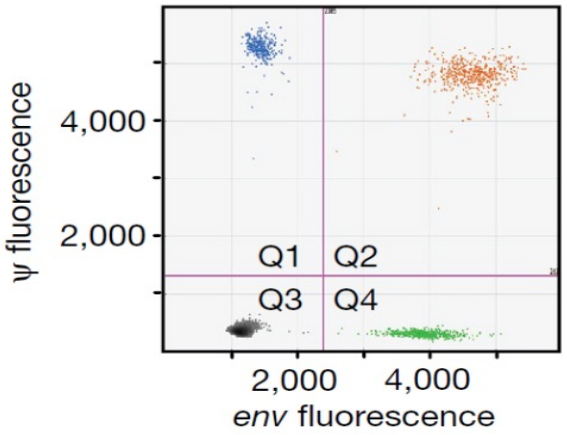


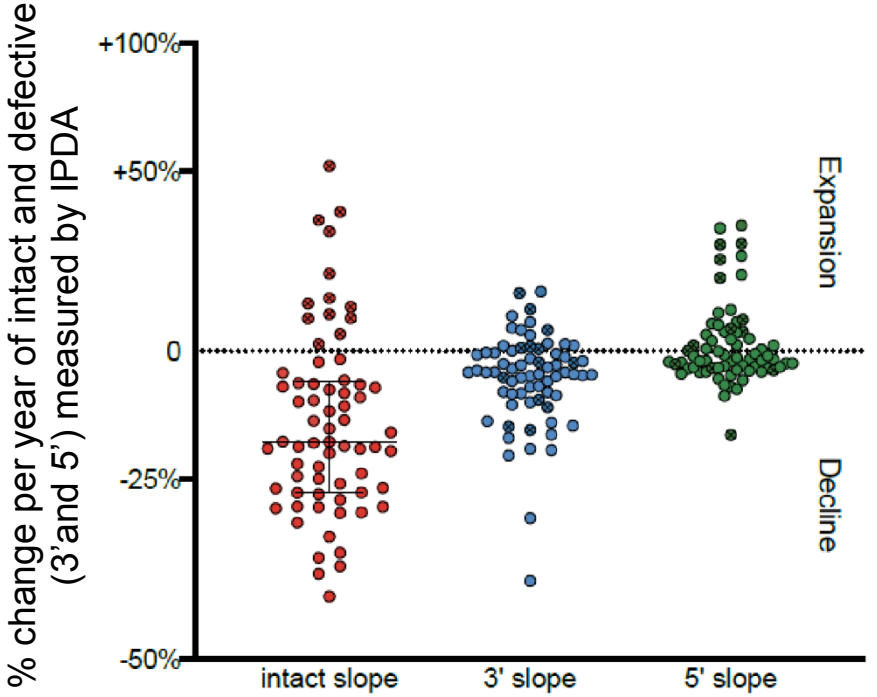
- Integration sites determines the likelihood of a virus being active or silent[1,2]
- Intact viruses are more likely than defective viruses to be integrated in sites which keep the virus silent[3,4]

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 Lindqvist et al., Plos Path 2020

Defective and intact virus: new assays can rapidly quantify intact virus….the virus that matters

- PCR based assay with primers to separately detect and quantify **intact** and **defective** DNA[1,2]





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

1 Bruner et al., Nature 2019; 2 Gaebler et al., J Exp Med 2019

Peluso et al., JCI Insight 2020

Elimination of intact virus: a new definition of cure?

Exceptional Elite Control (EEC): no ART and infrequent intact HIV DNA (n=7)

Mendoza et al., Blood 2012; Casado et al Sci Rep 2020

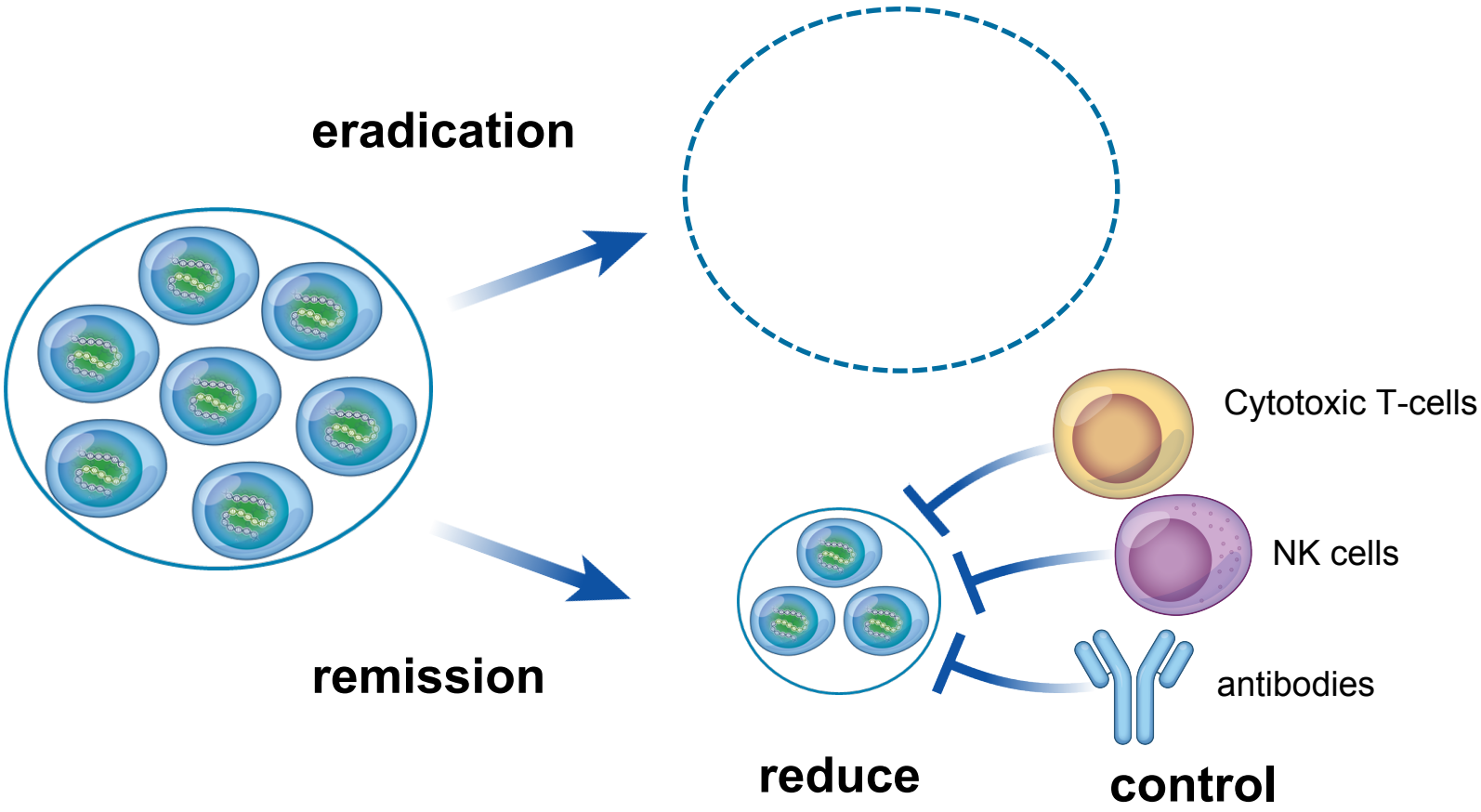
Test	Cell number	Cell type	Intact virus
Sequencing	>1.5 billion cells	PBMC	No
Viral outgrowth	340 million cells	Resting CD4	No
Intact DNA (PCR)	14 million cells	Resting CD4	No
	4 million cells	GI tract	No

Loreen Willenberg: HIV diagnosed in 1992, no ART, undetectable plasma HIV RNA 24 years

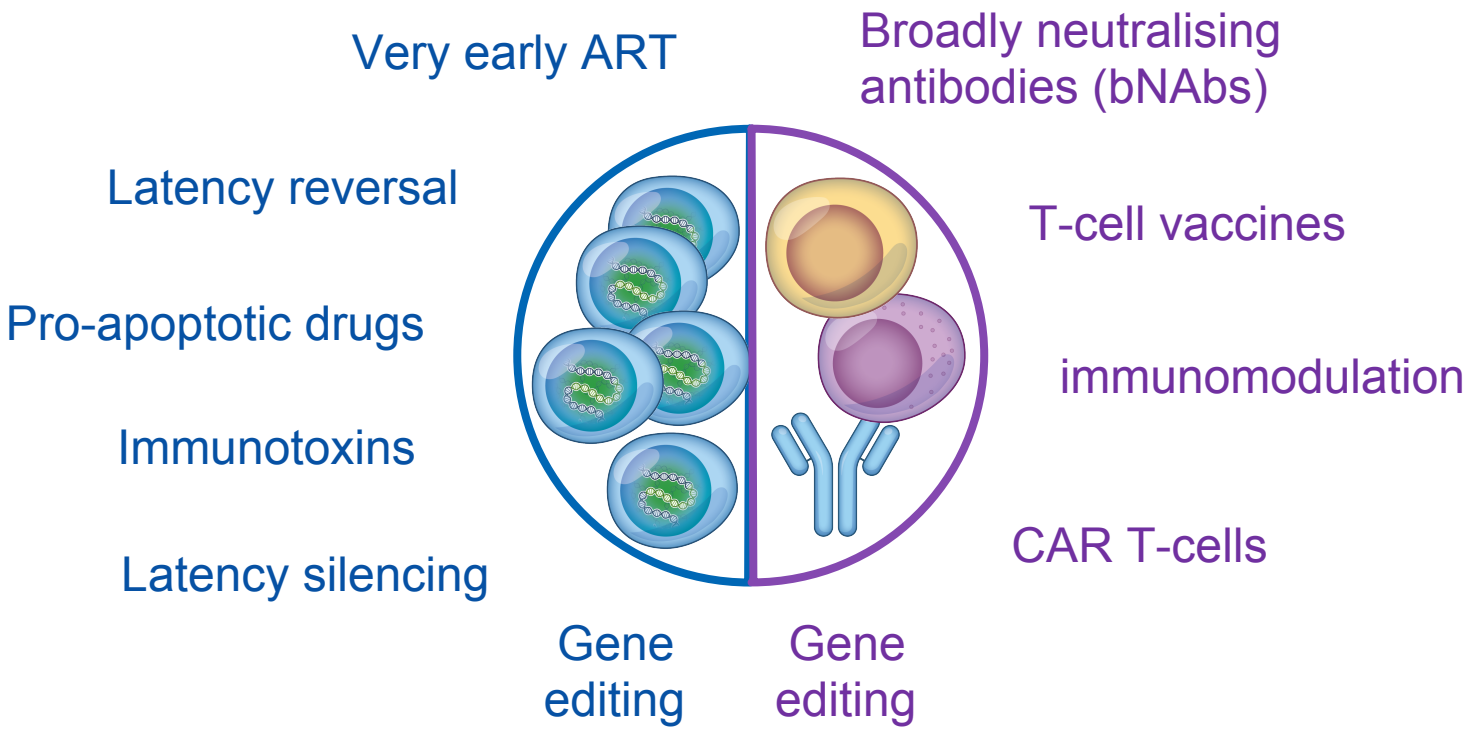
Yu X et al., IAS Science Conference, Mexico City, Mexico July 2019

Clinical strategies being tested

Overarching goals of cure strategies



Targeting the virus and immune system

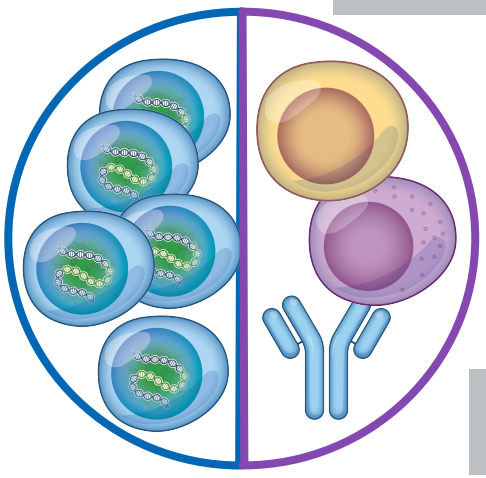


Targeting the virus and immune system

Very early ART

Broadly neutralising antibodies (bNAbs)

Latency reversal



T-cell vaccines

Pro-apoptotic drugs

Immunomodulation

Immunotoxins

CAR T-cells

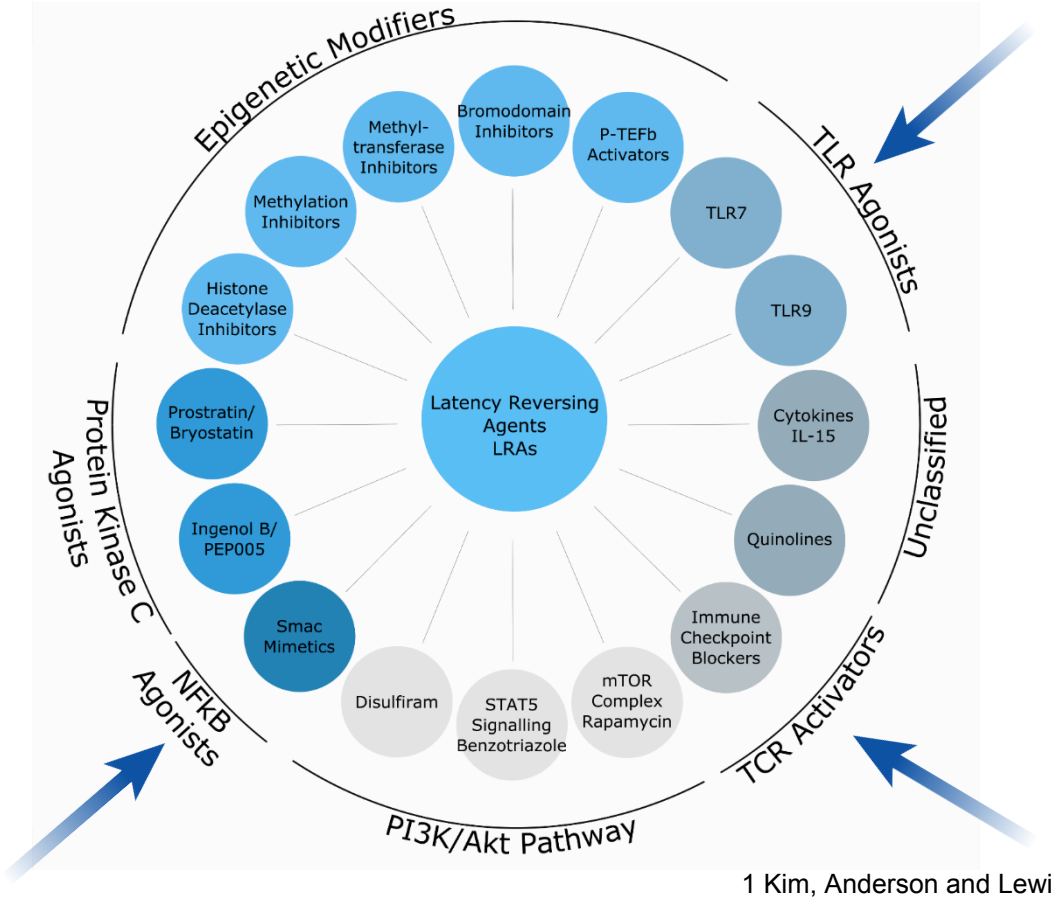
Latency silencing

Gene editing

Gene editing

No human clinical trials

Latency reversing agents (LRA): can ‘shock’ but not ‘kill’

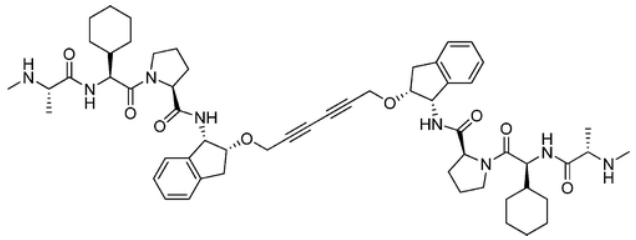


- Need for **more potent** and **less toxic** LRAs
- Need to get the ‘kill’ into shock and kill: **pro-apoptotic drugs**[1]
- Immune modulating latency reversing agents such as **toll like receptor (TLR) agonists** or **anti-PD1** have dual activity of targeting the virus and immune system[2]

1 Kim, Anderson and Lewin, Cell Host Microbe 2018; 2 Zerbato et al., Curr Op Virol 2019

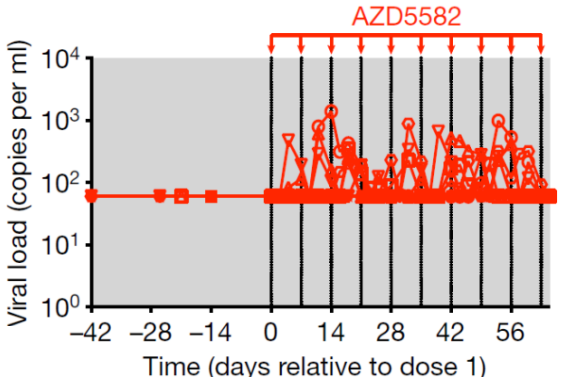
More potent and less toxic latency reversing agents

SMAC mimetics

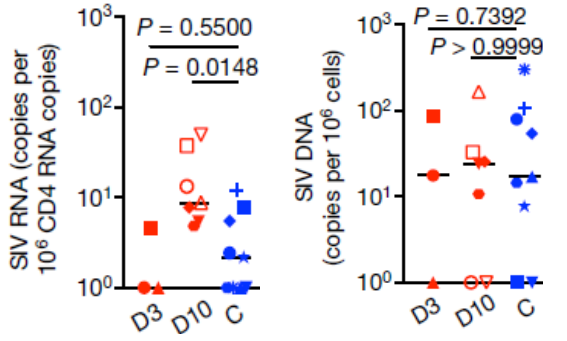


AZD5582

- Developed for cancer to inhibit proteins that block apoptosis ie pro-apoptotic[1]
- Activates NFkB (non-canonical pathway) [2]
- Activates latency in blood and tissue in animal models with minimal toxicity[3]



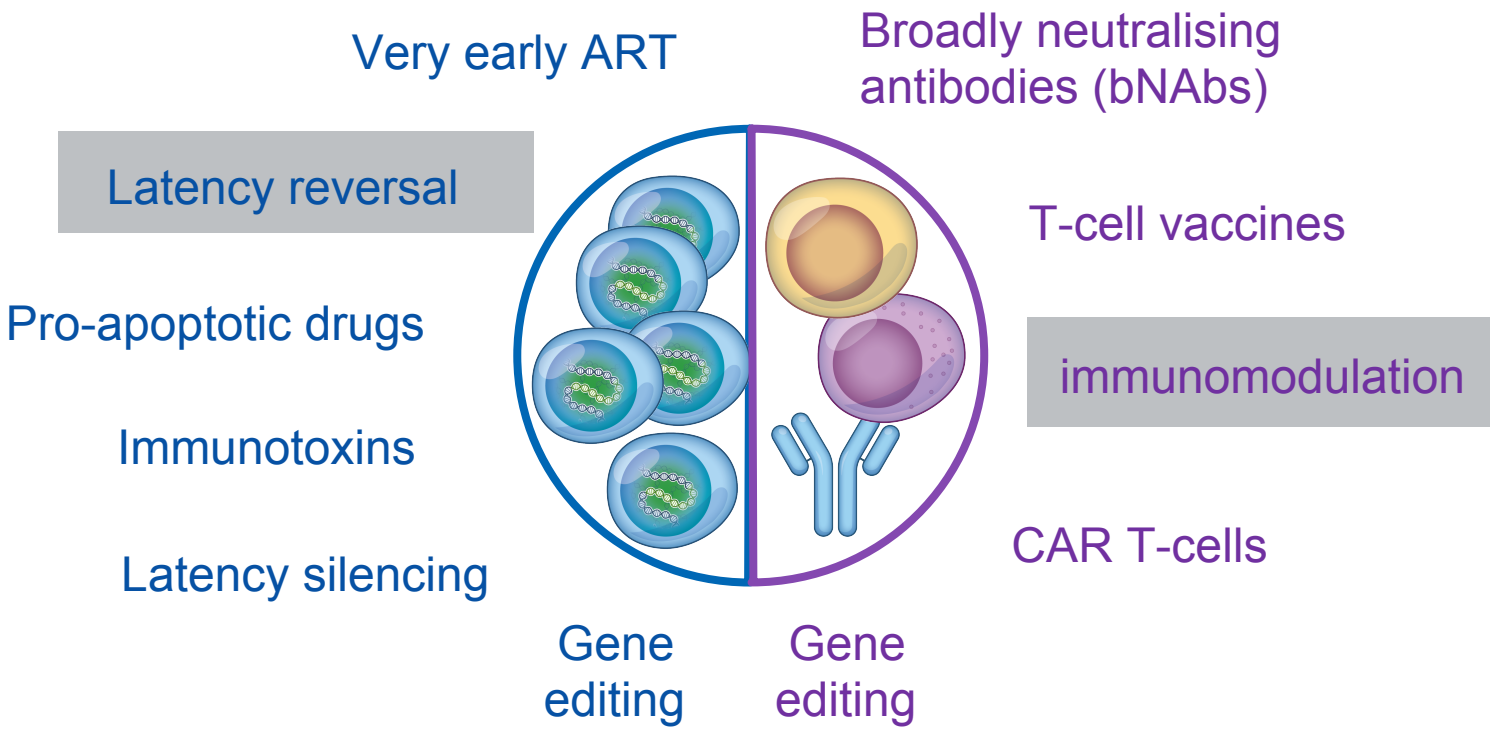
blood



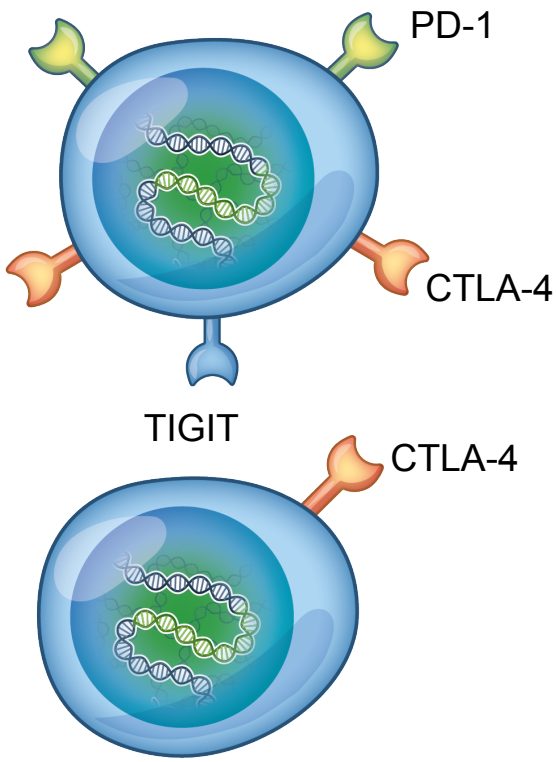
lymph node

1 Hennesey et al., J Med Chem 2013; 2 Pache et al., Cell Host Microbe 2015; 3 Nixon et al., Nature 2020

Targeting the virus and immune system…… together



Immunomodulatory LRAs: immune checkpoint blockers



- Latent virus is enriched in cells that express PD-1 and other immune checkpoint markers (CTLA-4, TIGIT)[1-3]
- In vitro and in vivo anti-PD-1 reverses HIV latency and greater effect with anti-CTLA-4[4,5,6]
- Anti-PD-1 increases HIV/SIV-specific T-cell function and can lead to enhanced viral control in macaques[7]
- Significant challenges in using these agents in PLWH given immune related toxicity [8,9]

1 Chomont et al., Nat Med 2009; 2 Fromentin et al Plos Path 2016; 3 McGarry et al., Immunity 2017; 4 Fromentin et al., Nature Comms 2019; 5 Uldrick CROI 2019, Seattle, WA; 6 Van der Sluis et al., J Immunol 2020; 7 Velu et al., Nature 2006; 8 Gay et al J Infect Dis 2017; 9 https://actgnetwork.org/; Rasmussen et al CROI 2020 **abs 37**; Lau et al CROI 2020 **abs 334** ; Okoye et al., CROI 2020 **abs 117**

Combination immunotherapy

Very early ART

Broadly neutralising antibodies (bNAbs)

Latency reversal

T-cell vaccines

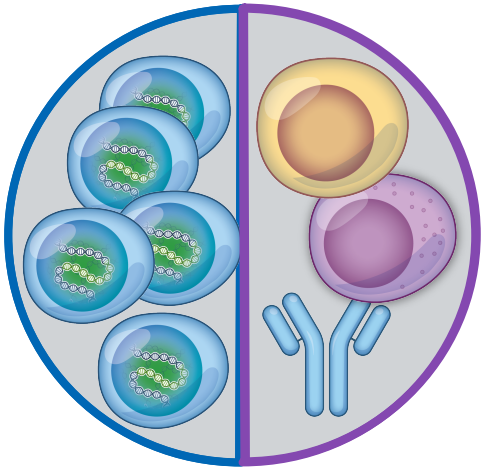
Pro-apoptotic drugs

immunomodulation

Immunotoxins

CAR T-cells

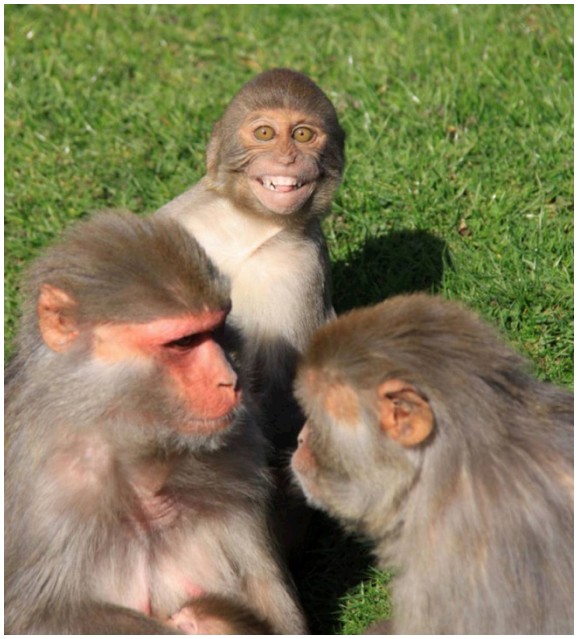
Latency silencing



Gene editing

Gene editing

Combination immunotherapy: promising results in monkey models



nature

Immune clearance of highly pathogenic SIV infection

Scott G. Hansen[1]*, Michael Piatak Jr[2]*, Abigail B. Ventura[1], Colette M. Hughes[1], Roxanne M. Gilbride[1], Julia C. Ford[1], Kelli Oswald[2], Rebecca Shoemaker[2], Yuan Li[2], Matthew S. Lewis[1], Awbrey N. Gilliam[1], Guangwu Xu[1], Nathan Whizin[1], Benjamin J. Burwitz[1], Shannon L. Planer[1], John M. Turner[1], Alfred W. Legasse[1], Michael K. Axthelm[1], Jay A. Nelson[1], Klaus Früh[1], Jonah B. Sacha[1], Jacob D. Estes[2], Brandon F. Keele[2], Paul T. Edlefsen[3], Jeffrey D. Lifson[2] & Louis J. Picker[1]

nature

Ad26/MVA therapeutic vaccination with TLR7 stimulation in SIV-infected rhesus monkeys

Erica N. Borducchi[1], Crystal Cabral[1], Kathryn E. Stephenson[1], Jinyan Liu[1], Peter Abbink[1], David Ng'ang'a[1], Joseph P. Nkolola[1], Amanda L. Brinkman[1], Lauren Peter[1], Benjamin C. Lee[1], Jessica Jimenez[1], David Jetton[1], Jade Mondesir[1], Shanell Mojta[1], Abishek Chandrashekar[1], Katherine Molloy[1], Galit Alter[2], Jeffrey M. Gerold[3], Alison L. Hill[3], Mark G. Lewis[4], Maria G. Pau[5], Hanneke Schuitemaker[5], Joseph Hesselgesser[6], Romas Geleziunas[6], Jerome H. Kim[7]†, Merlin L. Robb[7], Nelson L. Michael[7] & Dan H. Barouch[1,2]

nature

Early antibody therapy can induce long-lasting immunity to SHIV

Yoshiaki Nishimura[1], Rajeev Gautam[1], Tae-Wook Chun[2], Reza Sadjadpour[1], Kathryn E. Foulds[3], Masashi Shingai[1], Florian Klein[4,5], Anna Gazumyan[6], Jovana Golijanin[6], Mitzi Donaldson[3], Olivia K. Donau[1], Ronald J. Plishka[1], Alicia Buckler-White[1], Michael S. Seaman[7], Jeffrey D. Lifson[8], Richard A. Koup[3], Anthony S. Fauci[2], Michel C. Nussenzweig[6,9] & Malcolm A. Martin[1]

nature

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

Erica N. Borducchi[1,6], Jinyan Liu[1,6], Joseph P. Nkolola[1,6], Anthony M. Cadena[1,6], Wen-Han Yu[2], Stephanie Fischinger[2], Thomas Broge[2], Peter Abbink[1], Noe B. Mercado[1], Abishek Chandrashekar[1], David Jetton[1], Lauren Peter[1], Katherine McMahan[1], Edward T. Moseley[1], Elena Bekerman[3], Joseph Hesselgesser[3], Wenjun Li[4], Mark G. Lewis[5], Galit Alter[2], Romas Geleziunas[3] & Dan H. Barouch[1,2]*

Slide courtesy of Steve Deeks

Combination immunotherapy: larger and/or randomised clinical trials currently underway

name	Reduce and control		Reservoir	ATI
RIVER[1]	vorinostat	Vaccine (ChAd)	No change	no

ATI = antiretroviral treatment interruption 1 Fidler et al., Lancet 2020; 2 Gruell CROI 2020 **abs 38**; Sengupta et al., CROI 2020 **abs 40**

Gene therapy: targets and strategies

Attack: enhance anti-HIV immune responses

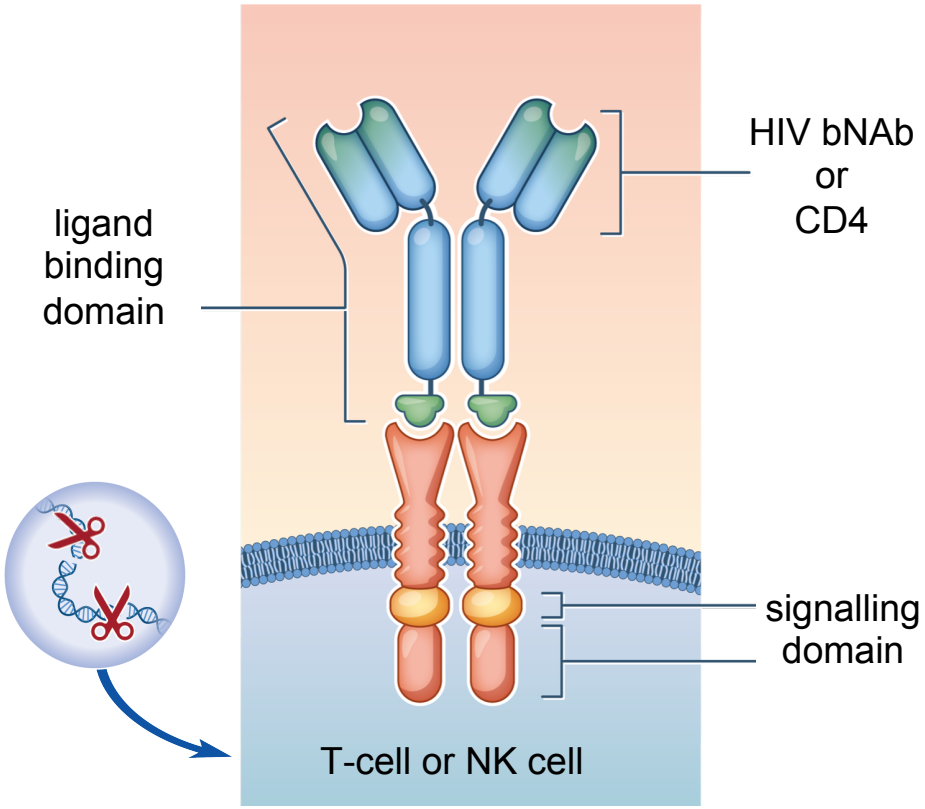
Protect: engineer uninfected cells to be resistant to HIV

Purge: directly eliminate the virus itself

Delivery of gene therapy a major challenge :
ex vivo (gene editing of cells outside the body) or **in vivo** (gene editing in the body)

Slide courtesy of Paula Cannon

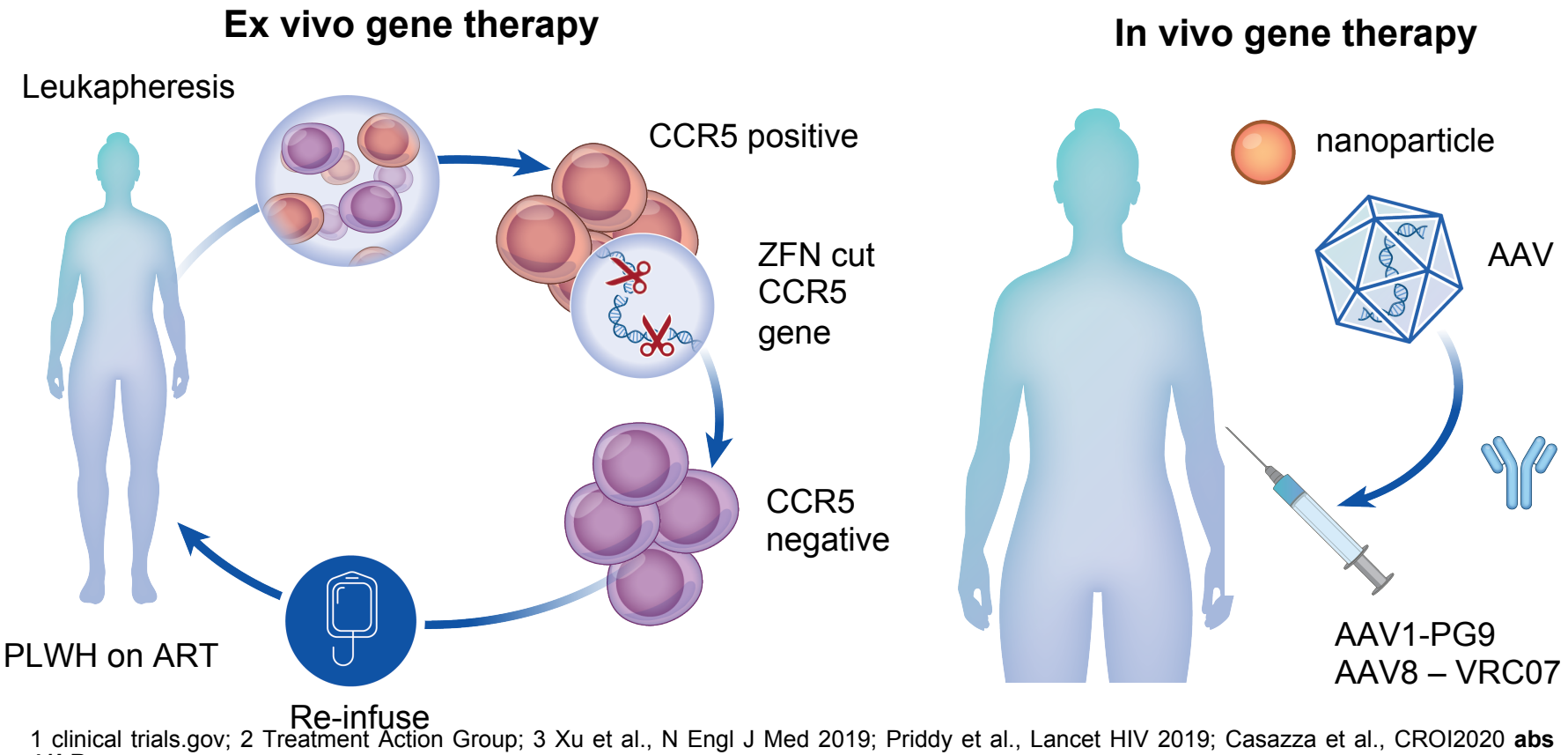
Chimeric antigen receptor (CAR)-T cells



- Autologous T-cells or NK cells undergo gene editing to express a CAR to bind and kill cells that express HIV envelope [1-4]
- CAR T-cells for HIV tested in mice, macaque models and in clinical trials in China (x3) and the US (x1)[5]
- Major challenges include toxicity (potentially preventable), delivery to tissue sites and low expression of HIV envelope on ART

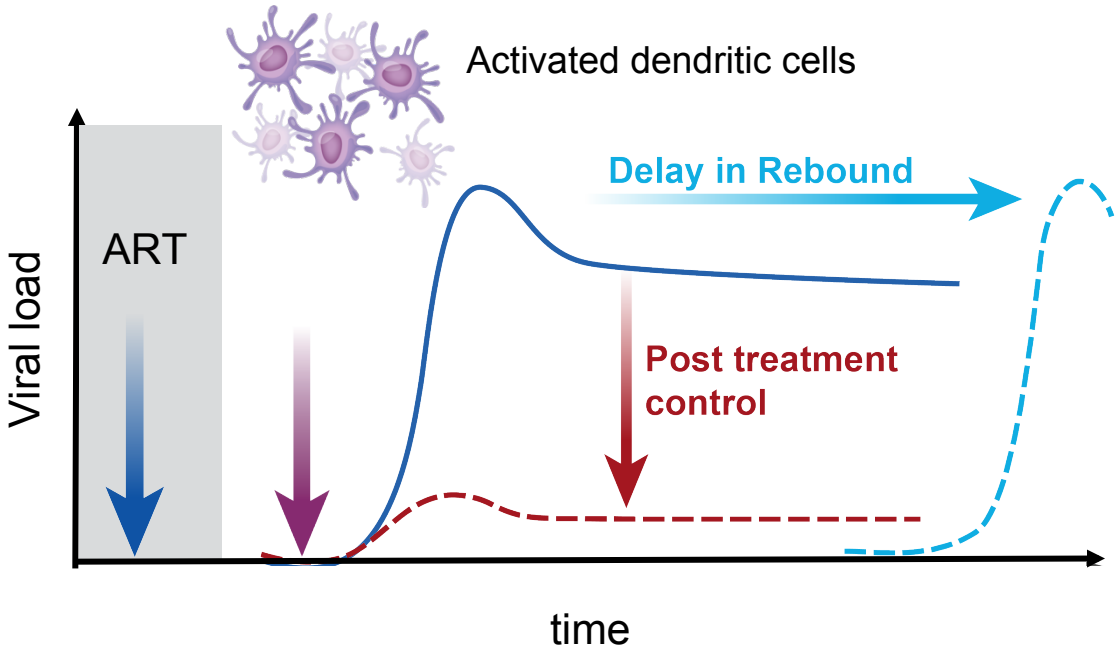
1 Deeks et al., Mol Ther 2002; 2 Sung et al., Mol Ther 2018; 3 Herzig et al., Cell 2019; 4 Anthony-Gonda Sci Transl Med 2019; 5 clinical trials.gov

Gene therapy: ex vivo gene modification



1 clinical trials.gov; 2 Treatment Action Group; 3 Xu et al., N Engl J Med 2019; Priddy et al., Lancet HIV 2019; Casazza et al., CROI2020 **abs 41LB**

Endpoints for clinical trials: treatment interruption



Lancet HIV 2019

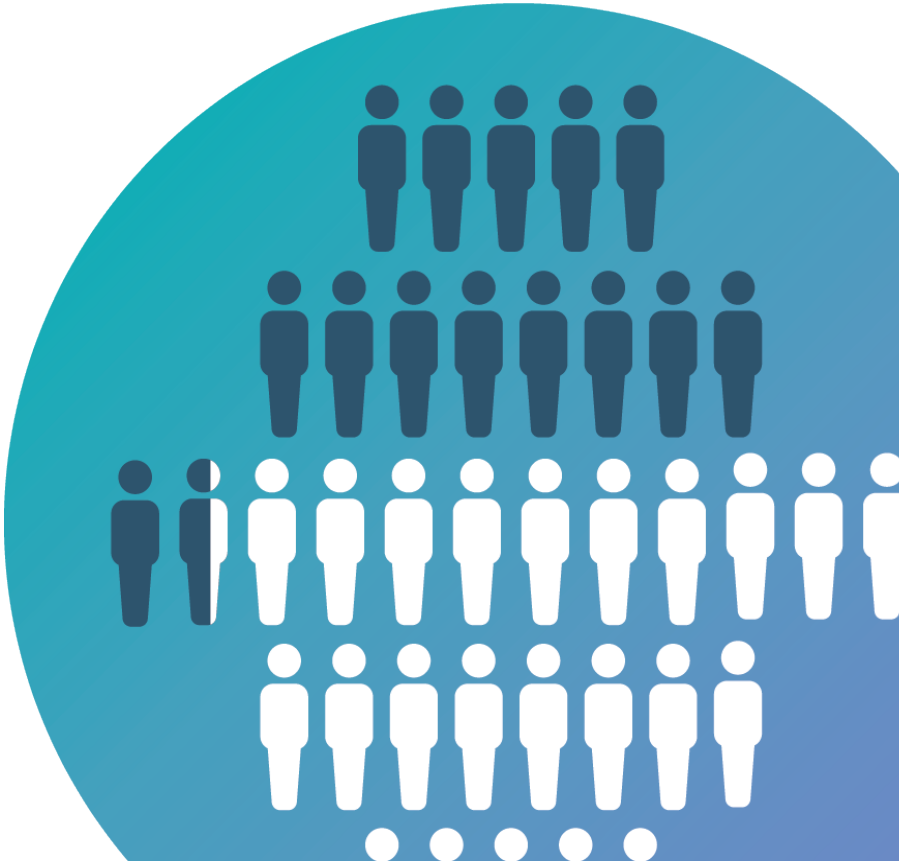
Recommendations for analytical antiretroviral treatment interruptions in HIV research trials – report of a consensus meeting.

Julg et al

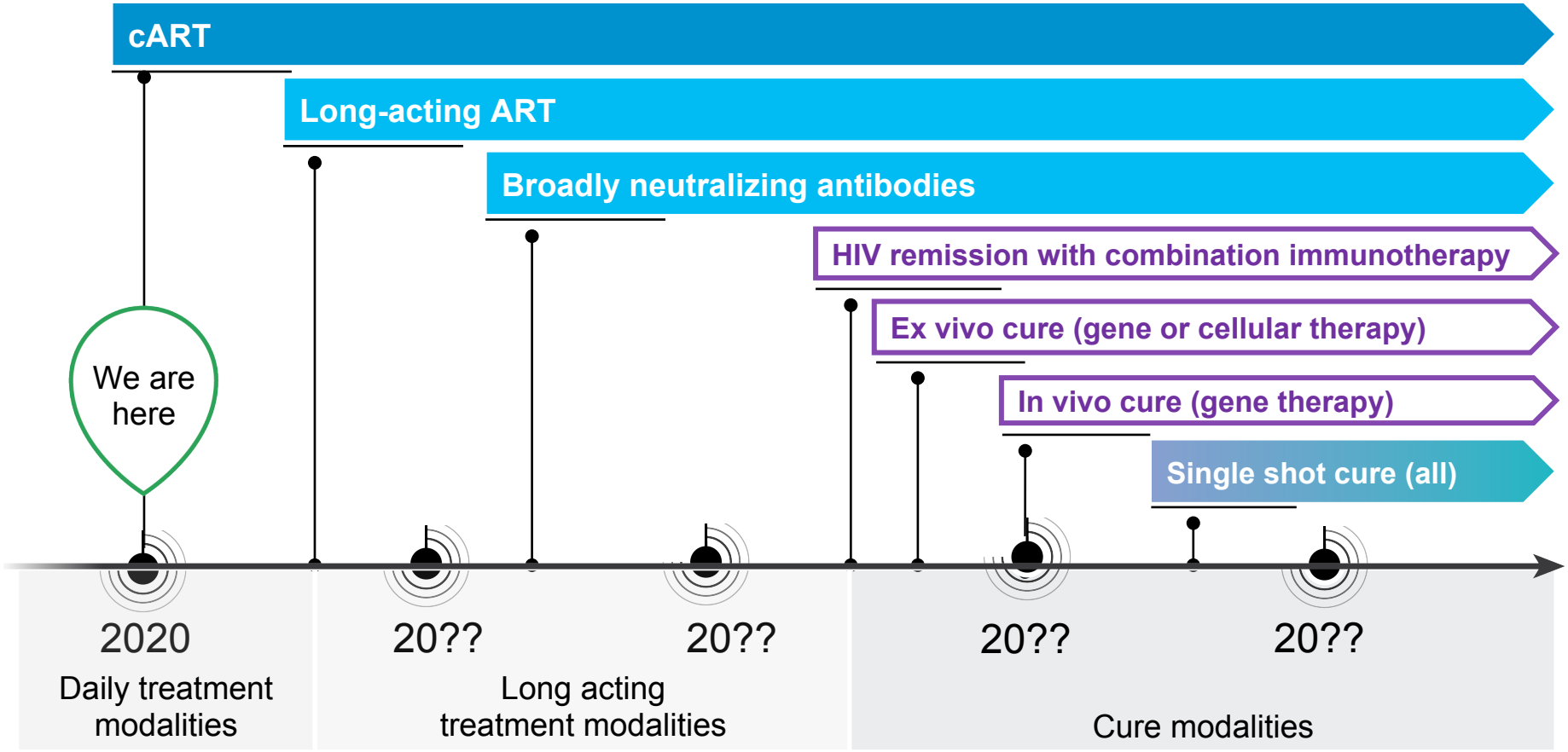
No biomarker available that can predict time to rebound or post treatment control and therefore treatment interruption is needed as a clinical endpoint.

Julg et al., Lancet HIV 2019; Mitchell et al J Clin Inv 2020

To the community: implementation of an HIV cure



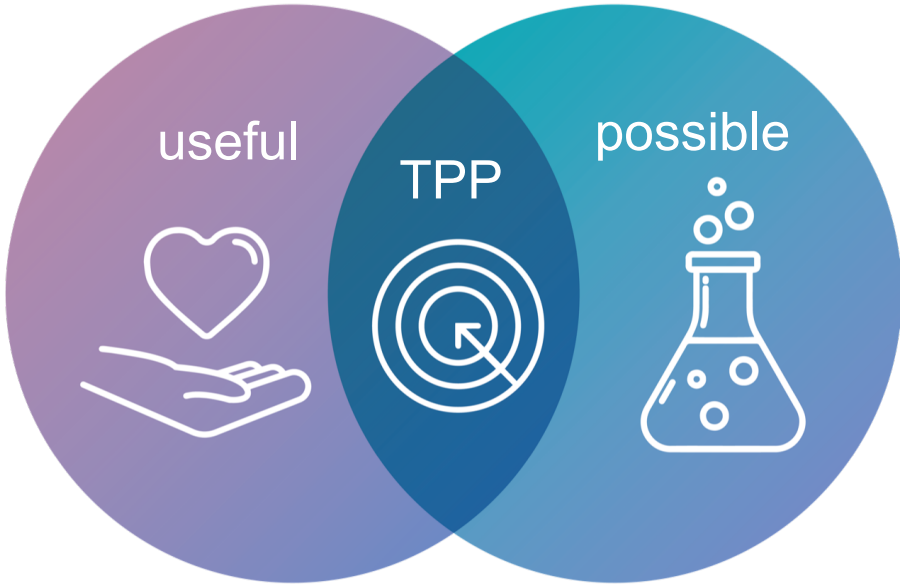
Current and future landscape for HIV treatment



Developing a target product profile (TPP) for an HIV cure

BILL & MELINDA GATES foundation

IAS



Summary and implications

- Many new **concepts in understanding HIV latency**: active reservoir, proliferation and site of integration - may provide novel approaches

- Combination immunotherapy interventions have achieved **SHIV/SIV remission in monkey models**. Whether similar results will be seen in HIV clinical trials remain to be determined. Many trials underway

- More invasive and complex interventions such as **CAR T-cells and gene therapy** have the potential for eradication and are therefore of high interest

- Approaches to an HIV cure will need to adapt to the **treatment landscape**, the **needs of the individual** and to have maximal **public health impact**. Early engagement of community, regulators and all funders will be needed

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Zuwena Richardson
Matthew Pitman
Youry Kim
Haoming Liu
Abdalla Abbas
Paula Cavaal
Ajantha Solomon
Ashanti Dantanarayana
Judy Chang
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Barbara Scher
Paul Cameron*
Renee van der Sluis*
Vanessa Evans*
Jenny Anderson*
Nitasha Kumar*
Surekha Tenakoon*

* previous lab members


Delaney AIDS Research Enterprise
DARE
to find a cure

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Jared Stern
Chris Chiu
Celine Gubser
Jenn Zerbato
Wei Zhao
Rachel Pascoe
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