Strategies to reduce and control the HIV reservoir: lessons learnt from translation to clinical trials

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The Forum for Collaborative Research
HIV cure: Clinical research considerations and strategies
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Doherty Institute

THE UNIVERSITY OF MELBOURNE

The Royal Melbourne Hospital

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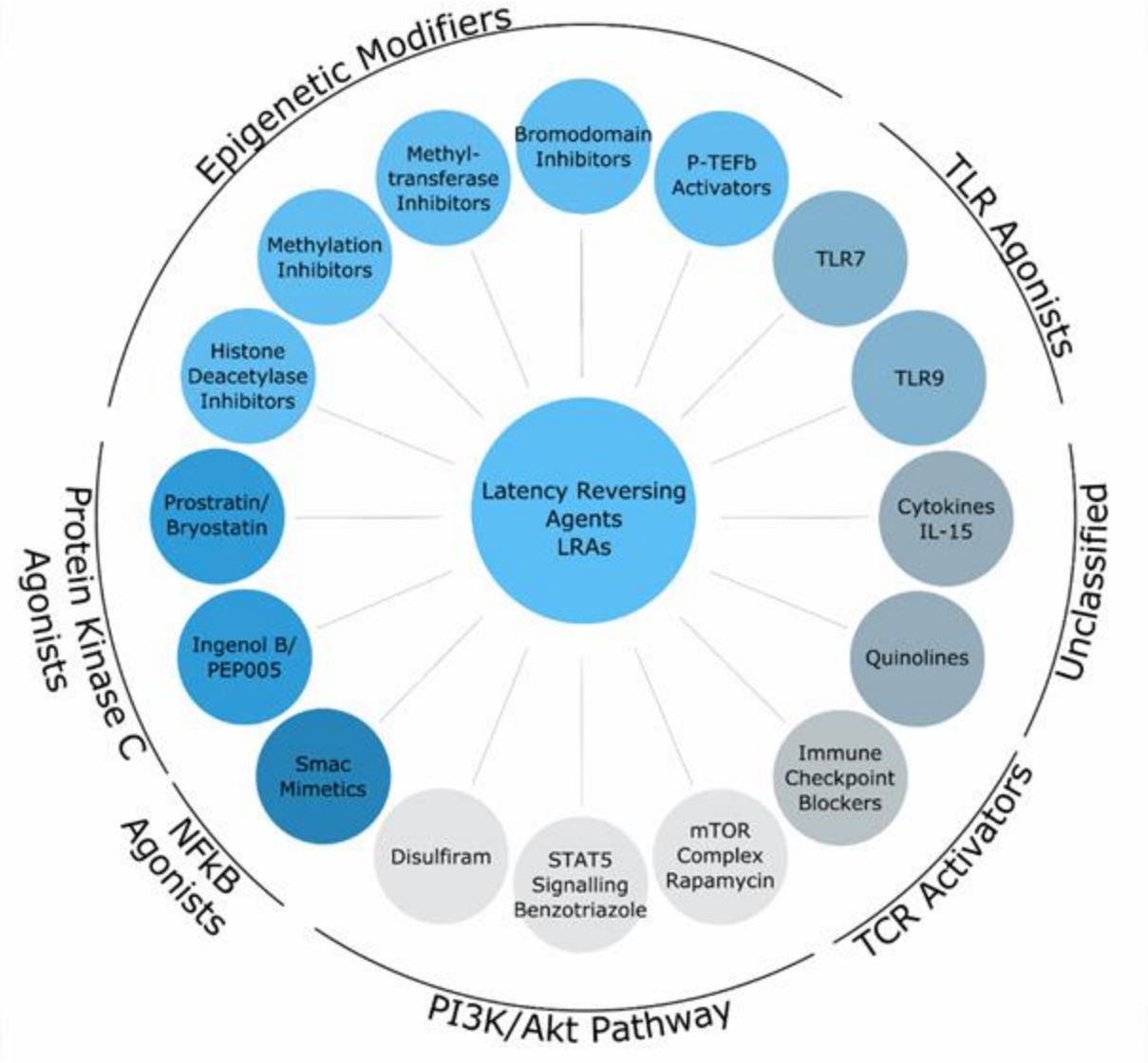
Outline

- **Reservoir reduction**
  - First generation LRAs
  - Second generation HIV-specific LRAs
  - Pro-apoptotic compounds
- **Increase immune control**
  - Immune checkpoint blockade
  - Broadly neutralising antibodies

Considerations for and lessons from **clinical trials**

Latency reversing agents: first and second generation

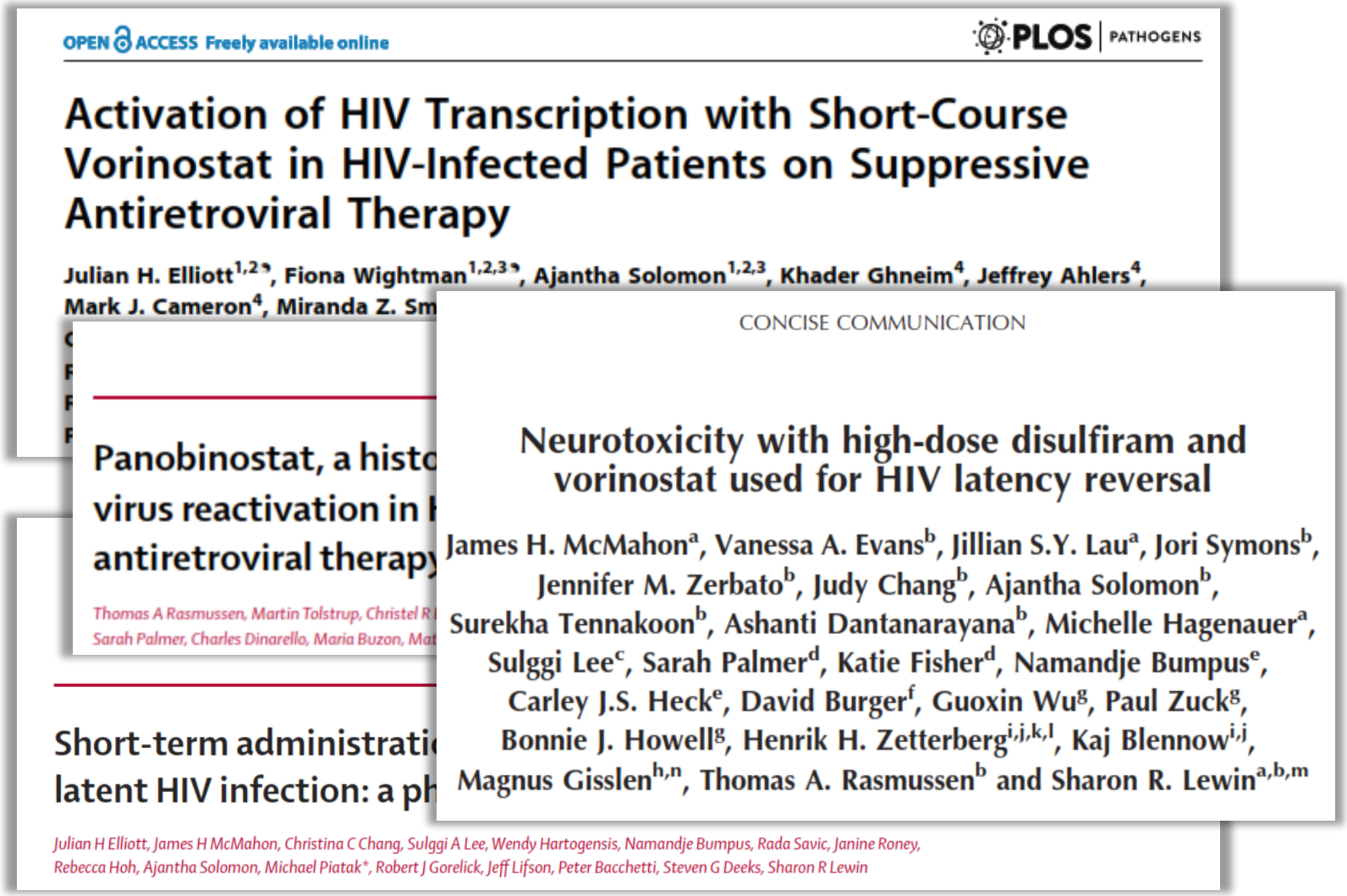
Latency reversing agents (LRA) need improvement



- In vivo, **LRAs increase transcription** but changes are modest and no decline in the number of infected cells
- LRAs can have **off target effects on immune function** including reduced CD8+ T cell number and/or function with HDAC inhibitors and some SMAC mimetics
- Latently infected cells express a range of **pro-survival proteins** which may need to be overcome to deplete the reservoir
- Better LRAs are needed with **greater specificity, greater potency** and **lower toxicity**

Kim Cell Host Microbe 2018; Jones Plos Path 2016; Sun Nature 2023; Clarke Nature 2023; Dashti Nat Med 2023; Tanaka HIV Persistence 2024

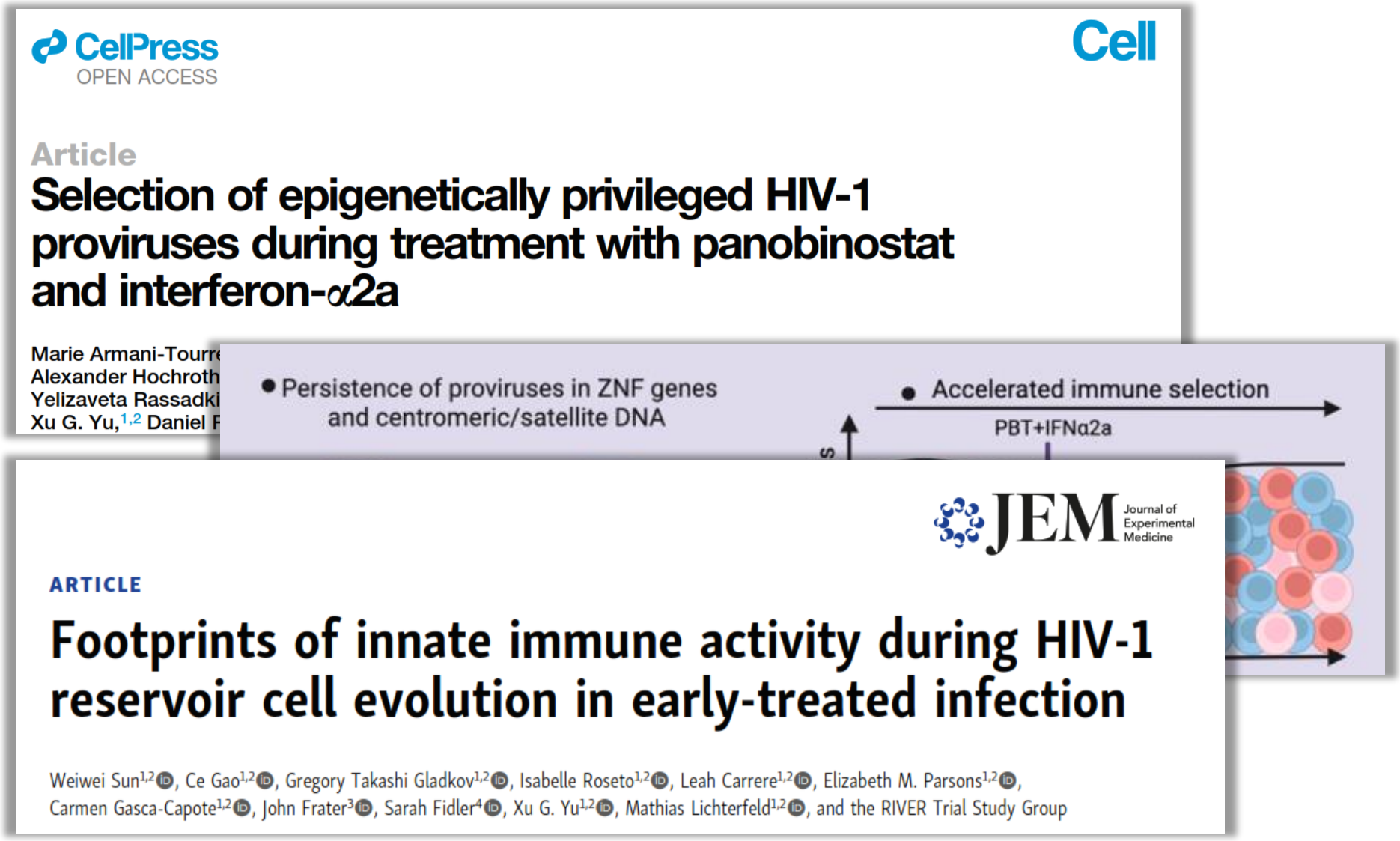
Lessons from clinical trials of first generation LRAs



- **Safety** is the number one goal
  - Unexpected toxicities with new combinations
- **Primary endpoint** for latency reversal?
  - Unspliced HIV RNA (transcription initiation)
  - Multiply spliced HIV RNA (required for protein)
  - Plasma HIV RNA
  - Reservoir size
- **Additional information**
  - Latency reversal in **tissue** especially CNS
  - Off target effects eg immune function
  - Long term effects on the reservoir

Archin Nature 2012; Elliott Plos Path 2014; Rasmussen Lancet HIV 2014; Elliott Lancet HIV 2018

Newer qualitative assays will provide greater insights



Armani-Tourret et al Cell 2023; Sun et al JEM 2025

Second generation HIV-specific LRAs: role of mRNA

nature communications

Article

https://doi.org/10.1038/s41467-025-60001-2

Efficient mRNA delivery to resting T cells to reverse HIV latency

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Check for updates

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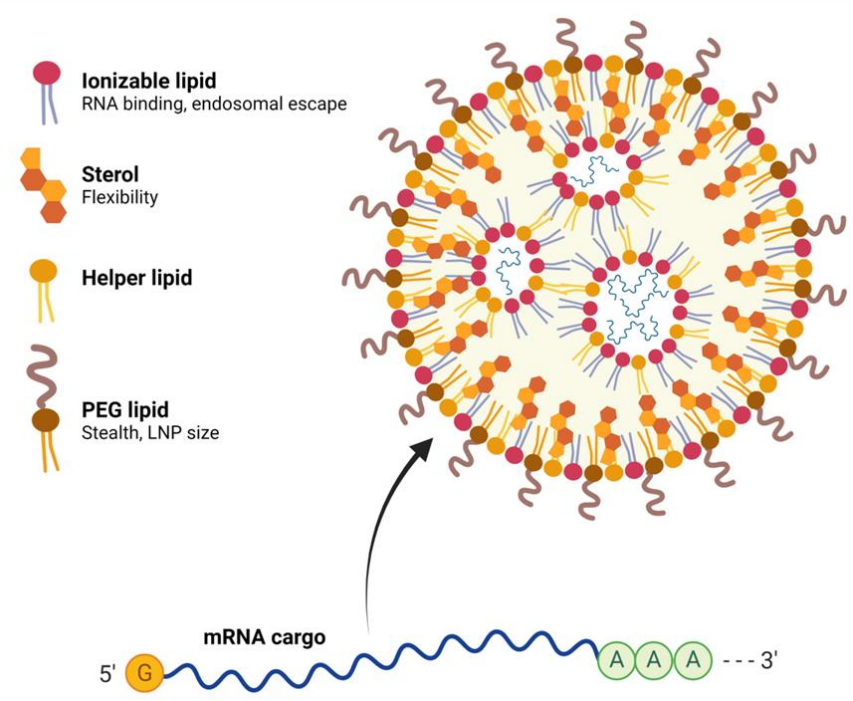
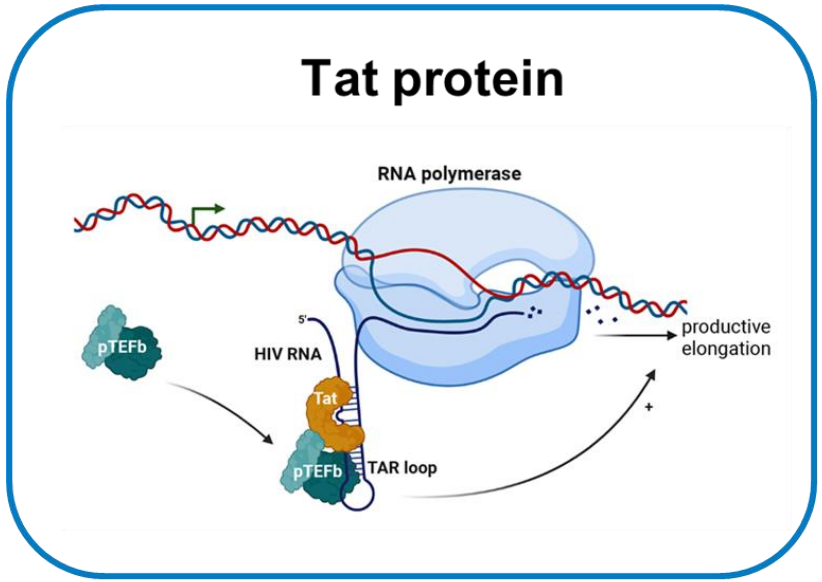
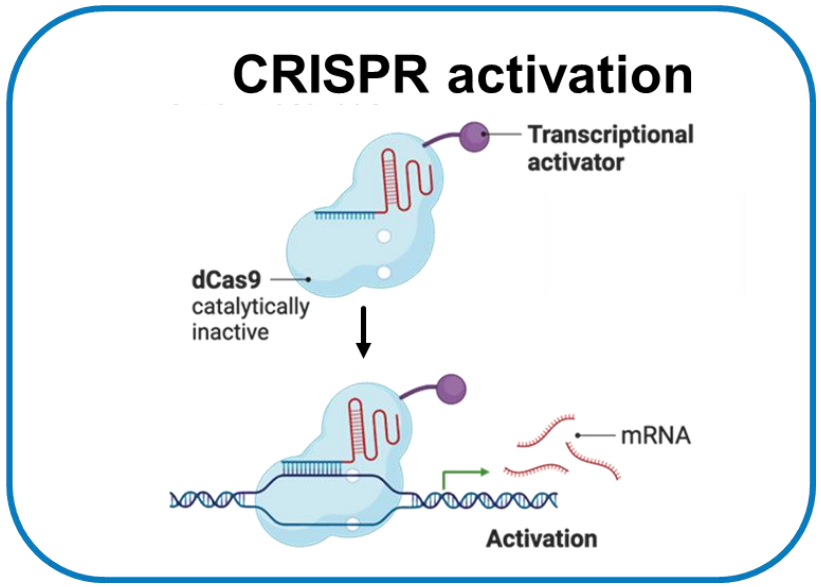
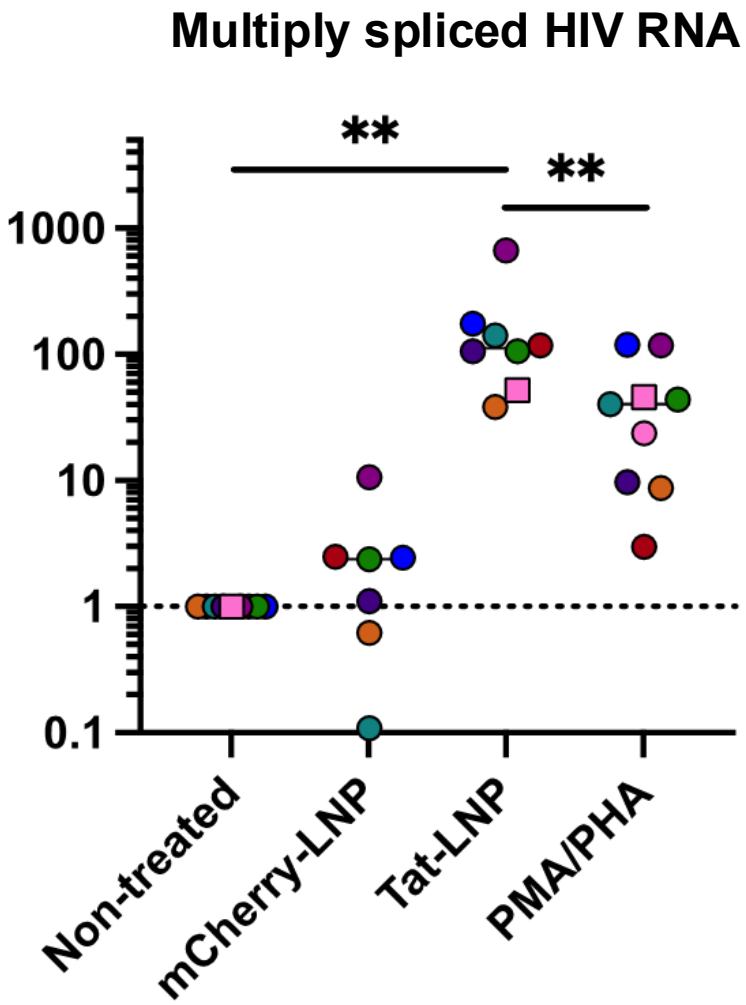


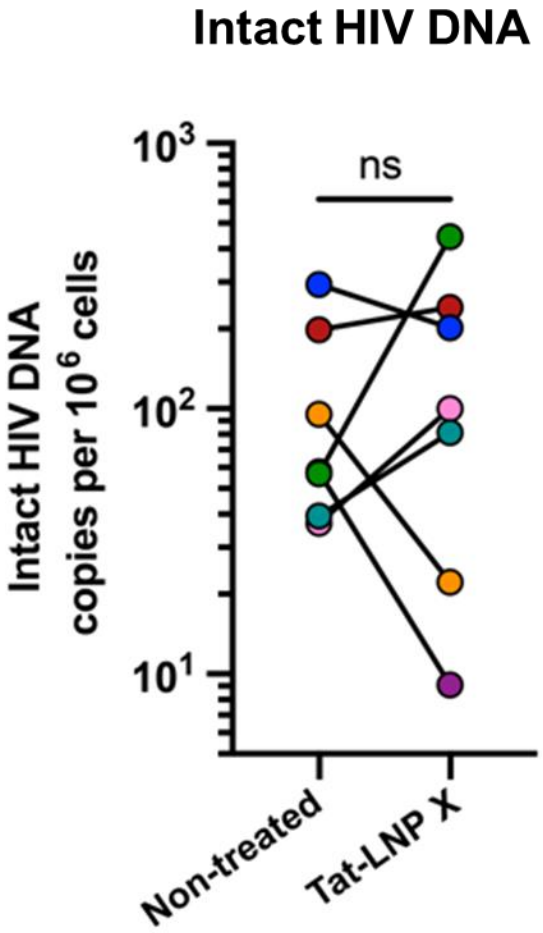
Cevaal, Kan, Fisher, Moso et al., Nat Comms 2025

LNP-X efficiently delivers Tat mRNA to resting T-cells

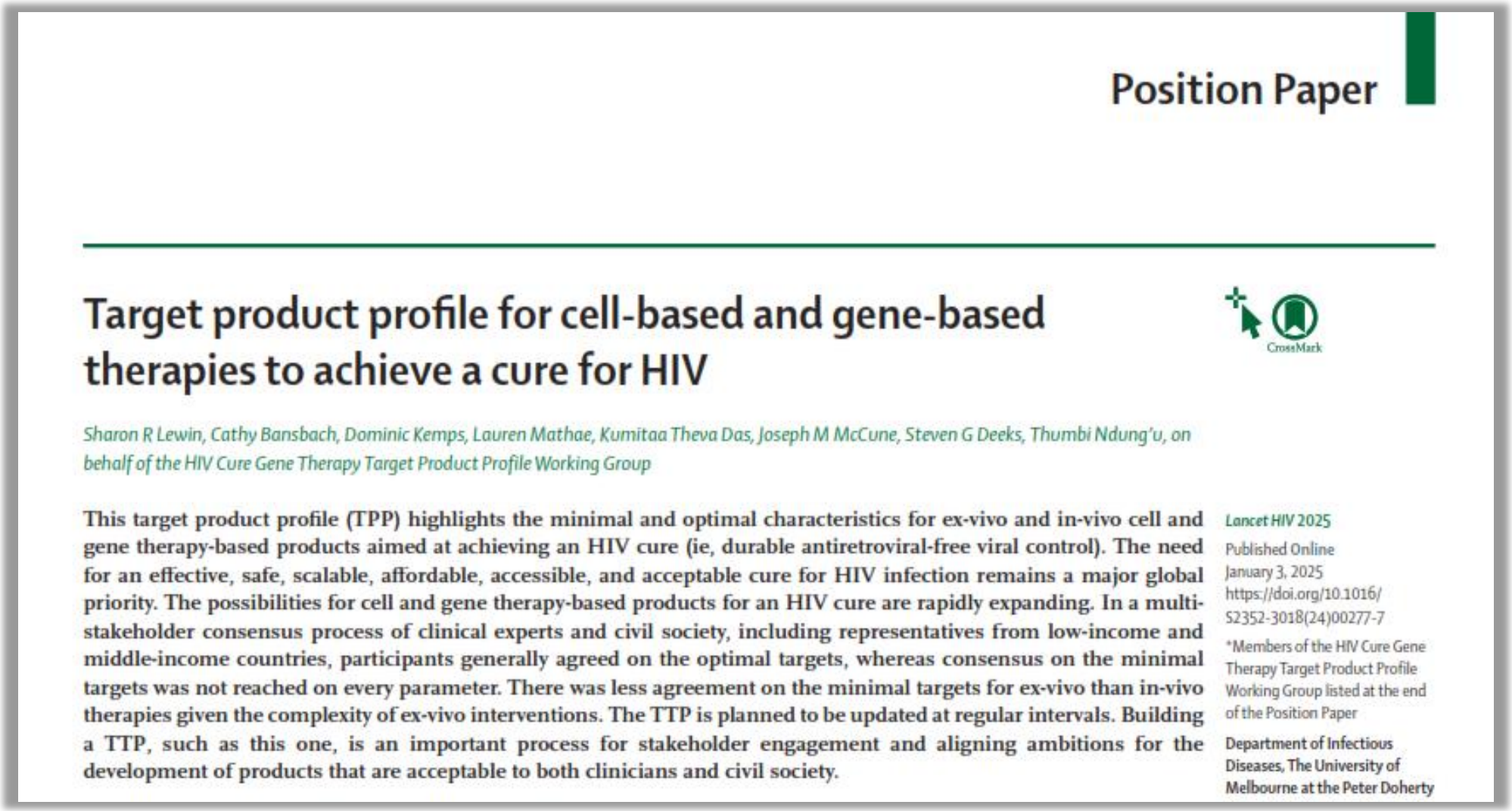








Target product profiles for an mRNA therapeutic?



Position Paper

Target product profile for cell-based and gene-based therapies to achieve a cure for HIV

Sharon R Lewin, Cathy Bansbach, Dominic Kemps, Lauren Mathae, Kumitaa Theva Das, Joseph M McCune, Steven G Deeks, Thumbi Ndung'u, on behalf of the HIV Cure Gene Therapy Target Product Profile Working Group

This target product profile (TPP) highlights the minimal and optimal characteristics for ex-vivo and in-vivo cell and gene therapy-based products aimed at achieving an HIV cure (ie, durable antiretroviral-free viral control). The need for an effective, safe, scalable, affordable, accessible, and acceptable cure for HIV infection remains a major global priority. The possibilities for cell and gene therapy-based products for an HIV cure are rapidly expanding. In a multi-stakeholder consensus process of clinical experts and civil society, including representatives from low-income and middle-income countries, participants generally agreed on the optimal targets, whereas consensus on the minimal targets was not reached on every parameter. There was less agreement on the minimal targets for ex-vivo than in-vivo therapies given the complexity of ex-vivo interventions. The TTP is planned to be updated at regular intervals. Building a TTP, such as this one, is an important process for stakeholder engagement and aligning ambitions for the development of products that are acceptable to both clinicians and civil society.

Lancet HIV 2025

Published Online January 3, 2025 https://doi.org/10.1016/S2352-3018(24)00277-7

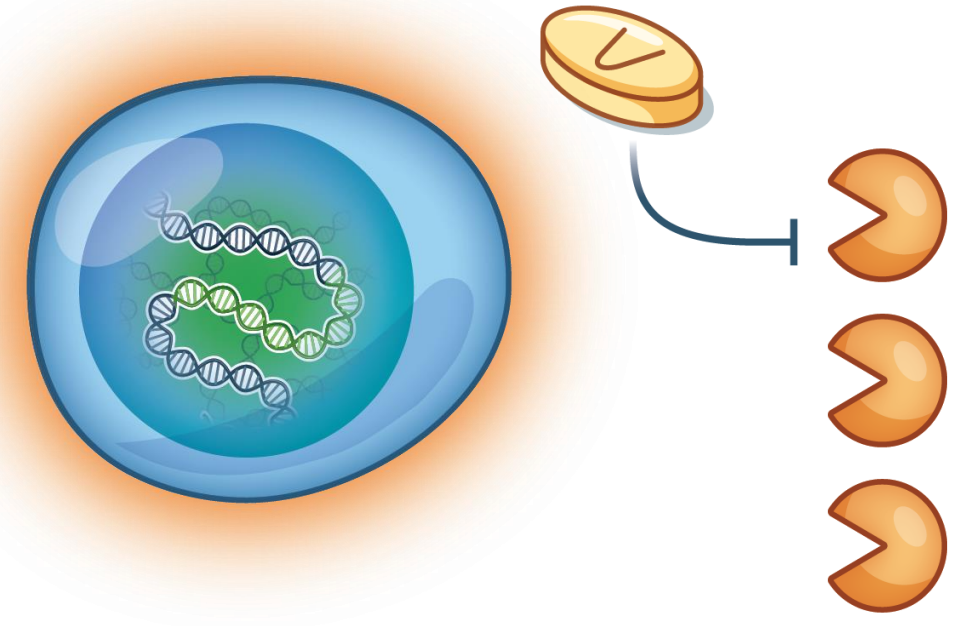
*Members of the HIV Cure Gene Therapy Target Product Profile Working Group listed at the end of the Position Paper

Department of Infectious Diseases, The University of Melbourne at the Peter Doherty

Lewin SR Lancet HIV 2025

Pro-apoptotic drugs: inhibition of BCL-2

Pro-apoptotic drugs: BCL-2 antagonists

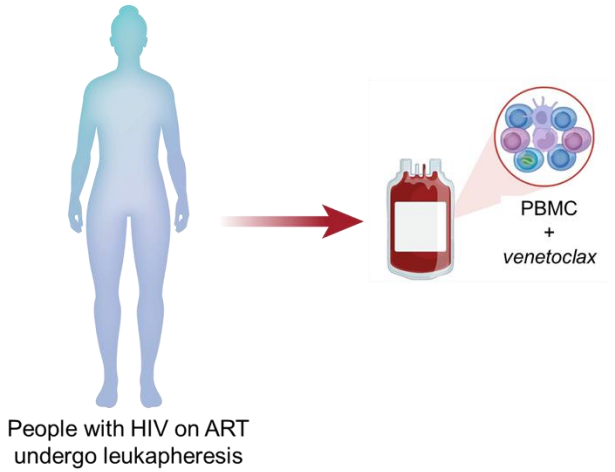


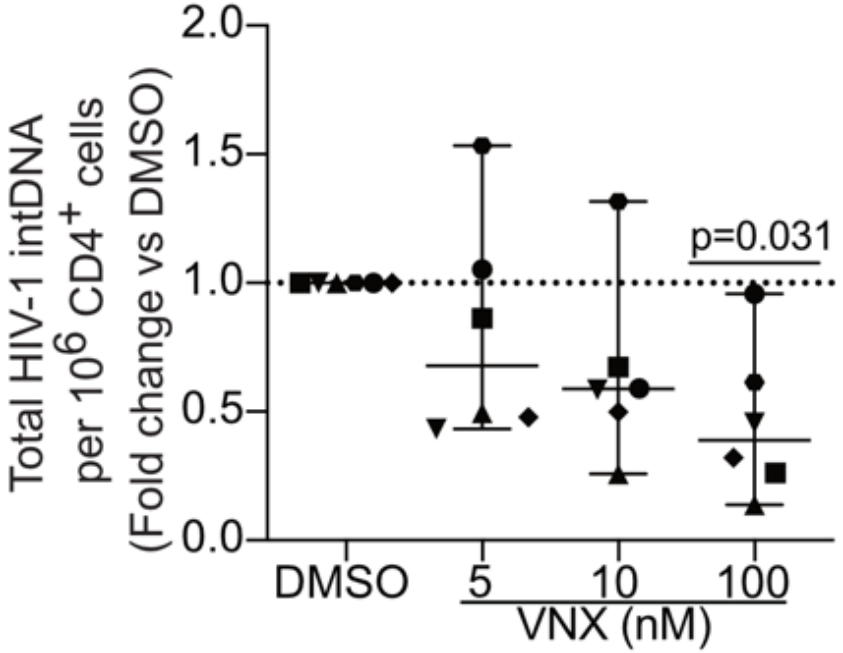
Latent infection
DNA positive
RNA negative
HIV protein negative
SURVIVAL

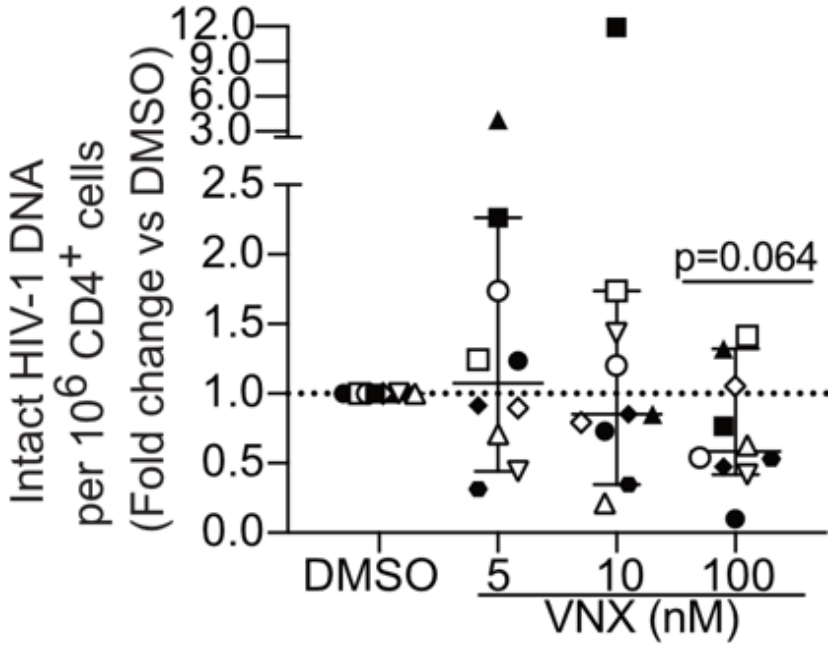
- Venetoclax is a **BCL-2 antagonist** and a licensed treatment for chronic lymphocytic leukemia[1]
- Ex vivo, using **CD4+ T-cells from PWH on ART**, venetoclax leads to the selective death of latently infected cells which is enhanced in the presence of CD8+ T-cells[2,3,4]
- In **humanised mice**, venetoclax leads delay in viral rebound following cessation of ART[4]
- In **SIV-infected macaques**, venetoclax accelerates decay of SIV DNA when used at ART initiation and on stable ART when used in combination with AZD5582[5,6]

1 Roberts N Engl J Med 2016; 2 Cummins J Virol 2017; 3 Ren J Clin Inv 2020 4 Arandjelovic Cell Rep Med 2023;; 5 Ukhueduan CROI 2025; 6 Paiardini Res Sq 2025

Venetoclax alone ex vivo depletes integrated and intact HIV DNA – but only ~50% reduction



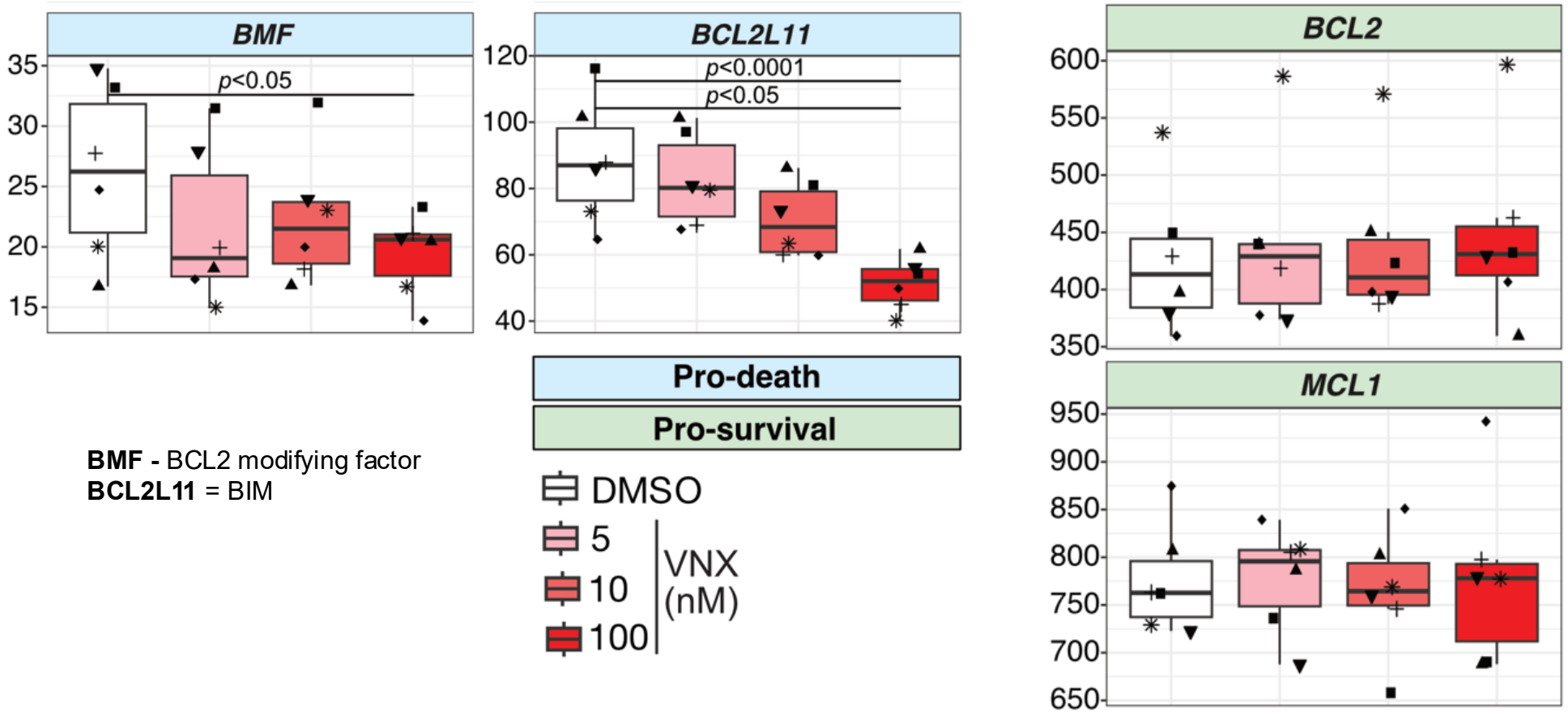




Arandjelovic et al Cell Reports Medicine 2023

Venetoclax can select for cells that express high levels of pro-survival proteins

CD4+ T-cells from PWH on ART were treated ex vivo with Venetoclax and scRNAseq performed

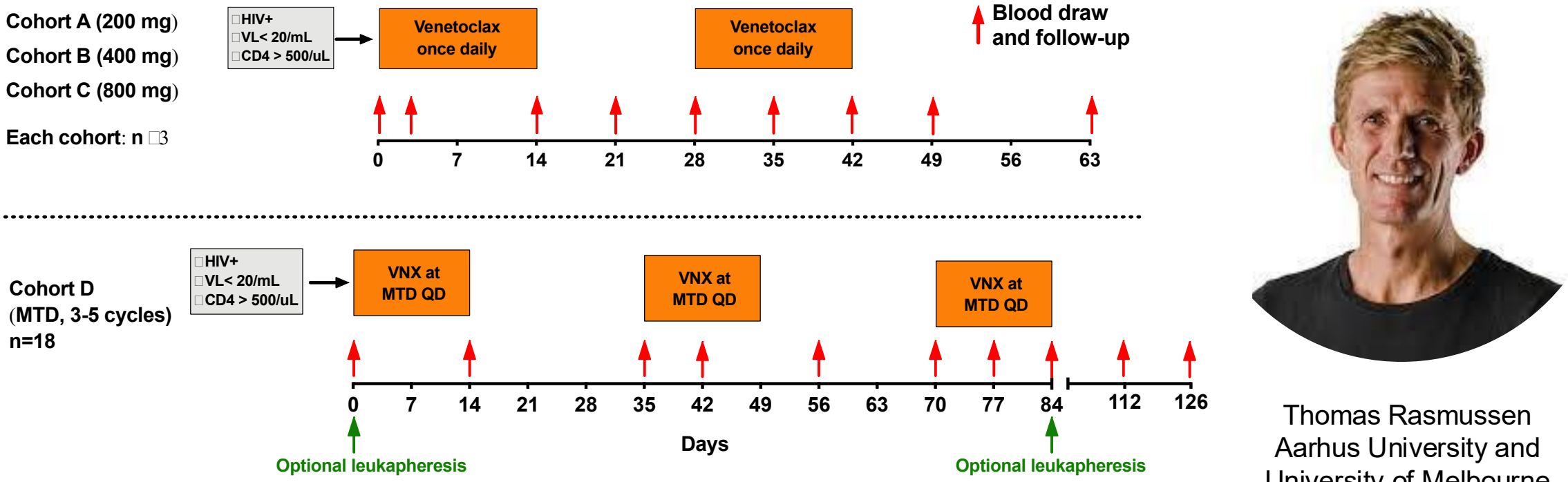


BMF - BCL2 modifying factor
BCL2L11 = BIM

Implications of these findings is that **combination approaches** may be needed eg BCL2 and MCL-1 inhibition

Arandjelovic et al Cell Reports Medicine 2023; Paiardini et al Res Sq 2025

The AMBER study: dose finding study of venetoclax in PWH



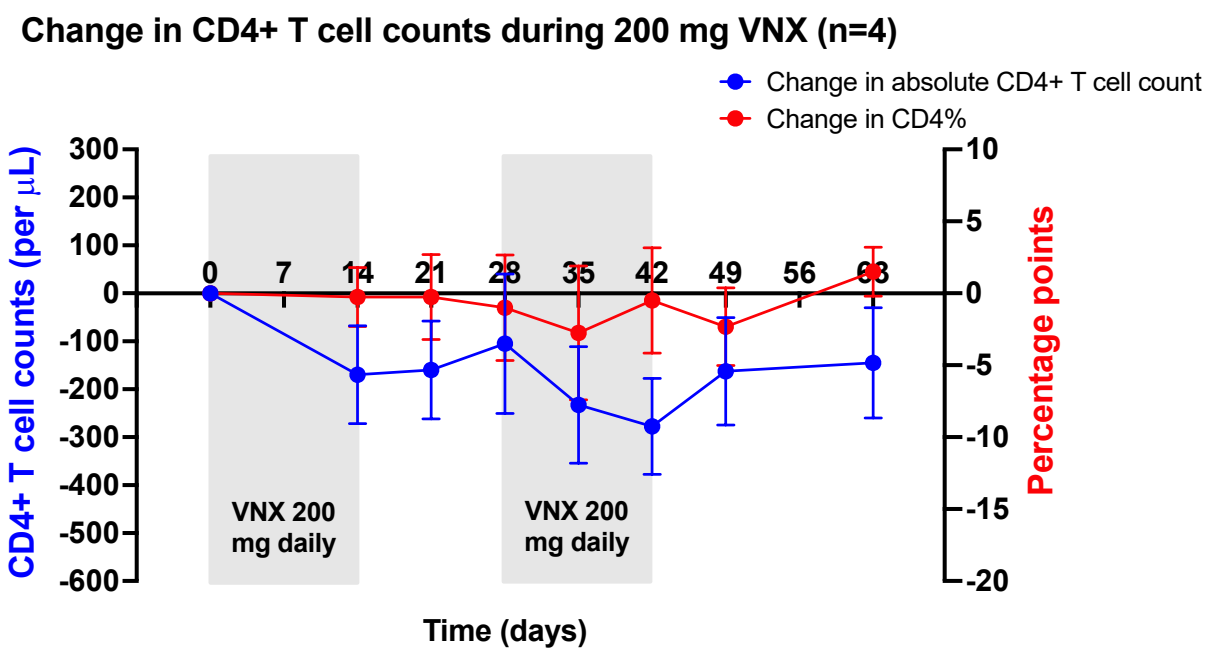
Thomas Rasmussen
Aarhus University and
University of Melbourne

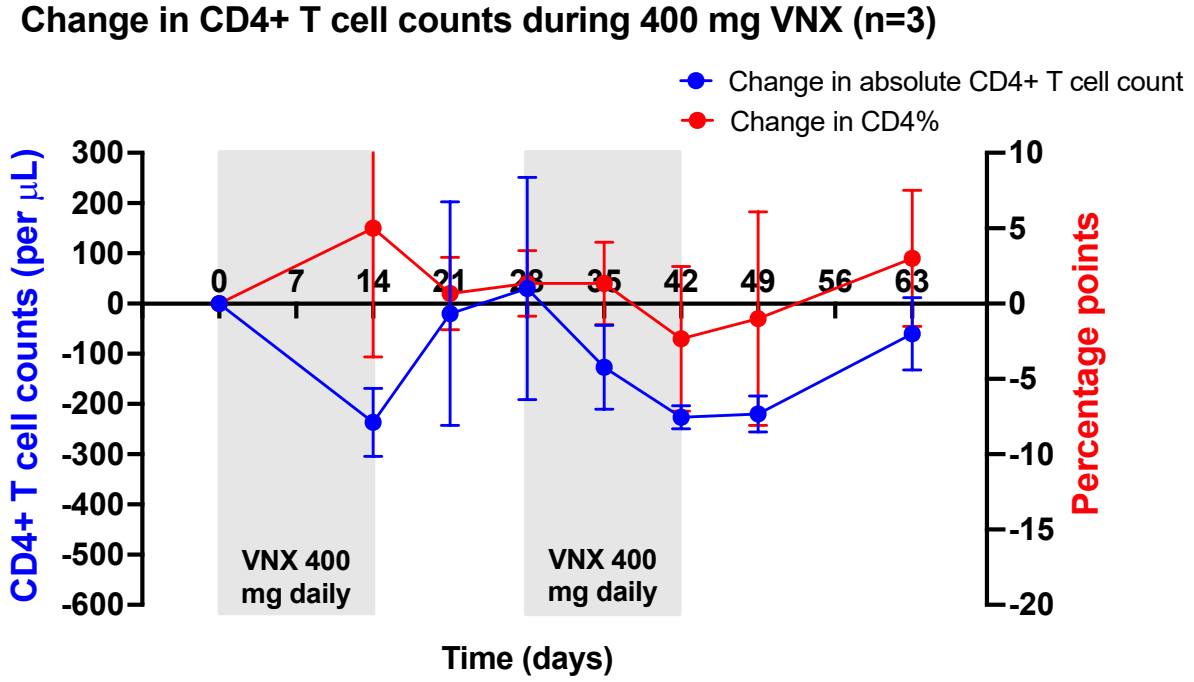
Cohorts A-C: dose escalation complete (Aarhus)

Cohort D: Three 14 day courses of MTD Venetoclax with 3 week recovery between courses (Aarhus/Melbourne)

- **Primary endpoint:** Safety
- **Key secondary endpoints:** reservoir size and transcriptional activity

Venetoclax also reduces total CD4+ T-cells, at least transiently

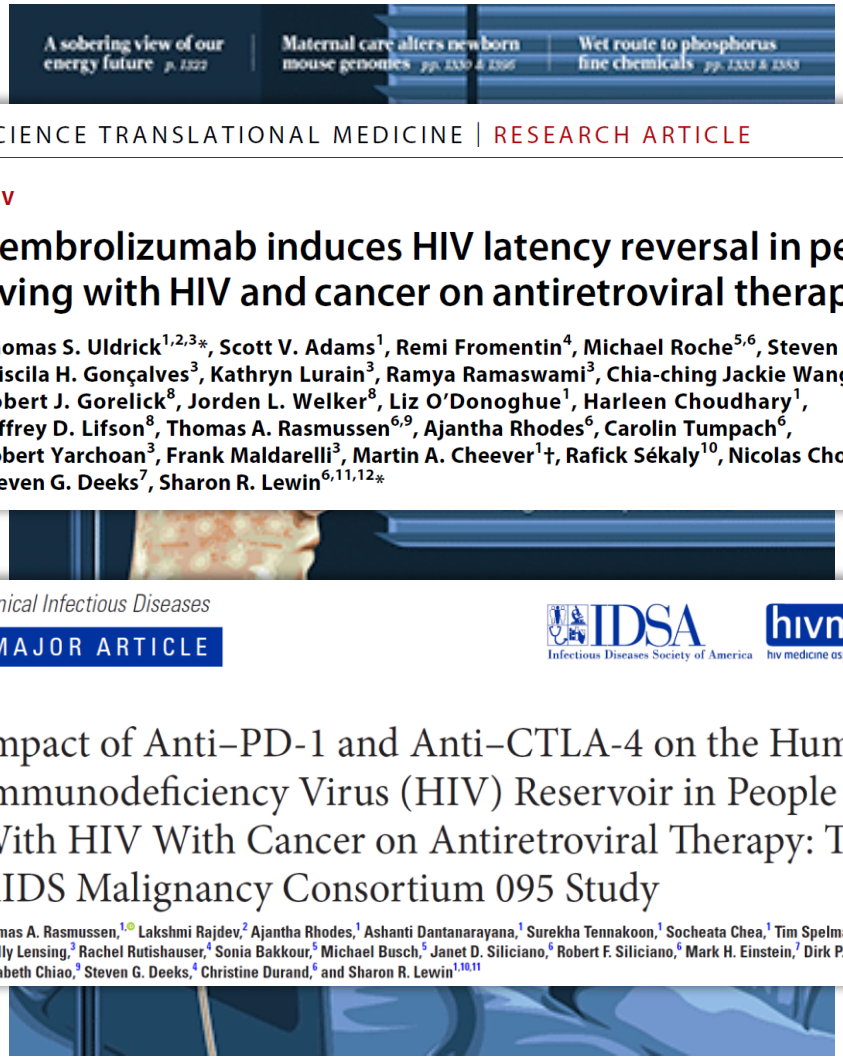




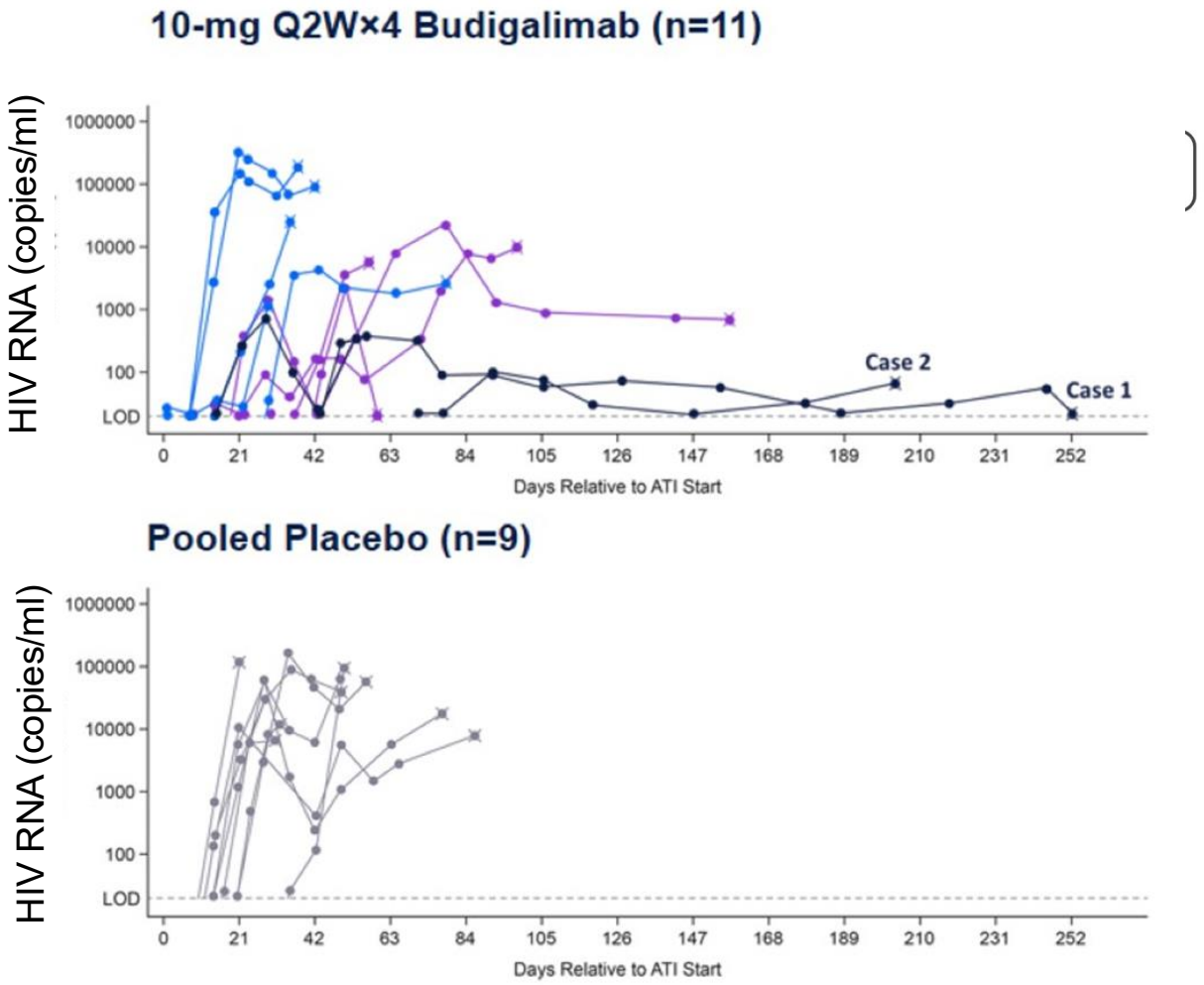
- Similar changes observed with CD8+ T-cells
- Clinical trial has nominated a 50% reduction of CD4 and also for CD4>350 cells/ul
- Acceptability of a reduction of absolute CD4 and % CD4 unclear

Increase immune control: immune checkpoint blockade:

Anti-PD1 can also induce HIV remission: in a subset of participants

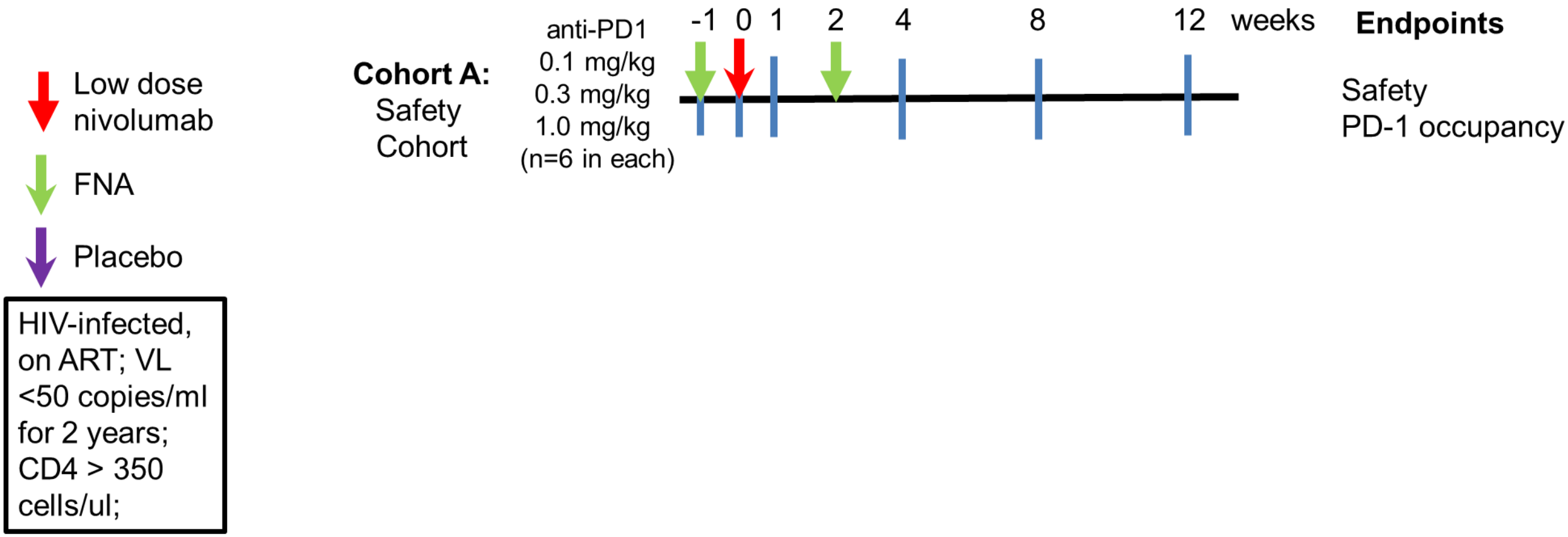


PWH on ART without cancer



Uldrick et al., Science Transl Med 2022; Rasmussen Clin Infect Dis 2022; Routy EACS 2023; King and Lewin, Immunological Reviews 2024

NIVO LD: A two-step dose finding phase 1b trial of low dose anti-PD1 (nivolumab) in HIV (NCT05187429)



- **Cohort A fully enrolled**. No safety concerns.
- **High receptor occupancy (~70%)** in LN and blood and more prolonged with 1mg/kg (up to 17 weeks)

Anti PD1 considerations

- **Safety, safety, safety**
  - Two prior studies of anti-PD1 in PWH on ART were terminated early due to grade 3 immune related AEs, not observed with low dose budigalimab or nivolumab
  - Unclear if PWH have increased sensitivity to immune related Aes, potentially related to immune dysregulation?

- **Viral set point study requires an ATI**
  - Macaque studies demonstrated the need for antigen to be present to enhance effects of anti-PD1

- **Unlikely to work on its own**
  - Combination of anti-PD1 with a vaccine, broadly neutralising antibody or another immune checkpoint blocker will be needed

- **ATI cure trial in new sites such as Singapore are needed, but have challenges**
  - Extensive community engagement required
  - Different policies on PREP for partners
  - Different clade ie AE requiring development of new assays including RNA, IPDA and ICS

Summary and implications

- The optimal design of clinical trials for cure will depend on the agent being tested. Single agent interventions must be done to **ensure safety**, **before efficacy** can be demonstrated in combination studies. Very slow process!

- The impact of interventions that target reservoir size eg LRAs and pro-apoptotic drugs require both **qualitative and quantitative assessments** of the reservoir to understand activity e.g., integration site differences, expanded clones etc

- Detailed understanding of **off target effects** such as impacts on CD8+ T-cell function or tissue reservoirs such as the CNS should be incorporated into the study design

- New clinical trial sites in **Africa, Asia and Latin America** are needed but this brings additional challenges, especially in relation to reservoir quantification

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Australian Government
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NIH National Institute of Allergy and Infectious Diseases

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