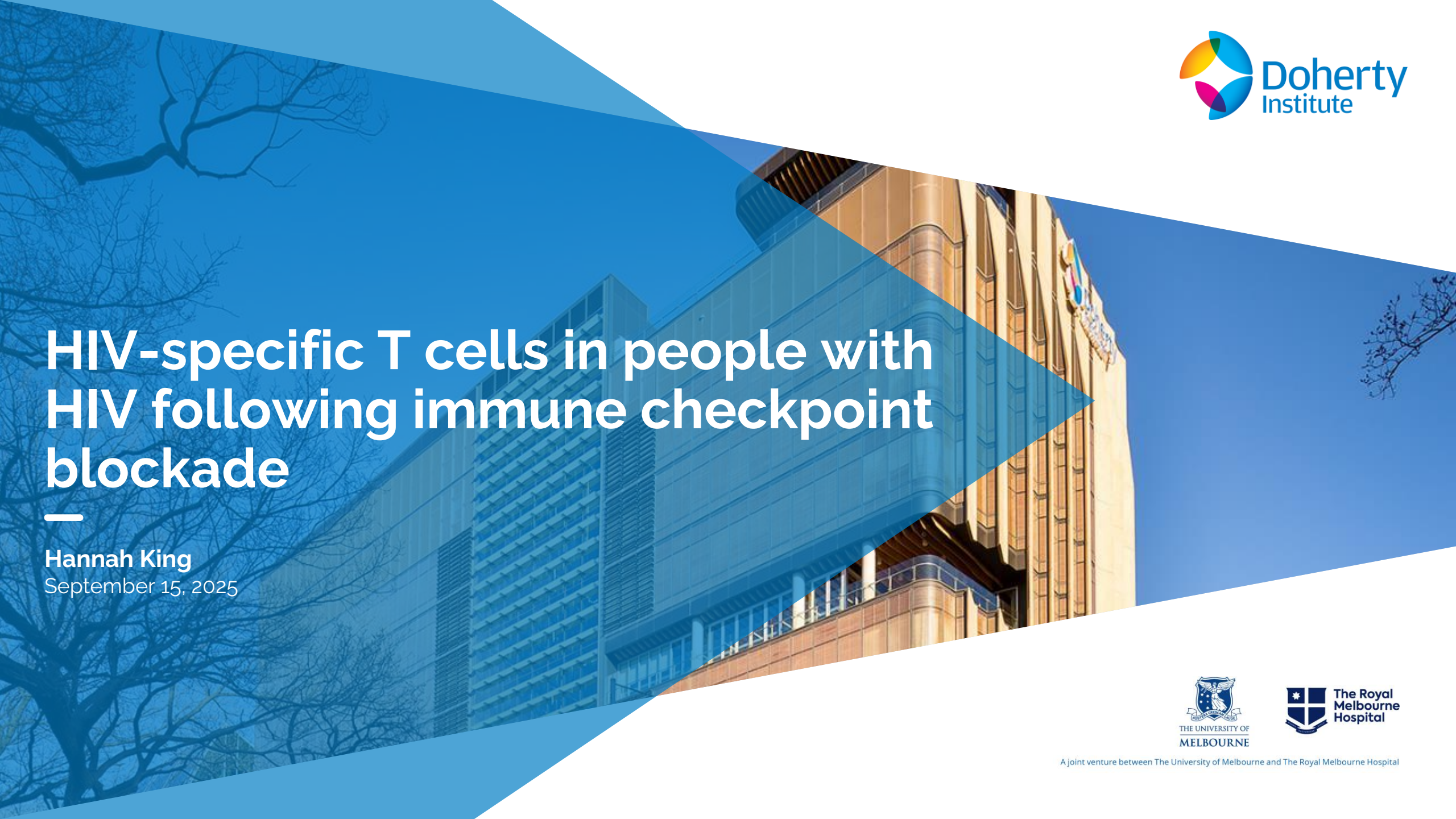


HIV-specific T cells in people with HIV following immune checkpoint blockade

Hannah King

September 15, 2025

Doherty Institute

THE UNIVERSITY OF MELBOURNE

The Royal Melbourne Hospital

A joint venture between The University of Melbourne and The Royal Melbourne Hospital

Disclosure of Interest

I have no disclosures to report

ART effectively suppresses viral replication, but cannot eliminate latently infected cells

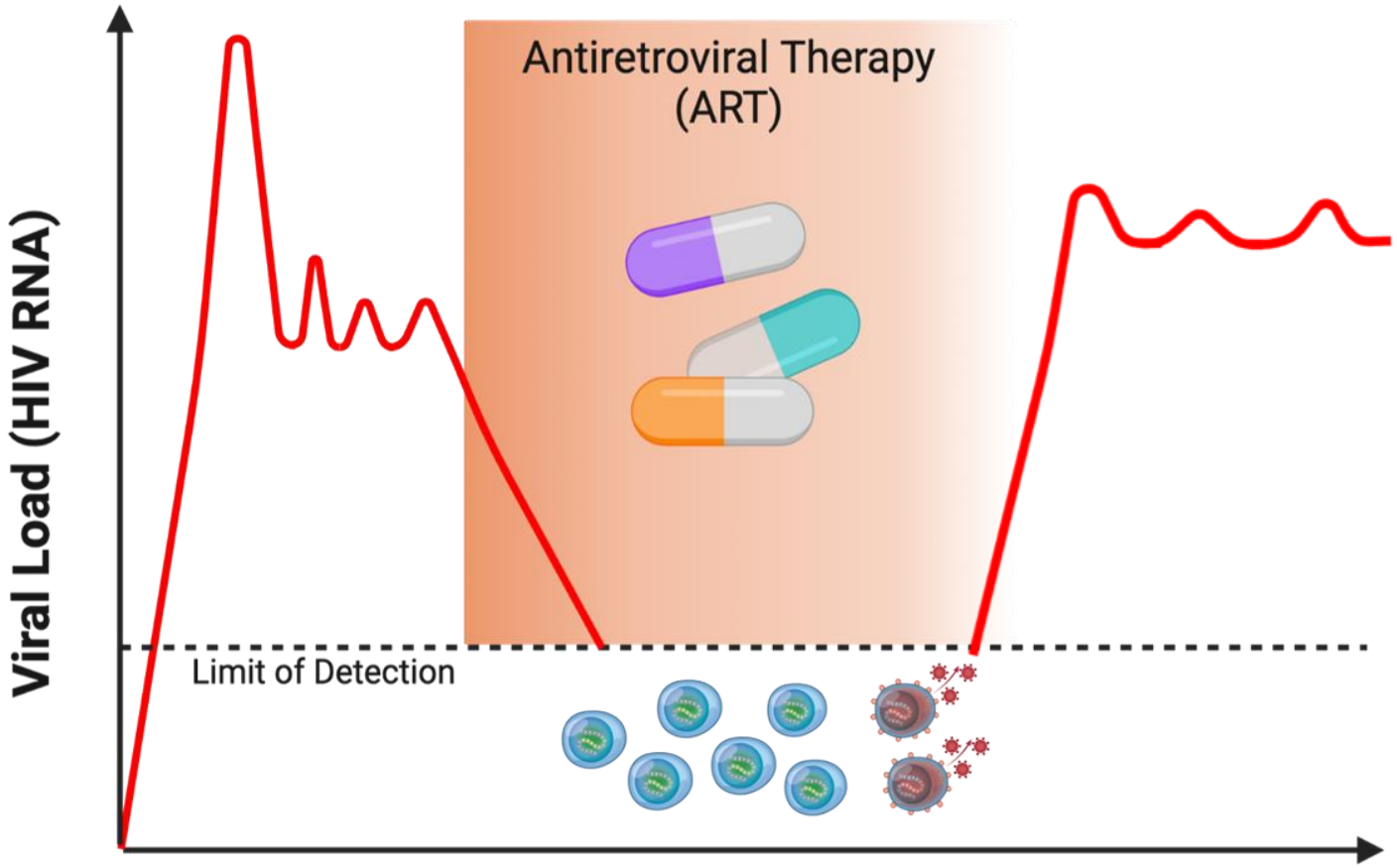
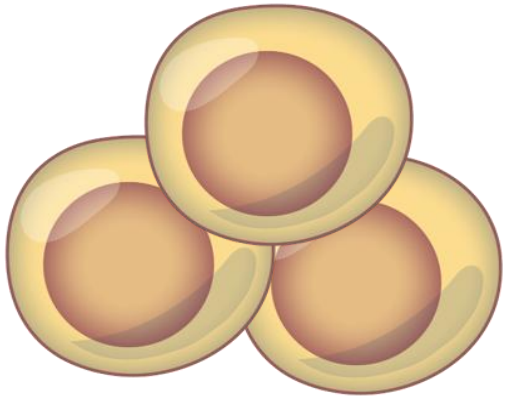


Figure courtesy of Michael Roche

CD8+ T cells: Key players in anti-HIV immunity

- Elite controllers
  - People living with HIV (PWH) who can spontaneously maintain undetectable viral loads in the absence of ART[1]

- Potent, fully functional CD8+ T cells required[1-4]
  - Enhanced expansion capacity
  - Enhanced cytotoxicity
  - Enhanced polyfunctionality

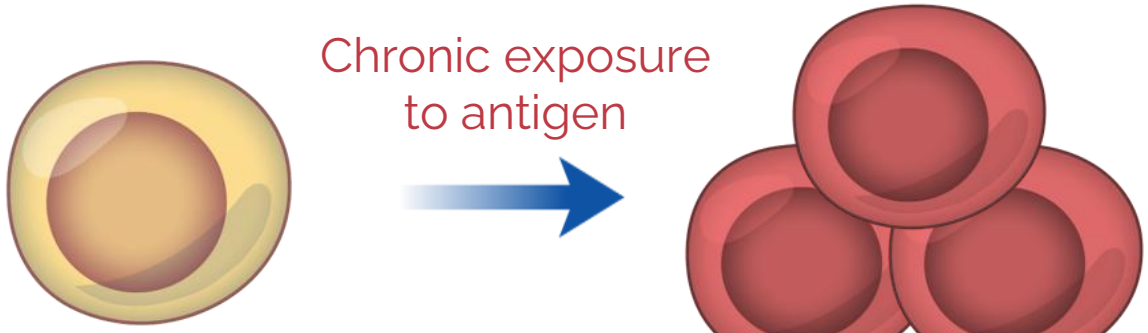


➢ **If we increase T cell function in people who do not control viremia can we induce durable control?**

[1] Migueles et al., *Nat Immunol* (2002), [2] Shasha et al., *Journal of Leukocyte Biology* (2016), [3] Betts et al., *Blood* (2006), [4] Nguyen et al., *Sci Transl Med* (2019)

Immune exhaustion – a barrier to overcome

- Chronic HIV exposure in PWH leads to CD8+ T cell exhaustion[1]
- Exhausted CD8+ T cells have impaired ability to control HIV infection[2]



Effector CD8+ T cell

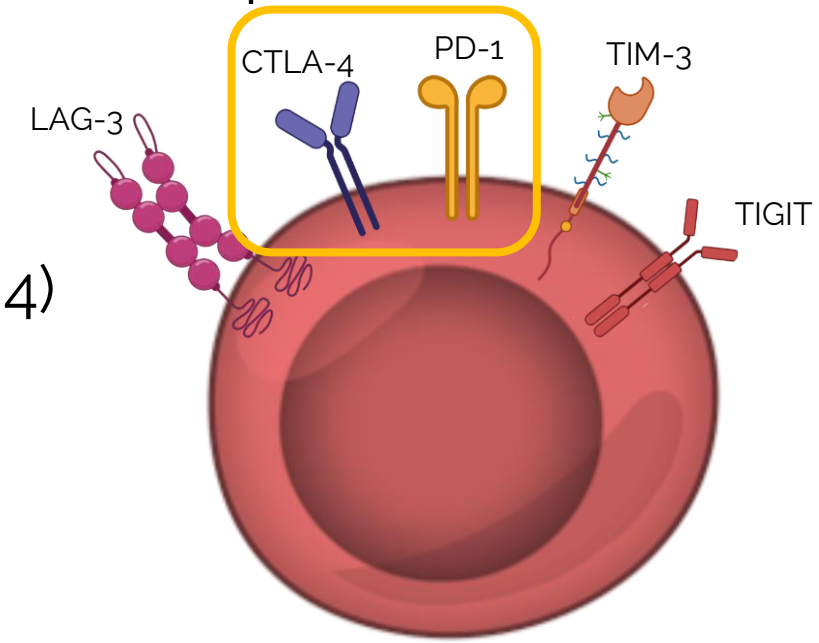
Exhausted CD8+ T cells[2]

- Impaired cytotoxicity
- Reduced cytokine production
- Reduced proliferative capacity

[1] Wallace et al., *Sci Rep* (2022), [2] Trautmann et al., *Nat Med* (2006)

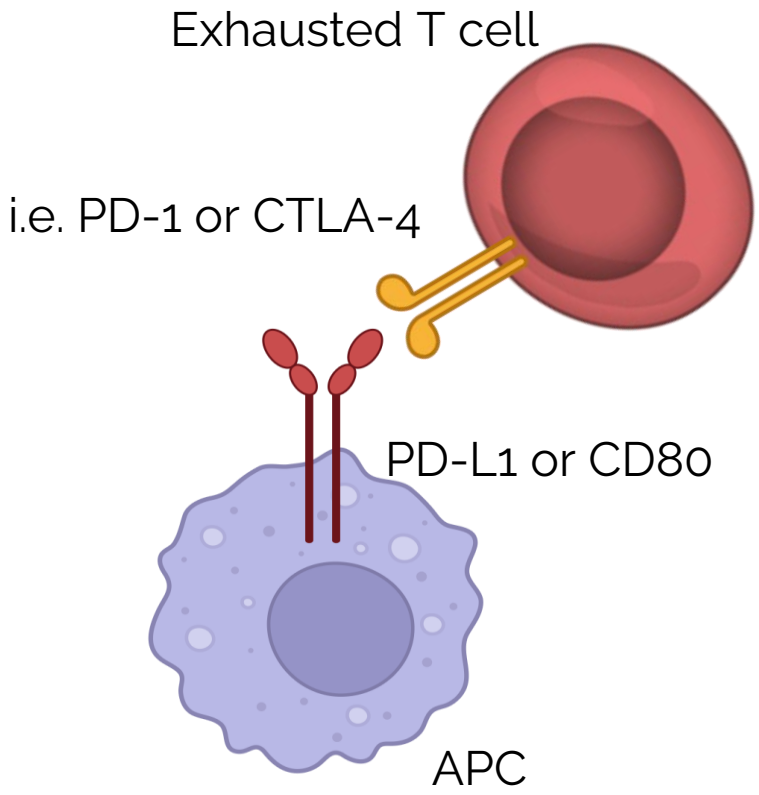
Immune exhaustion – a barrier to overcome

- Chronic HIV exposure in PWH leads to CD8+ T cell exhaustion[1]
- Exhausted CD8+ T cells have impaired ability to control HIV infection[2]
- Exhaustion is characterised by upregulation of immune checkpoint molecules
- Programmed cell-death 1 (PD-1)
  - Inhibits T cell receptor (TCR) signalling
- Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4)
  - Competes with CD28 to inhibit costimulatory signalling



[1] Wallace et al., *Sci Rep* (2022), [2] Trautmann et al., *Nat Med* (2006)

Immune checkpoint blockade can restore T cell function



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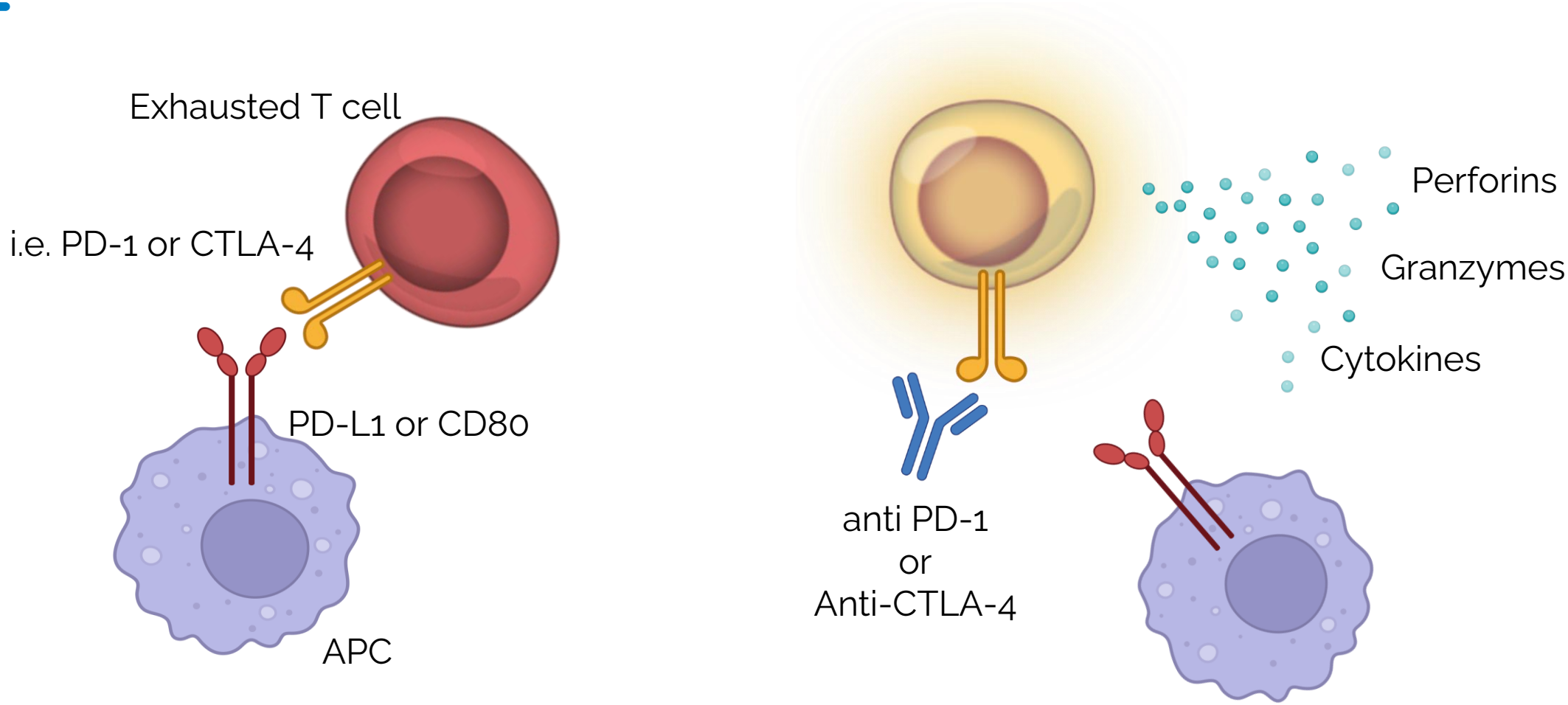
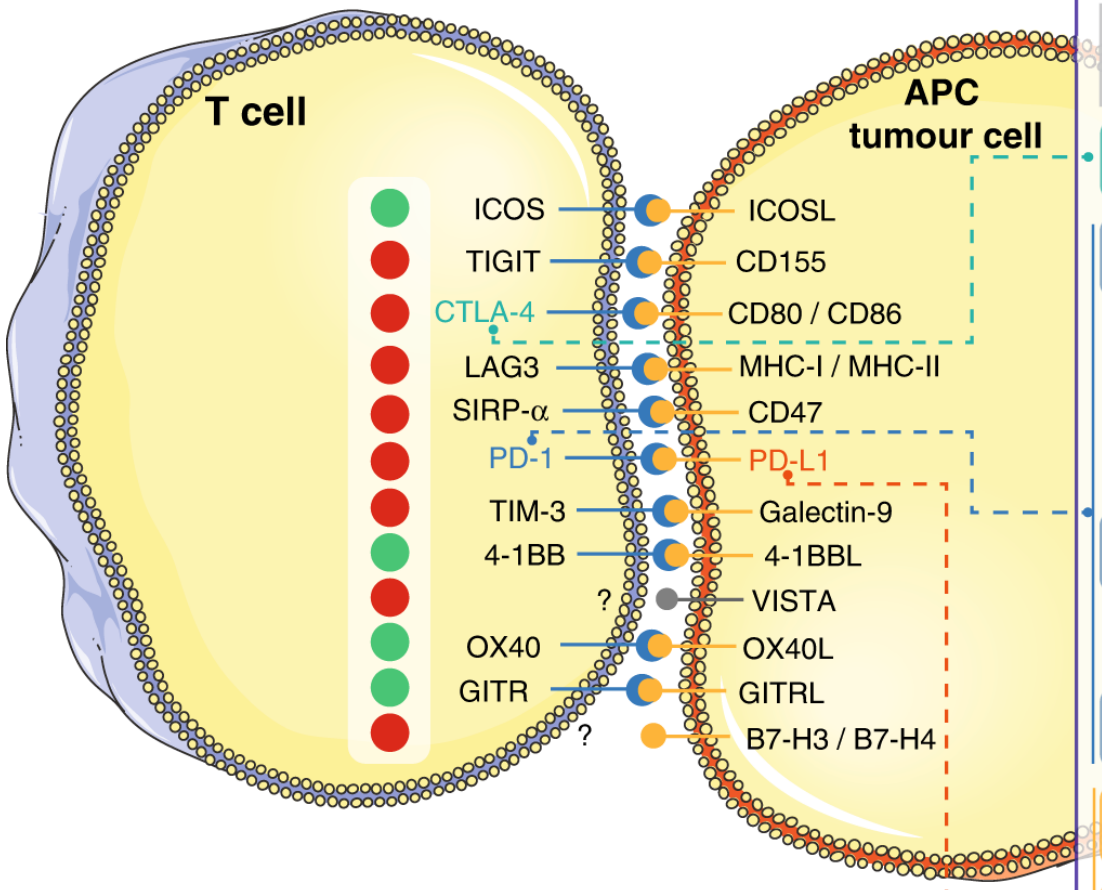


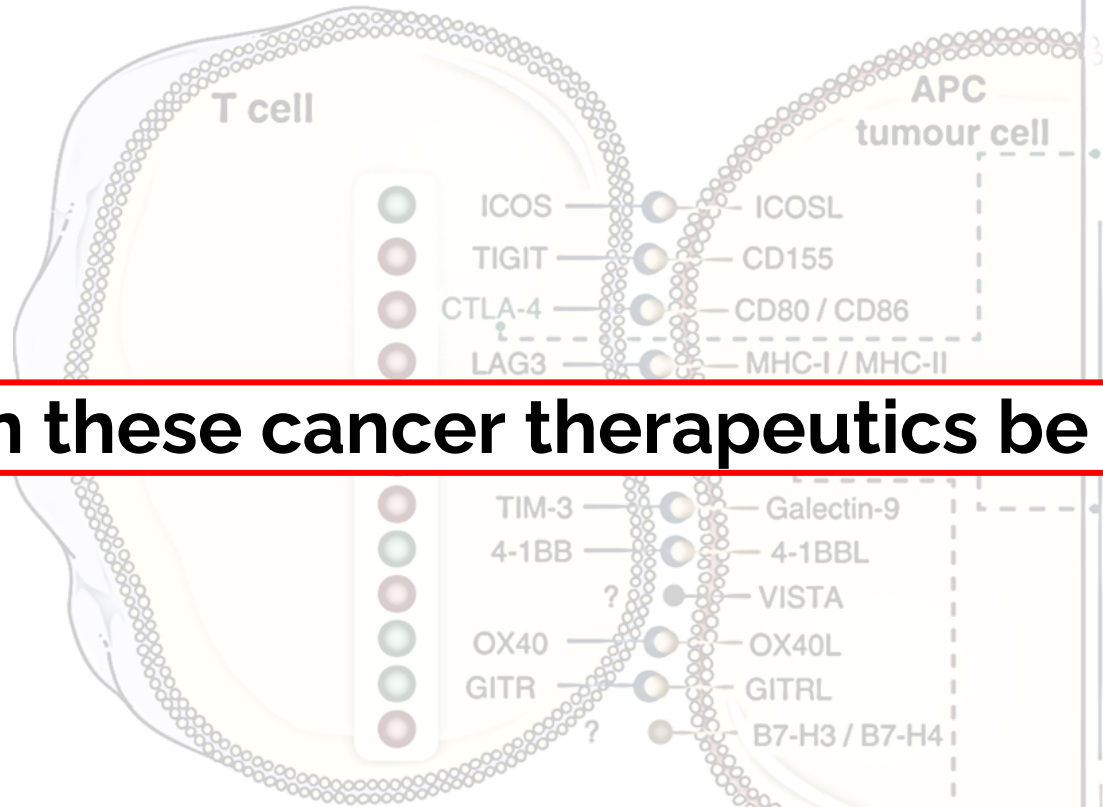
Immune checkpoint blockade is an effective cancer therapeutic



FDA-approved molecule	Year of 1st approval	Cancer type
Ipilimumab	2011	*Melanoma*, *RCC, Metastatic colorectal cancer, HCC, NSCLC, Malignant Pleural Mesothelioma*
Pembrolizumab	2014	Melanoma, *NSCLC*, Bladder cancer, Hodgkin's lymphoma, *HNSCC*, *RCC*, Merkel cell carcinoma, MSI-high cancer, Gastric cancer, HCC, Cervical cancer, PMBCL, *Endometrial Carcinoma* , *Esophagus Cancer* , Colorectal cancer, Cutaneous Squamous-cell carcinoma, *Breast cancer* , TMB-high cancers
Nivolumab	2014	*Melanoma*, *NSCLC*, *RCC*, Bladder cancer, Hodgkin's lymphoma, HNSCC, *Colorectal Cancer*, *Hepato-cellular carcinoma*, SCLC, Esophagus cancer, *Malignant Pleural Mesothelioma*
Cemiplimab	2018	Cutaneous squamous-cell carcinoma, NSCLC, Basal cell carcinoma
Atezolizumab	2016	*Melanoma, NSCLC*, Bladder cancer, *SCLC*, *Hepatocellular carcinoma* , *Breast cancer*
Avelumab	2017	Merkel cell carcinoma, Bladder cancer, *RCC*
Durvalumab	2017	NSCLC, Bladder cancer, *SCLC*

[1] Pilard et al., *British Journal of Cancer* (2021)

Immune checkpoint blockade is an effective cancer therapeutic



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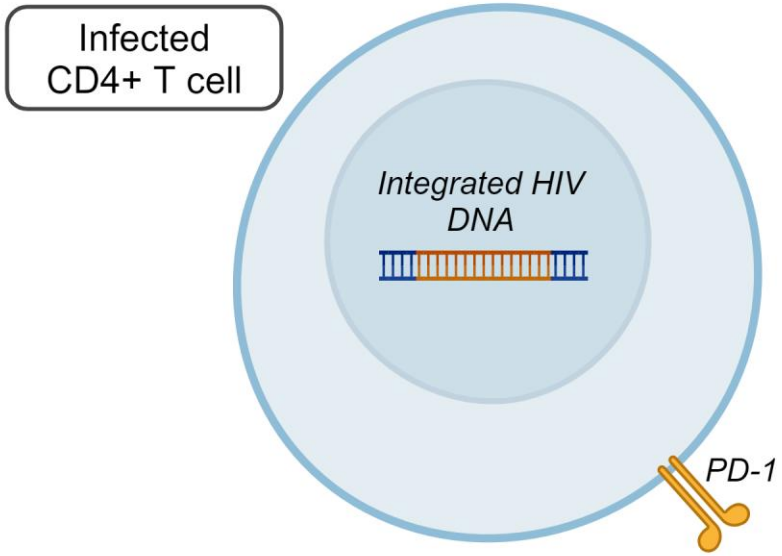
Durvalumab	2017	NSCLC, Bladder cancer, *SCLC*

→Can these cancer therapeutics be used for durable control of HIV?

[1] Pilard et al., *British Journal of Cancer* (2021)

PD-1 blockade exerts dual effects in PWH



- HIV latency is enriched in cells expressing PD-1
  - Fromentin et al, PLOS Path, 2016
  - Khoury et al, JID, 2017
  - Evans et al, AIDS, 2018
  - Rasmussen et al, Cell Rep Med, 2022

King & Lewin, *Immunological Reviews* (2024)

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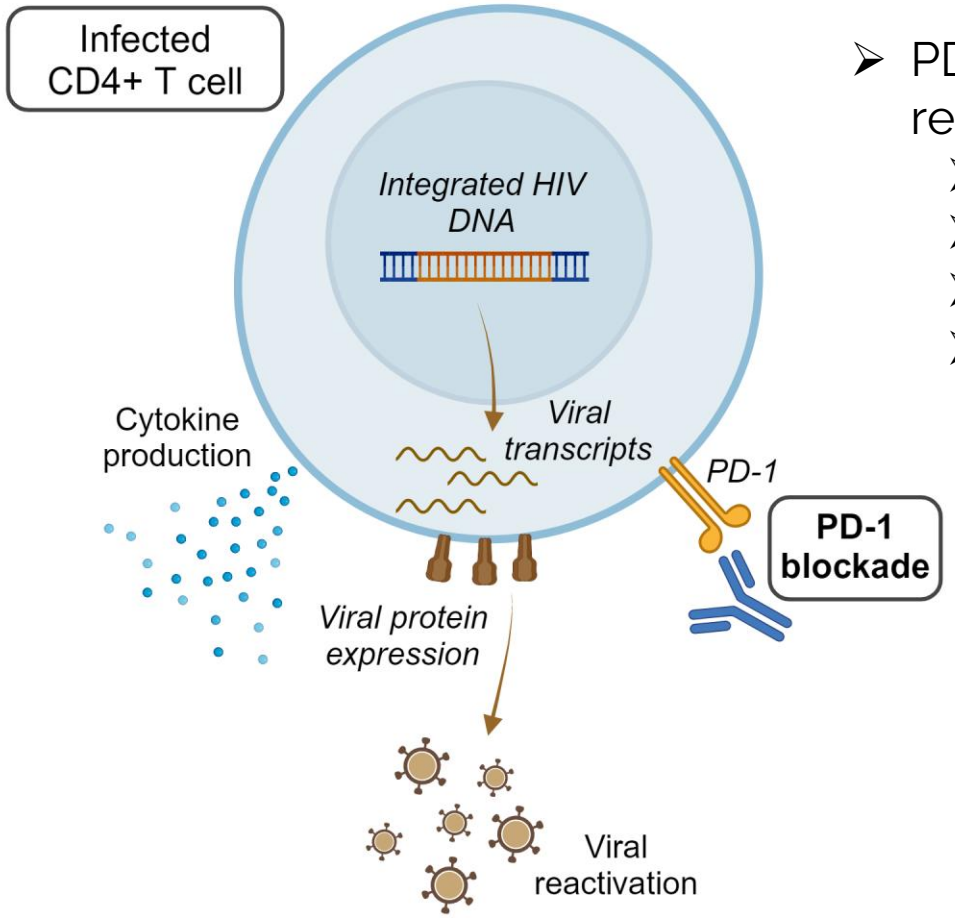
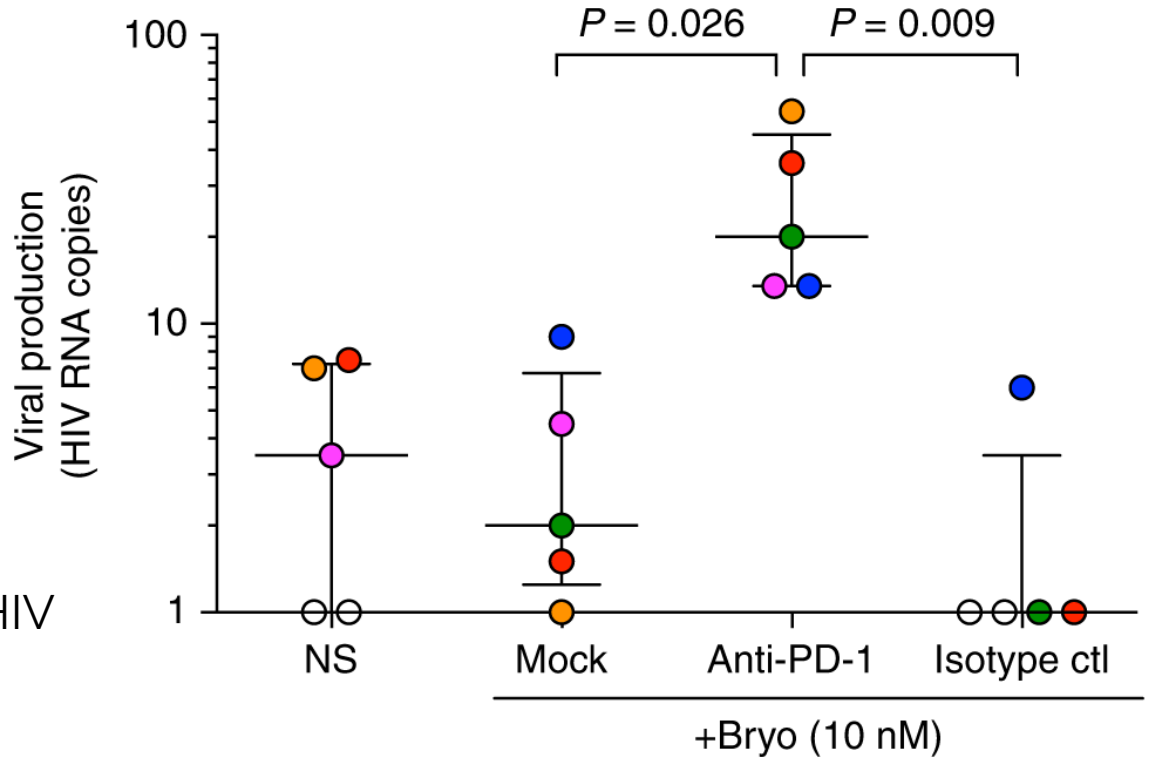


- PD-1 checkpoint blockade induces latency reversal
  - Fromentin et al, Nat Comms, 2019
  - Van der Sluis et al, J Immunol, 2020
  - Rasmussen et al, CID, 2021
  - Uldrick et al, STM, 2022

King & Lewin, *Immunological Reviews* (2024)

Immune checkpoint blockade in HIV – *ex vivo*

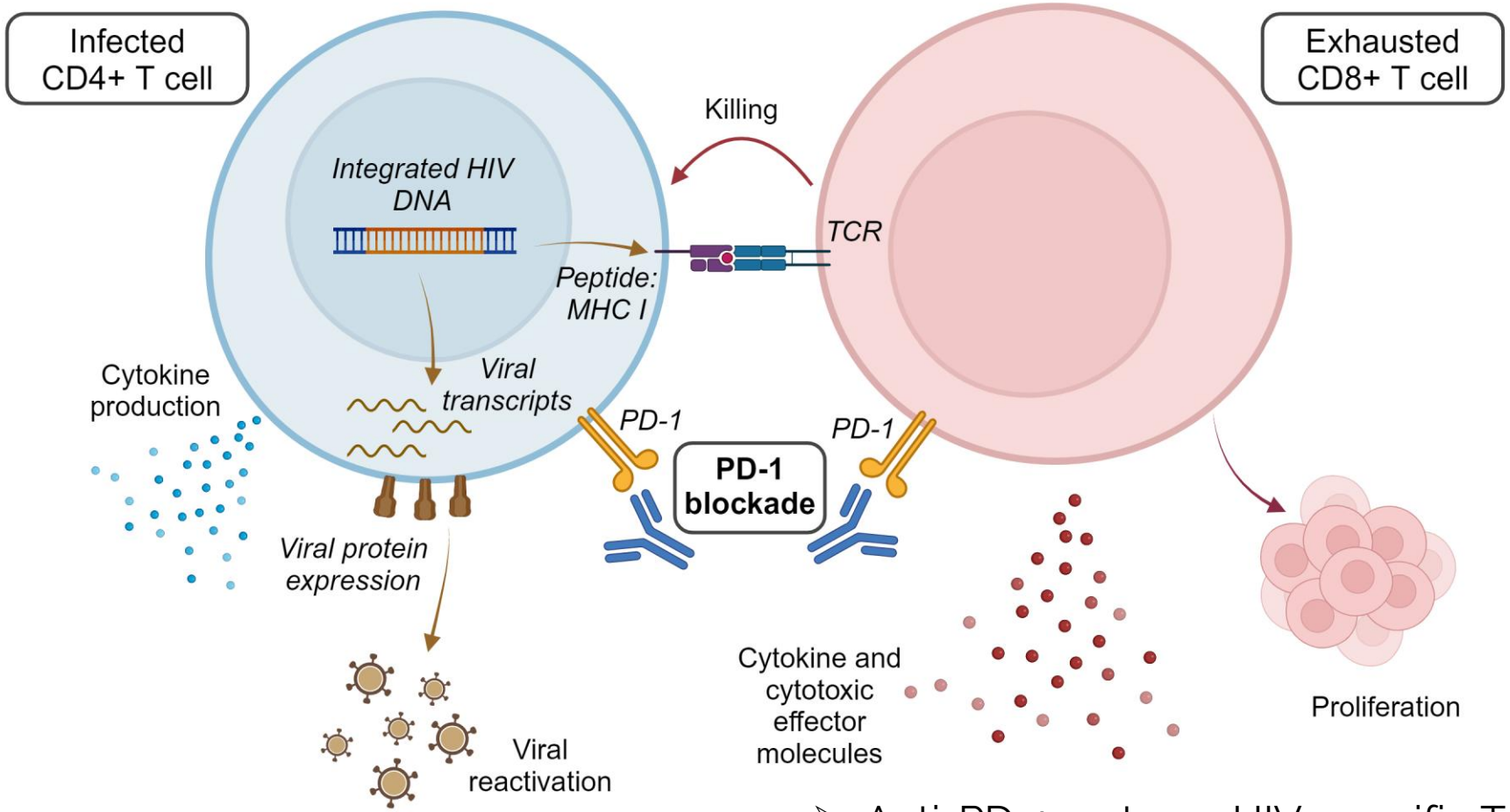
Anti-PD-1 can reverse latency in cells from PWH *ex vivo*[1,2]



Fromentin, Rémi et al. "PD-1 blockade potentiates HIV latency reversal ex vivo in CD4+ T cells from ART-suppressed individuals." Nat Commun (2019)[1]

[1] Fromentin et al., *Nat Commun* (2019), [2] Van der Sluis et al., *J Virol* (2020)

PD-1 blockade exerts dual effects in PWH

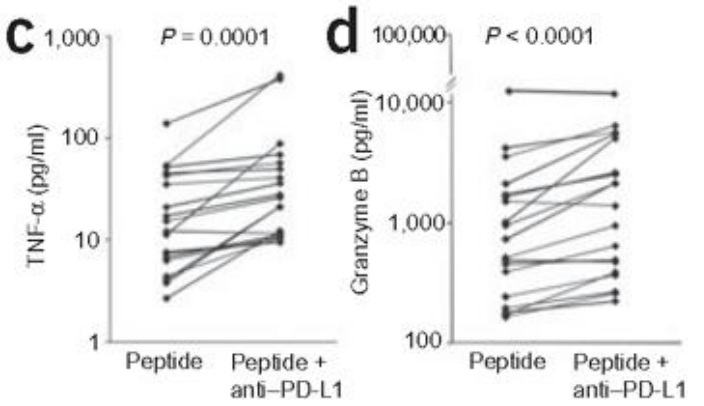


- Anti-PD-1 restores HIV-specific T-cell function
  - Chiu et al, J Immunol, 2022
  - Lau et al, AIDS, 2022

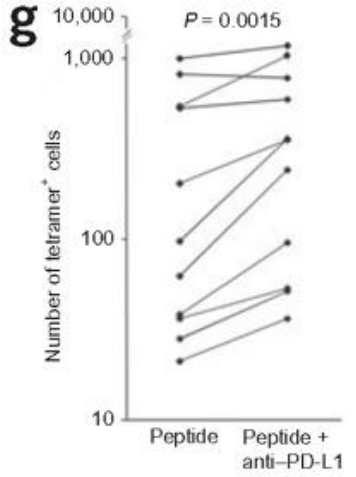
King & Lewin, *Immunological Reviews* (2024)

Immune checkpoint blockade in HIV – *ex vivo*

Ex vivo, blockade of PD-1 and CTLA-4 enhances the functionality and proliferation of HIV-specific T cells[1]



↑ Functionality



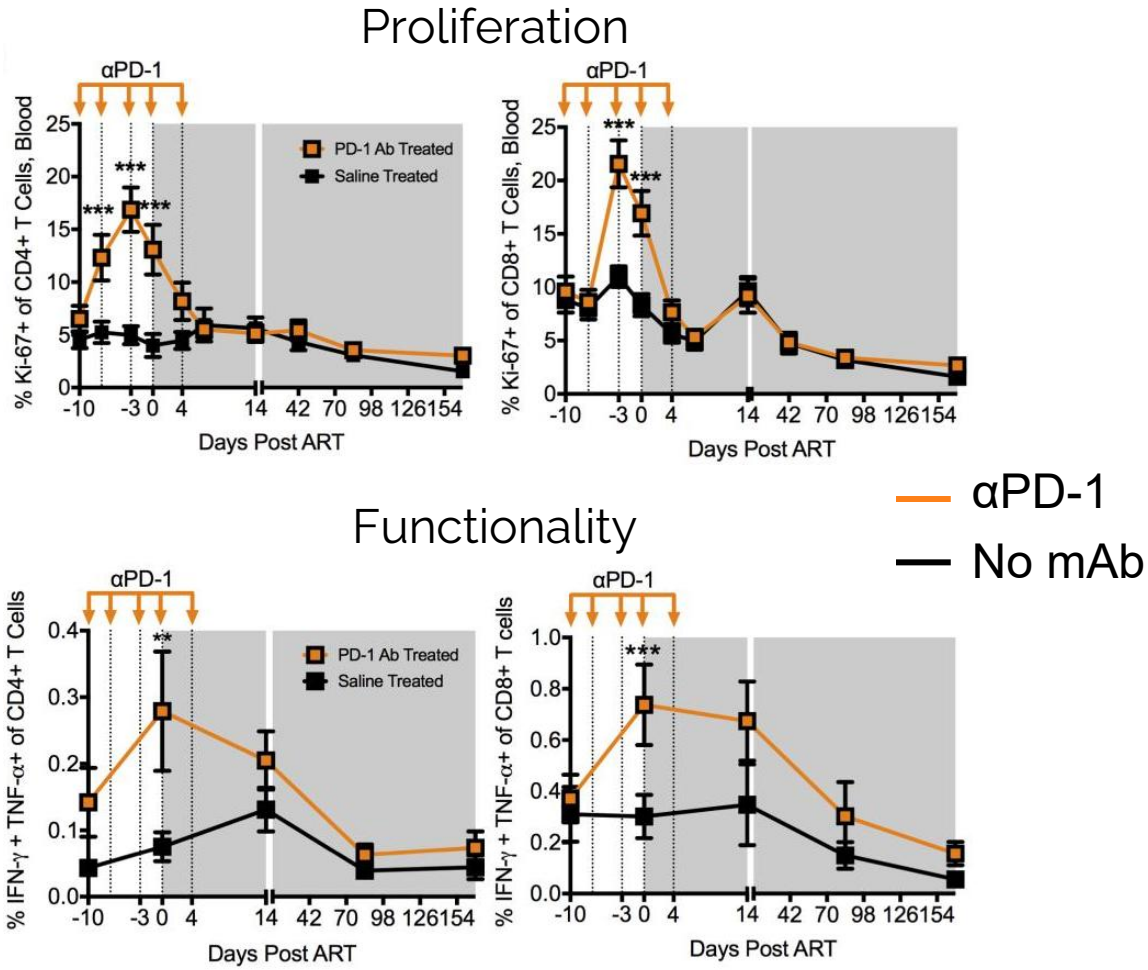
↑ Proliferation

Trautmann, Lydie et al. "Upregulation of PD-1 expression on HIV-specific CD8+ T cells leads to reversible immune dysfunction." *Nat Med* (2006)[2]

[1] King & Lewin, *Immunological Reviews* (2024), [2] Trautmann et al., *Nat Med* (2006)

Immune checkpoint blockade in HIV - preclinical

- ***In vivo* in pre-clinical models, PD-1 blockade can contribute to viral control and enhance HIV-specific T cell responses when administered during:**
- Chronic infection[1]
- Early ART[2,3]
- Surrounding analytical treatment interruption (ATI)[4,5]



Mylvaganam, Geetha H et al. "Combination anti-PD-1 and antiretroviral therapy provides therapeutic benefit against SIV." *JCI insight* (2018)[2]

[1] Velu et al., Nature (2009), [2] Mylvaganam et al., JCI Insight (2018), [3] Rahman et al., Sci Immunol (2021), [4] Okoye et al., CROI (2020), [5] Velu et al., PNAS (2022)

Immune checkpoint blockade in HIV - preclinical

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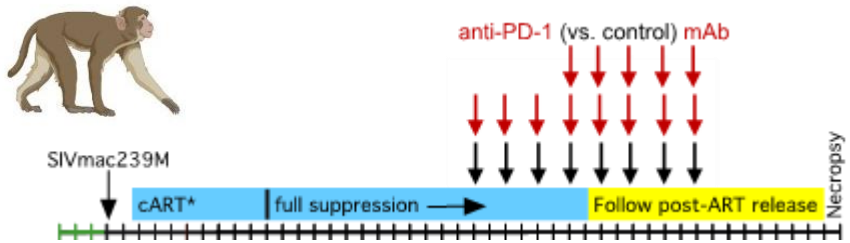
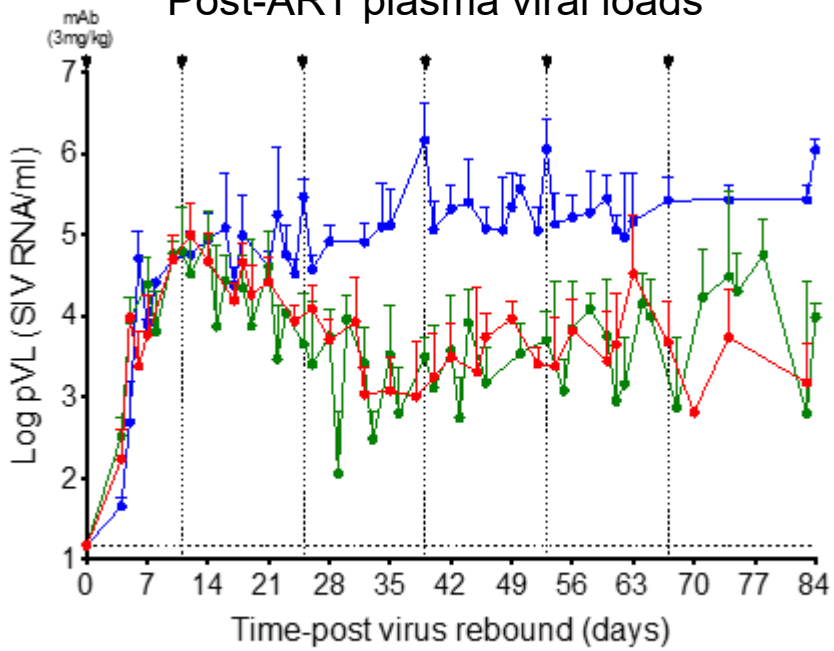
- Surrounding analytical treatment interruption (ATI)[4,5]

- **When αPD-1 is given to ART-suppressed macaques, no impacts on reservoir or HIV-specific T cells are observed[6]**



Late PD-1 (n=10)
Early PD-1 (n=10)
Controls (n=10)

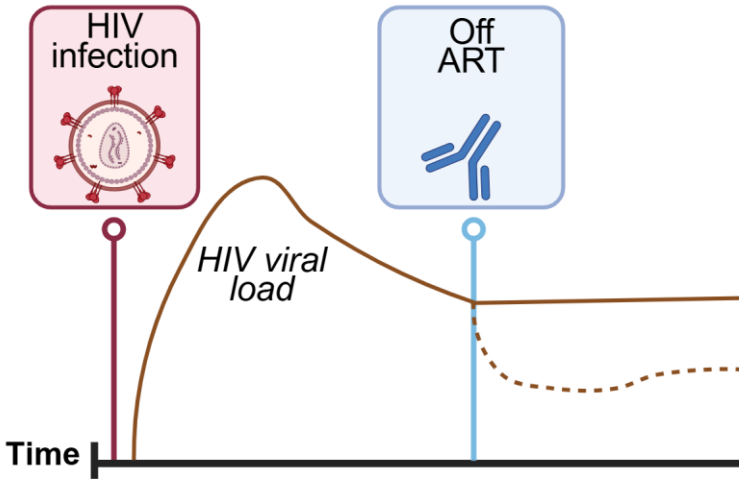
Post-ART plasma viral loads



[1] Velu et al., Nature (2009), [2] Mylvaganam et al., JCI Insight (2018), [3] Rahman et al., Sci Immunol (2021), [4] Okoye et al., CROI (2020), [5] Velu et al., PNAS (2022), [6] Bekerman et al., Antimicrob Agents Chemother (2019)

Figure courtesy of Afam Okoye[4]

The timing of immune checkpoint blockade is crucial



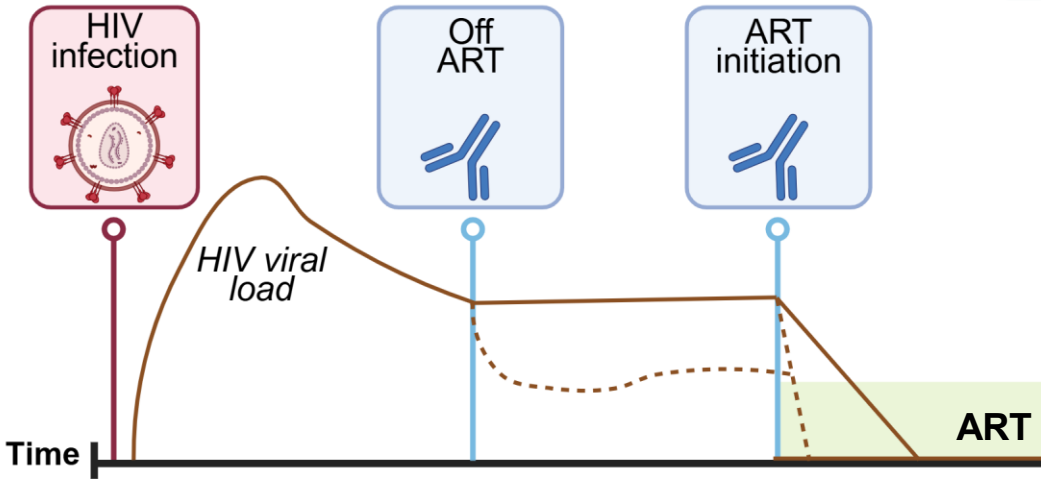
Antigen:	**++**
Immune stimulus:	**+**
HIV RNA:	**↓**
Time to viral rebound:	**NR**
Setpoint post-ATI:	**NR**

without intervention

with intervention?

King & Lewin, *Immunological Reviews* (2024)

The timing of immune checkpoint blockade is crucial



Antigen:	**++**	**++**
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without intervention

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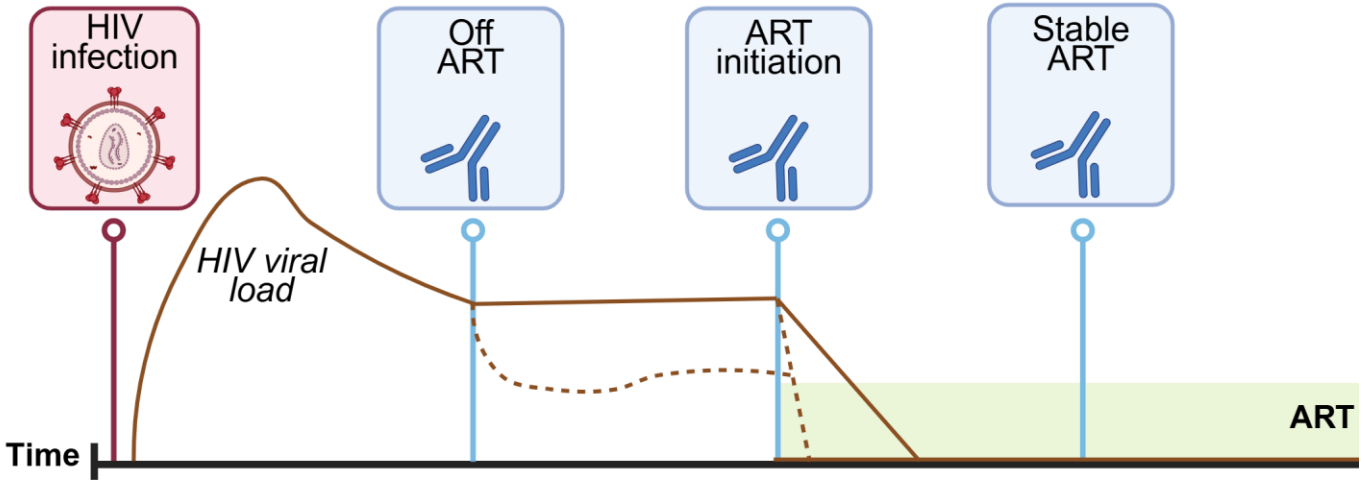

Antigen:	**++**	**++**	**+/-**
Immune stimulus:	**+**	**+**	**+/-**
HIV RNA:	**↓**	**↓**	**↑**
Time to viral rebound:	**NR**	**↑**	**↔**
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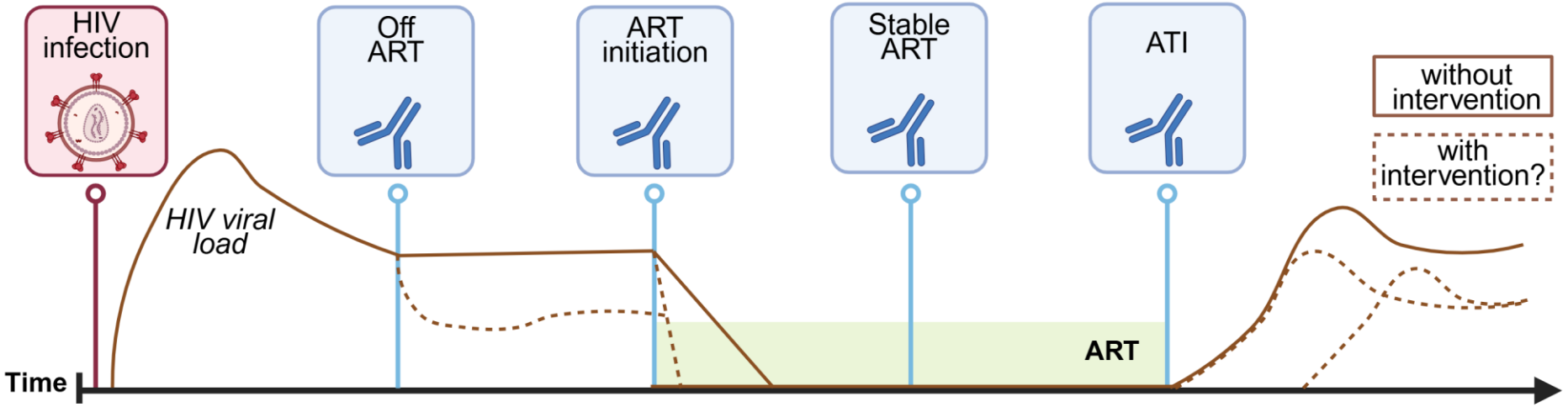


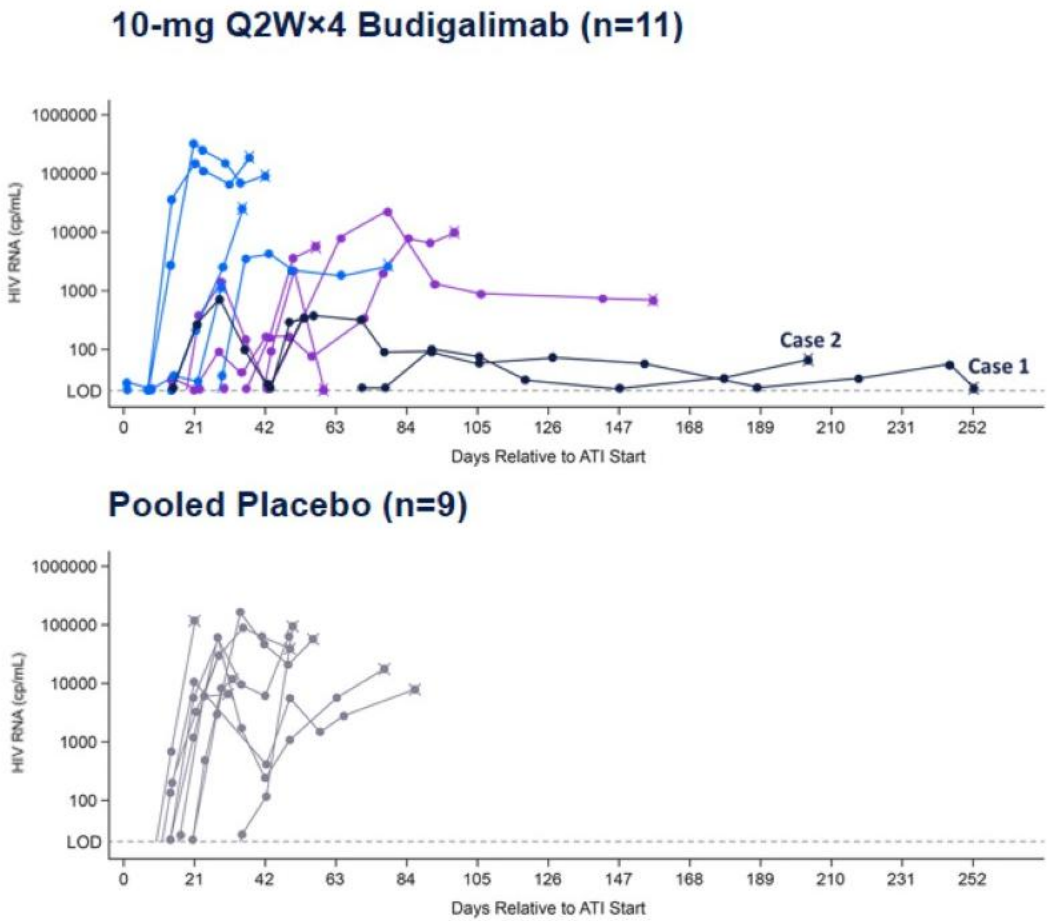
Antigen:	++	++	+/-	+
Immune stimulus:	+	+	+/-	+
HIV RNA:	↓	↓	↑	↓
Time to viral rebound:	NR	↑	↔	↔
Setpoint post-ATI:	NR	↓	↔	↓

King & Lewin, *Immunological Reviews* (2024)

Immune checkpoint blockade in HIV – clinical studies

Immune checkpoint blockade in HIV – clinical studies

- Delayed viral rebound in subset of participants receiving higher dose anti-PD-1 spanning ATI



Legend

- Case 1 and 2
- With delayed viral rebound or off-ART viral control[a]
- Without delayed viral rebound or off-ART viral control[a]
- Placebo
- Last observed data point before ART restart

Ramgopal et al., EACS, 2023 & Krishnan et al, CROI (2024)

Figure courtesy of Jean-Pierre Routy

Immune checkpoint blockade in HIV – clinical studies

- Clinical trials of immune checkpoint blockade in people with HIV have largely been small or single case reports, often not assessing immune function

Immune checkpoint blockade in HIV – clinical studies

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[1] Lavole, Lung Cancer (2021), Gay, Open Forum Infect Dis (2024), Krishnan, CROI (2024), Gay, J Infect Dis (2017)

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…in a subset of participants

→ **Outcomes are promising, but often variable**

[1] Lavole, Lung Cancer (2021), Gay, Open Forum Infect Dis (2024), Krishnan, CROI (2024), Gay, J Infect Dis (2017)

Mechanisms behind variable efficacy of immune checkpoint blockade

- In cancer, variable efficacy is associated with tumour mutational burden, tumour microenvironment and PD-L1 (PD-1 ligand) expression

- In HIV, the presence (or absence) of HIV antigen is likely important

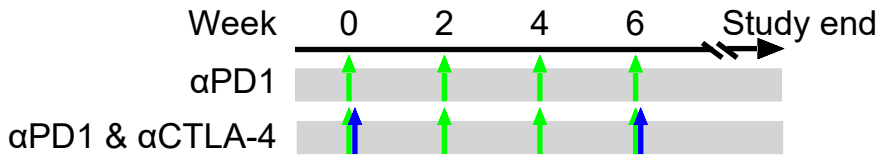
➢ **The predictors of therapeutic efficacy of checkpoint blockade in PWH remains unknown**

By characterising immune cell functionality in PWH, we aim to identify factors predictive of responsiveness to immune checkpoint blockade

Clinical trials

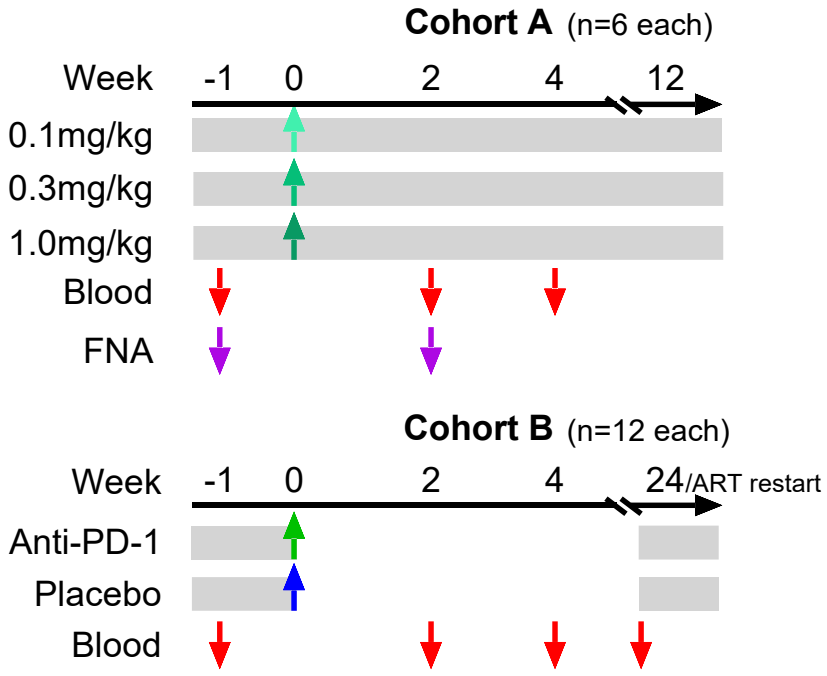
AMC095

- People with cancer with HIV receiving anti-PD-1 or anti-PD-1 & anti-CTLA-4 for cancer therapy

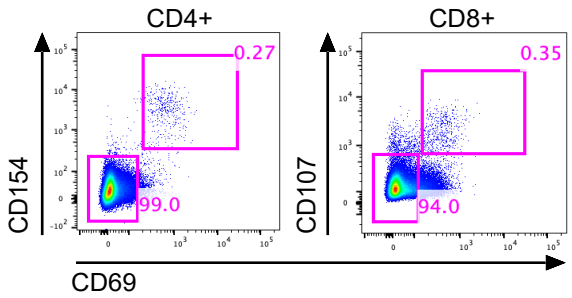


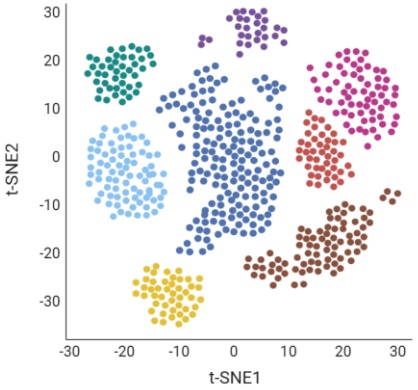
NIVO-LD

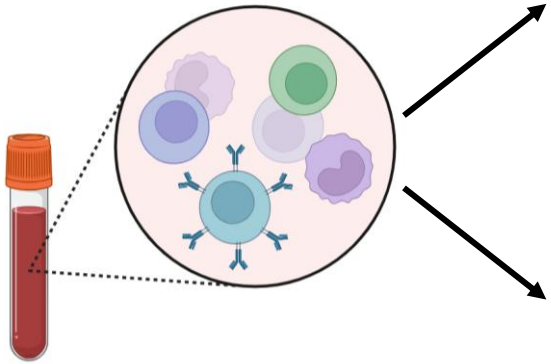
- Low-dose anti-PD-1 in people with HIV who are otherwise healthy
- Includes an ATI
- Includes lymph-node sampling



Planned analyses





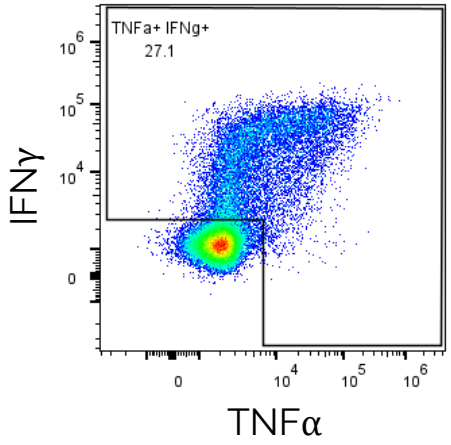


FACS

- HIV-specific CD8 & CD4
- Memory CD8 & CD4

10X scRNAseq

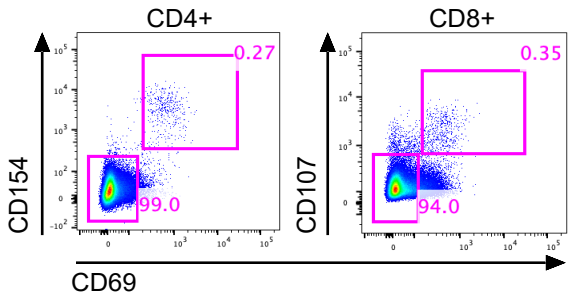
Data Analysis

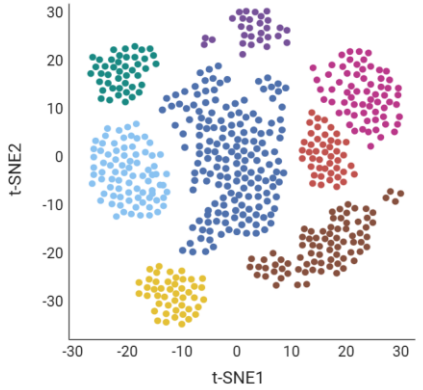


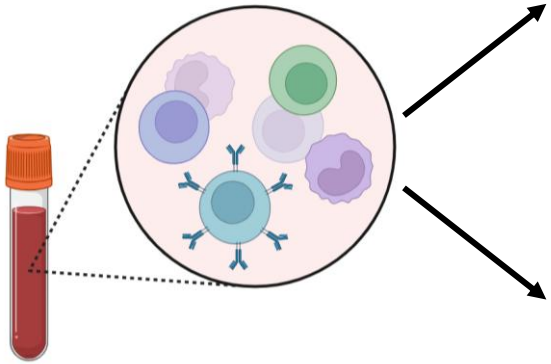
Flow cytometry

- T cell functions
- Activation of T cells, NK cells, B cells, monocytes

Planned analyses







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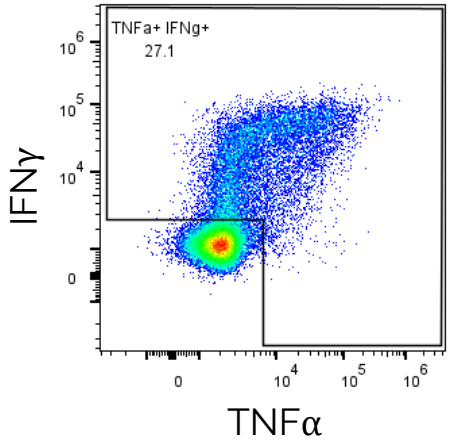


Flow cytometry

- T cell functions
- Activation of T cells, NK cells, B cells, monocytes

➢ **Compare immune characteristics between individuals who respond to immune checkpoint blockade and those who do not**

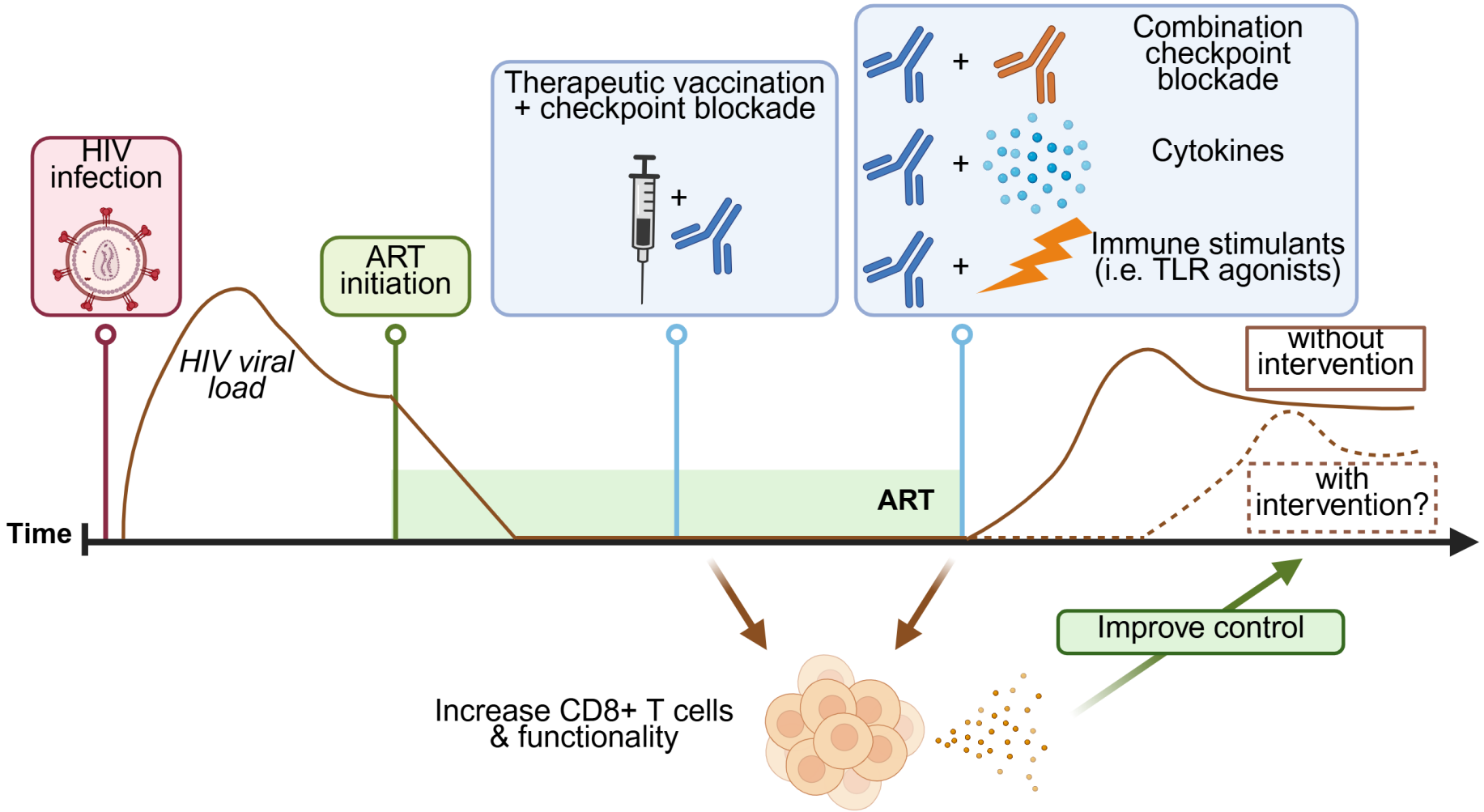
Conclusions

- **Responsiveness to immune checkpoint blockade in people with HIV is variable**

- **Gaining an understanding of the mechanisms behind this variability will be crucial to:**
  - Identify individuals who can most benefit from immune checkpoint blockade
  - Design more broadly efficacious cure strategies

- **Clinically, immune checkpoint blockade will likely form a part of a combination therapy, along with interventions aiming to increase antigen visibility and reduce reservoir size**

Future directions for immune checkpoint blockade



King & Lewin, *Immunological Reviews* (2024)

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