



# HIV CURE

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 @JavierMPicado

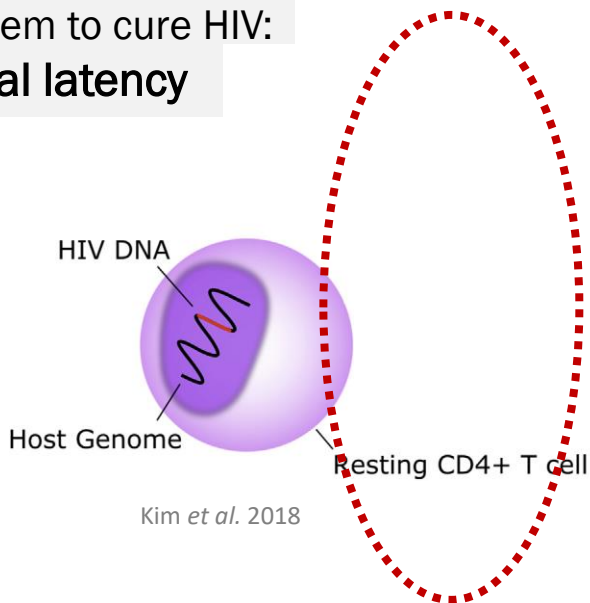




# Weaking latent viruses up!

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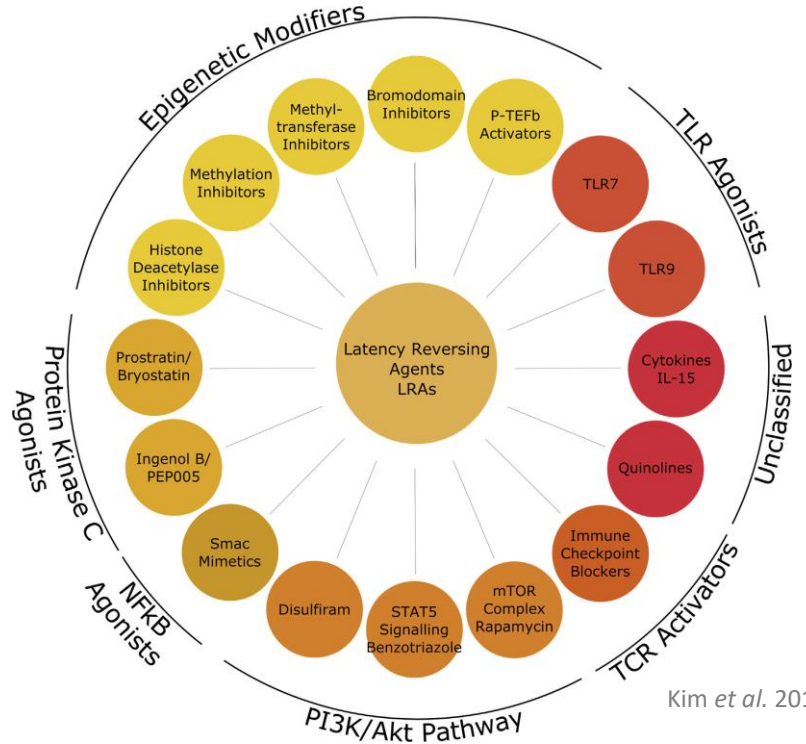
Major problem to cure HIV:  
**proviral latency**



# How can we drive the virus out of latency ?



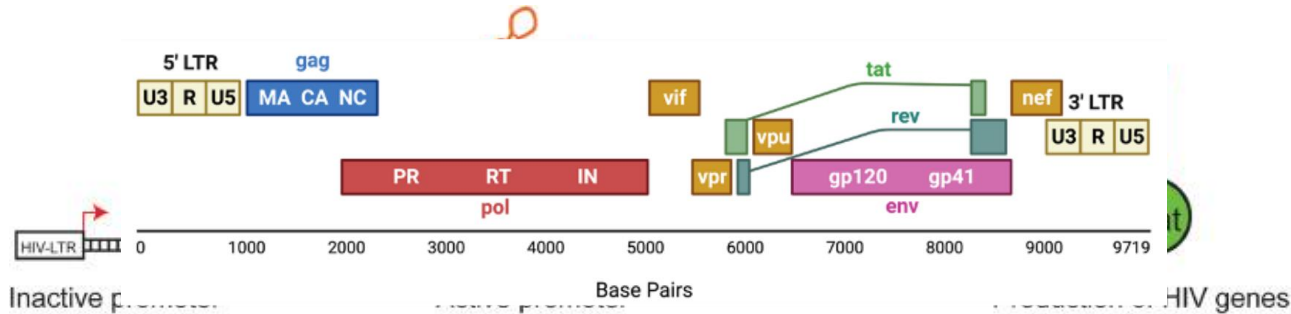
Illustration: *The Economist* 2011



Kim et al. 2018

# HIV latency reversal by lipid nanoparticles encapsulating HIV Tat mRNA

- Tat = "Trans-Activator of Transcription"
- Regulatory protein that drastically enhances the efficiency of viral transcription
- 86 - 101 amino acids

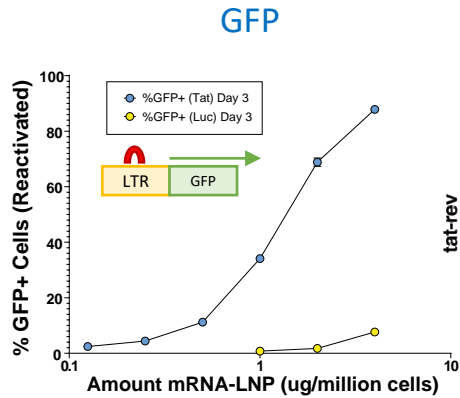


## Encapsulated mRNA of truncated Tat!

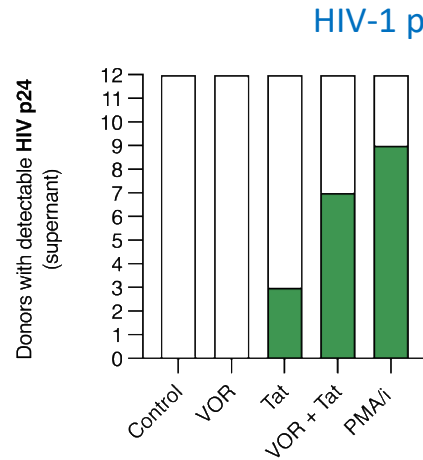
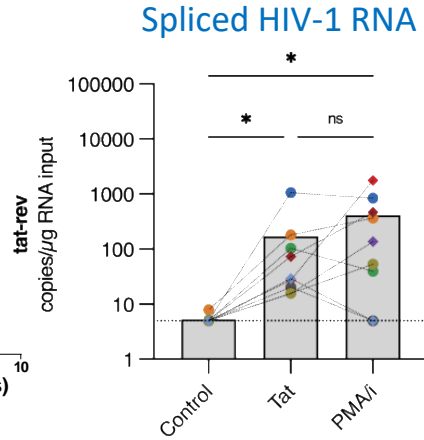
Van Gulck *et al.* 2023. Antimicrob Agents Chemother

Pardons *et al.* 2023. Nat Com

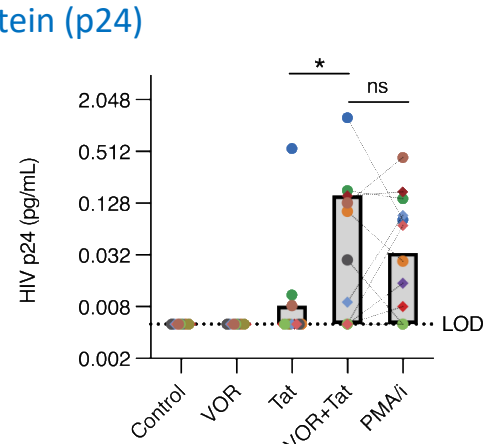
# HIV latency reversal by lipid nanoparticles encapsulating HIV Tat mRNA



Immortalized cell-line



Primary cells



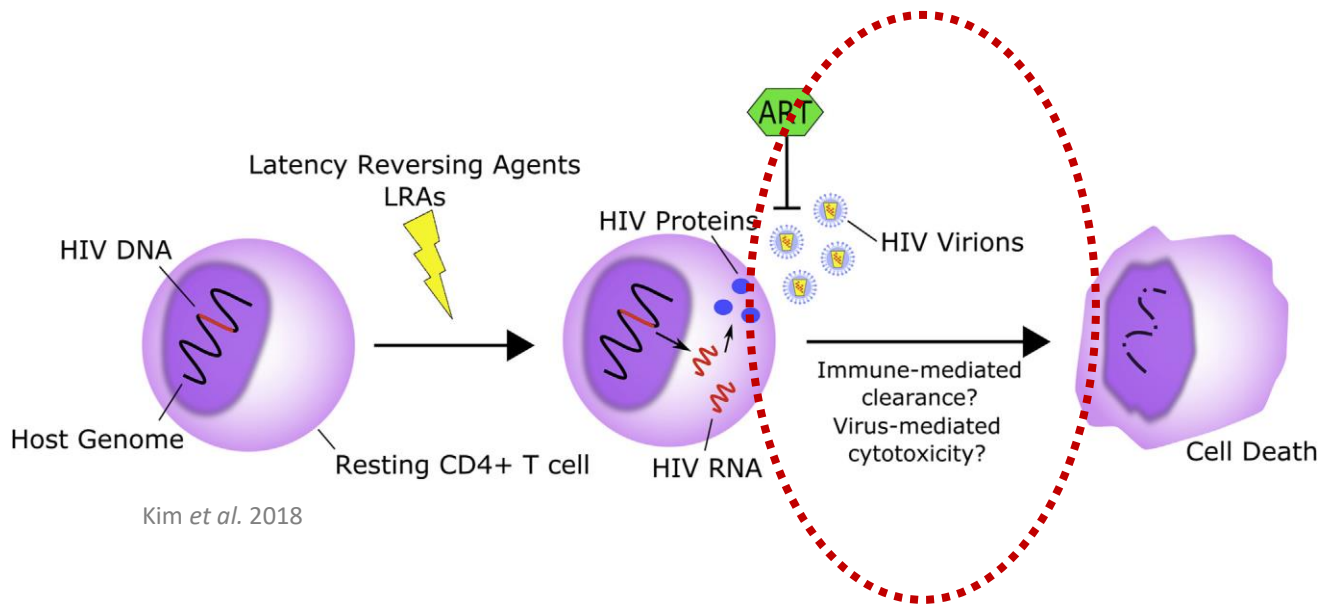
# HIV latency reversal by lipid nanoparticles encapsulating HIV Tat mRNA

- Tat LNPs\* induced unspliced, multiply-spliced, and polyadenylated HIV transcripts in CD4 T cells
- Tat LNPs induced detectable HIV p24 protein (24h)
- Combination with other LRA resulted in p24 induction similar to that observed with T-cell activation
- Prolonged exposure to combination regimens increased p24 detection, without:
  - inducing global T-cell activation in primary CD4+ T-cells (i.e. toxicity)
  - leading to any significant perturbation of the human T-cell transcriptome.

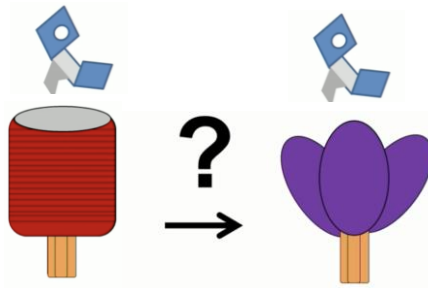
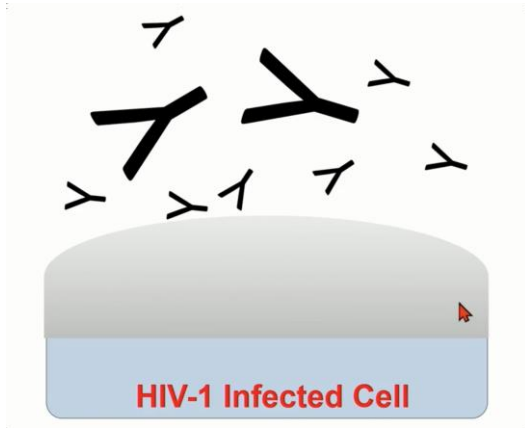
*\* Tat mRNA delivered by nanoparticles is likely due to more efficient cytosolic delivery as opposed to Tat protein transduction which depends on endocytic uptake mechanisms and endosomal escape of the entrapped protein*



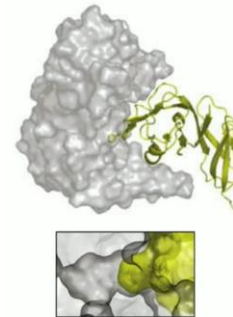
# Killing infected cells!



# How to sensitize HIV-infected cell for killing?

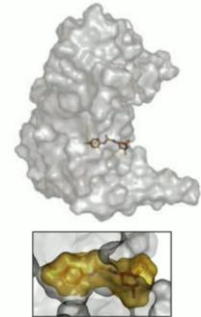


CD4



Kwong et al., Nature 1998

CD4-mimetics



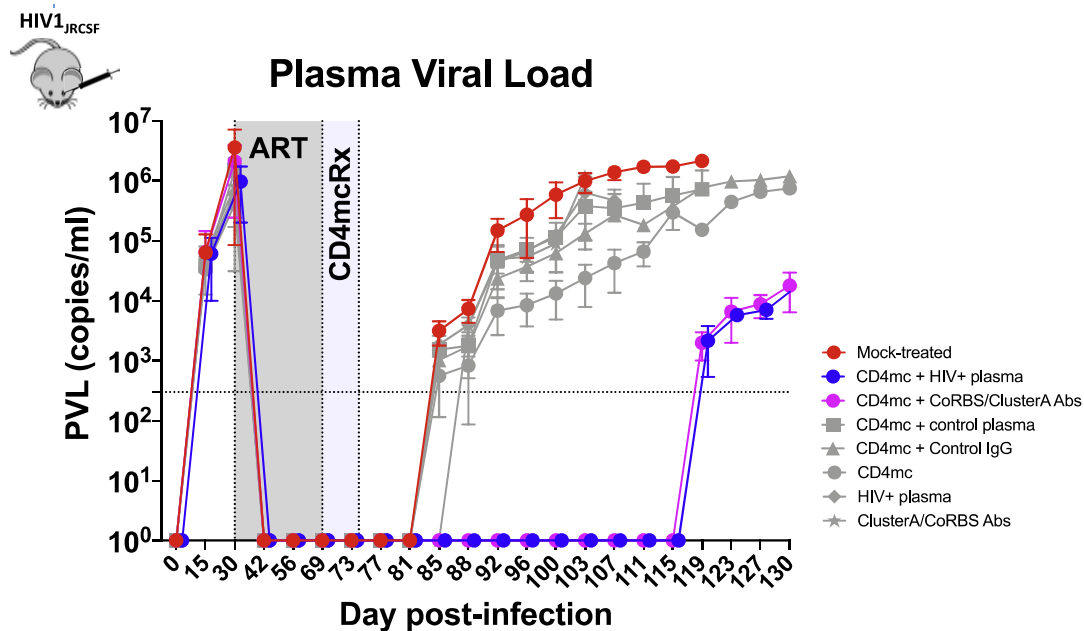
Madani et al., Structure 2008  
LaLonde et al., Bioorganic & Med Chem 2011







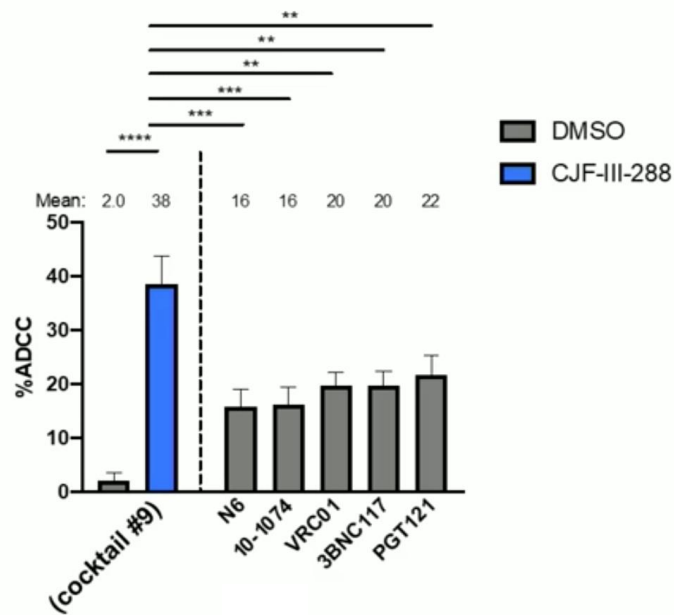
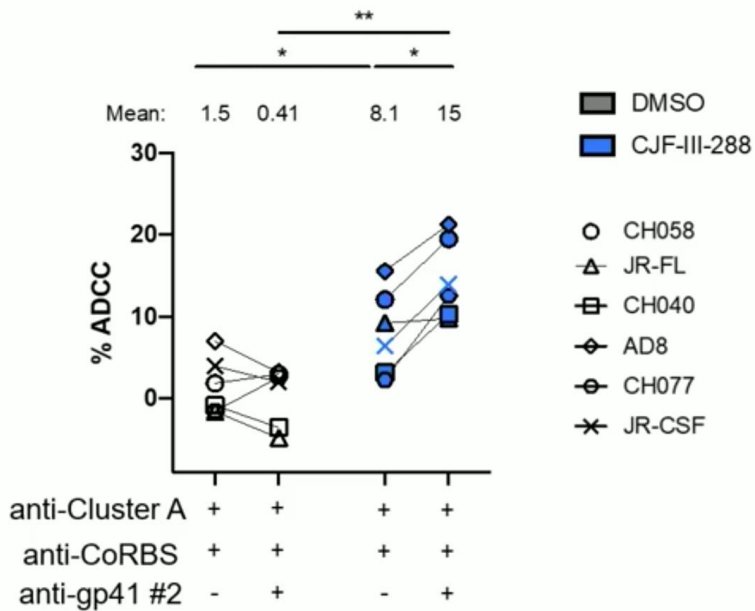
# CD4mimetics + CD4-induced Abs delays viral rebound after ART interruption



- Also decreases the HIV-1 reservoir in humanized mice
- It is dependent on Fc-effector function



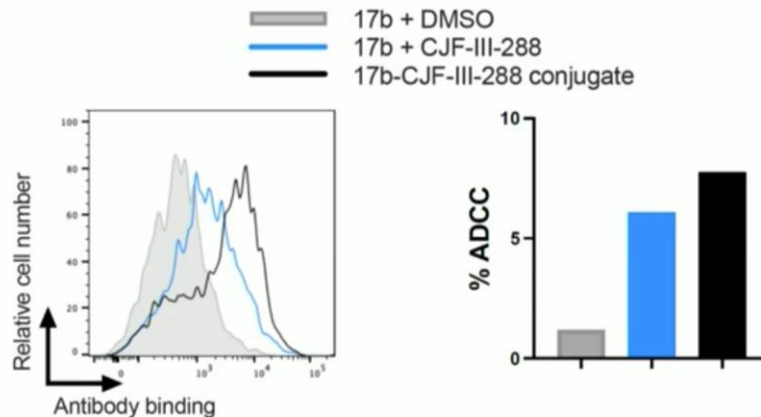
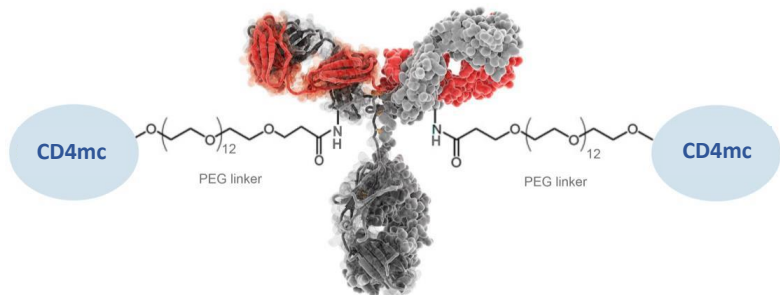
# α-gp41 Abs contribute to CD4mc sensitization of infected cells to ADCC





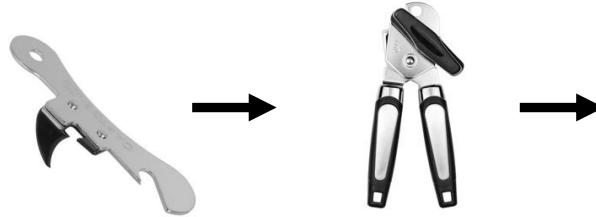
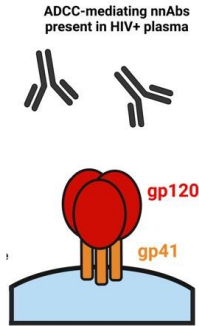
# CD4mimetics – CD4i Ab conjugates

Bispecific molecules consisting of 'an opener' attached through a linker to a CD4i Ab

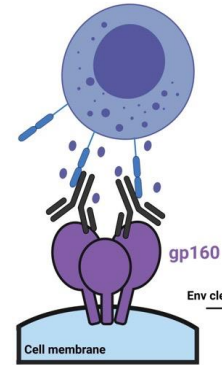


# How to sensitize HIV-infected cell for killing?

Protection from ADCC



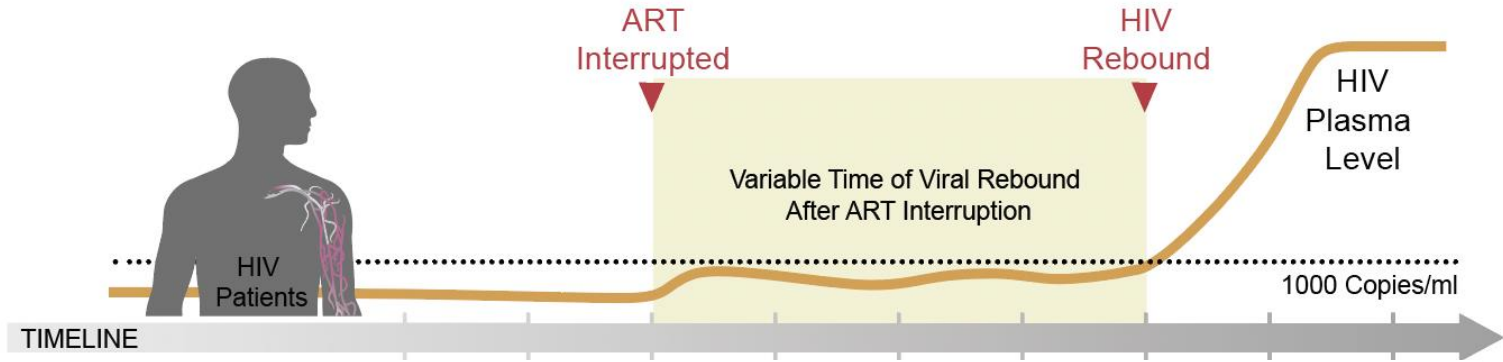
ADCC response



- CD4 mimetics allows improved Fc-effector functions
- Indoline CD4 mimetics (CJF-III-288) with improved antiviral potency and breath
- Favorable PK/Tox in humanized mice and non-human primates
- CJF-III-288, with CD4i antibodies, decreases the size of the reservoir in mice
- New therapeutic: CD4mc-Ab conjugates

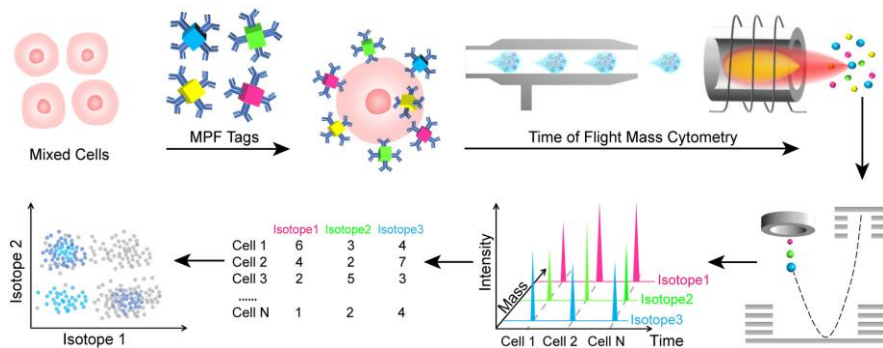


# Viral rebound after ART interruption!



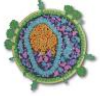
# Markers that may predict viral rebound

## Mass Cytometry (CyTOF\*)

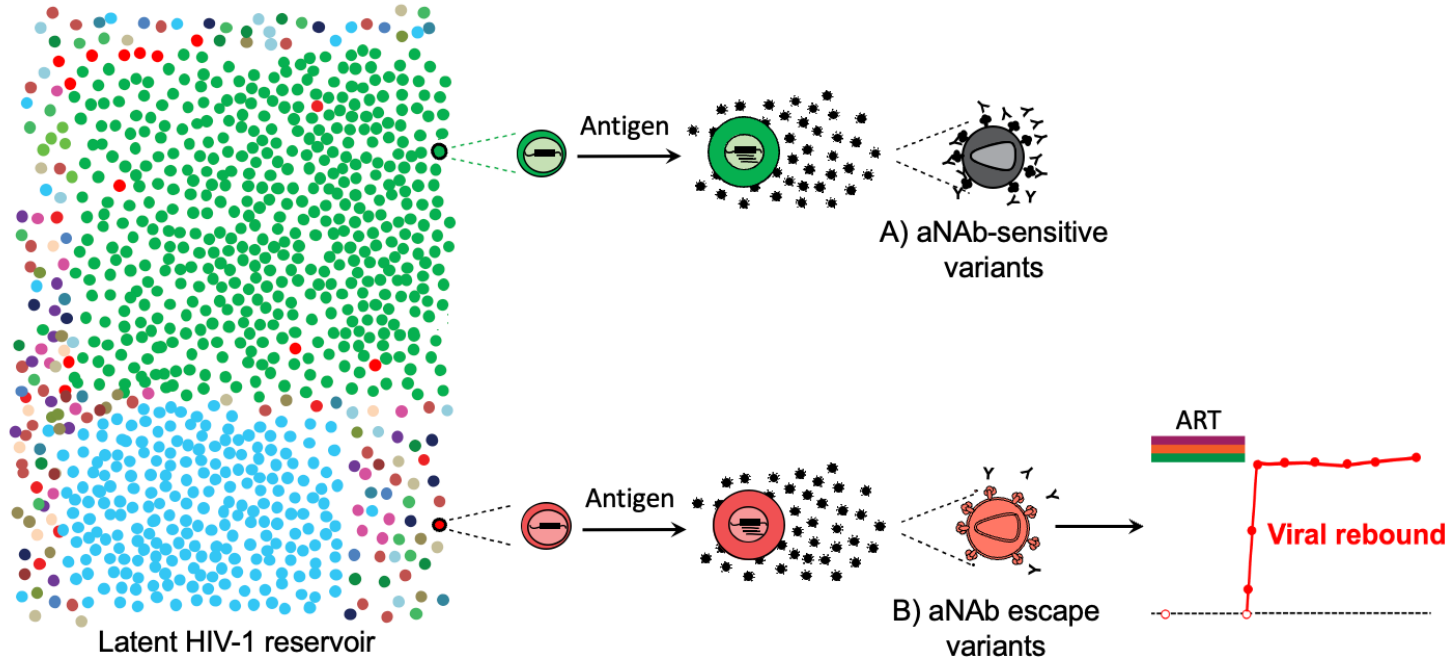


- **CD103+** T resident memory cells:
  - associated with longer time-to-rebound and lower intact provirus (ACTG A5345)
  
- **BIRC5+CXCR4+ CD8+** T cells:
  - associated with longer time-to-rebound and lower intact provirus (TEACH & ACTG A5345)

These long-lived cells may be better able to home to lymphoid tissues during the early post-ART period and together with resident memory T cells slow viral rebound upon ATI



# Role of autologous HIV-1 specific antibodies during virus rebound after ART interruption

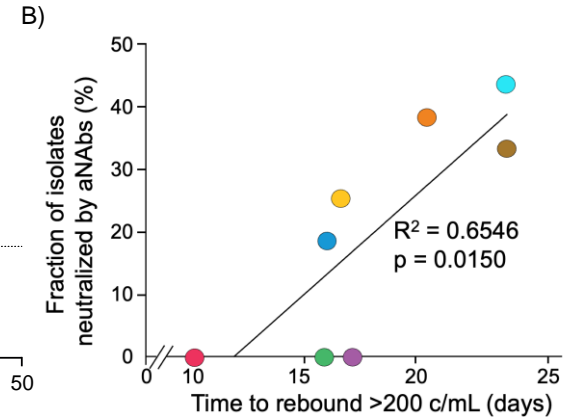
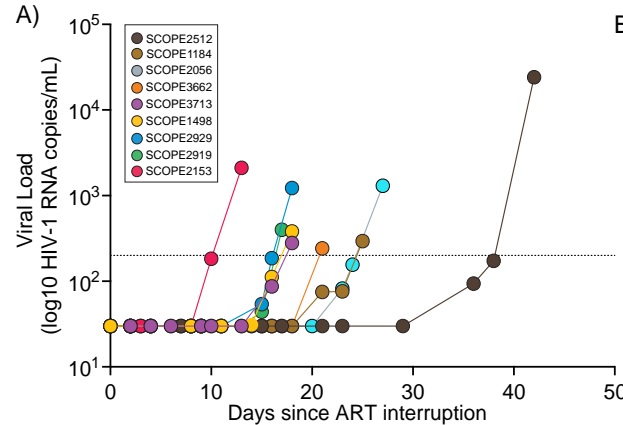
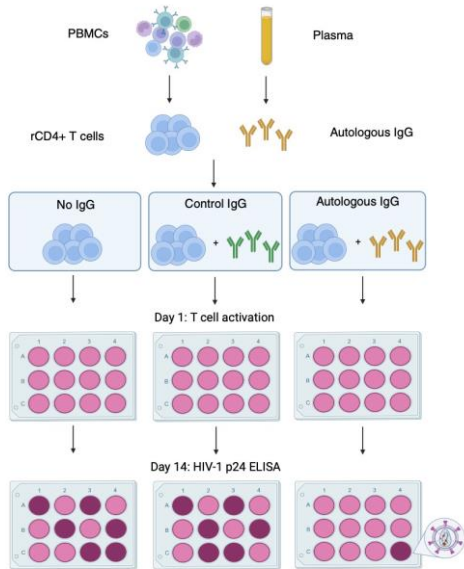






# The fraction of HIV reservoir variants neutralized by autologous IgG correlates with time to rebound

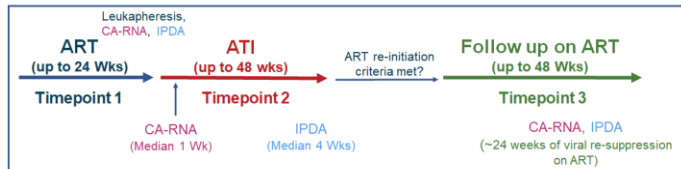
## Quantitative Virus Outgrowth Assay (qVOA)



- Autologous IgG-resistant outgrowth viruses in qVOA (in vitro) were genetically similar to virus that rebounds following ATI
- Inducing a potent immune response against autologous IgG-resistant variants prior to an ATI may represent a functional HIV cure

# Does the intact reservoir remain stable after ATI ?

## ACTG A5345 Study Design

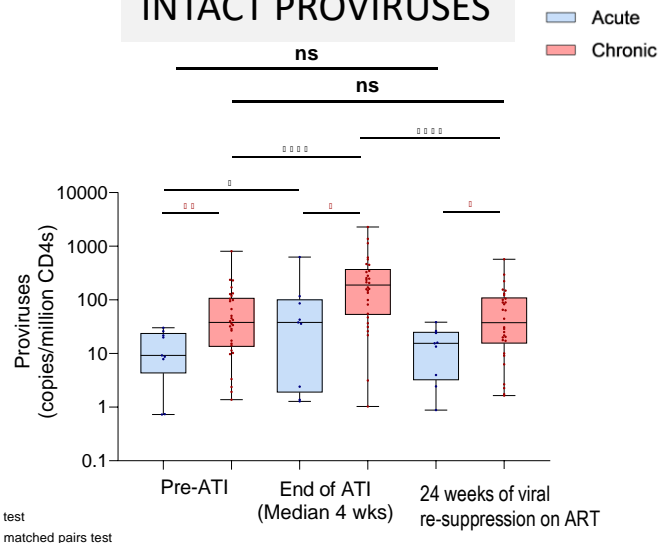


■ Acute (n=12)  
■ Chronic (n=33)

- Unspliced CA-RNA
- Intact Proviral DNA Assay (IPDA)

- ART: 4 years in the early-Tx; 10 years in the chronic-Tx
- Day of rebound: first viral load  $\geq 1,000$  copies/mL
- Median time to viral rebound: **22 days** (13–230)

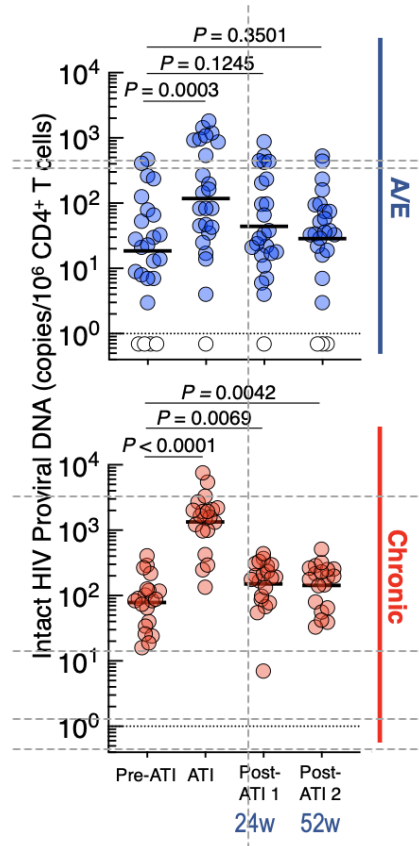
## INTACT PROVIRUSES



- Short-term ATI does not irreversibly change the reservoir size as reflected by stable levels of intact HIV DNA and cell-associated RNA after ~24 weeks of viral re-suppression on ART

# Does the intact reservoir remain stable after ATI ?

	A/E (N=24)	Chronic (N=19)
<b>Sex, no. (%)</b>		
Male	24 (100)	17 (89)
Female	0	2 (11)
<b>Age</b>		
Mean (Range)	42(21-65)	51(38-61)
<b>CD4<sup>+</sup> T Cell Count (cells/mm<sup>3</sup>) Prior to ATI</b>		
Median(Range)	738(363-2162)	724(466-1778)
<b>CD4<sup>+</sup> T Cell % (cells/mm<sup>3</sup>) Prior to ATI</b>		
Median(Range)	39(29-62)	42(29-51)
<b>CD8<sup>+</sup> T Cell Count (cells/mm<sup>3</sup>) Prior to ATI</b>		
Median(Range)	522(307-1600)	648(296-1587)
<b>CD8<sup>+</sup> T Cell % (cells/mm<sup>3</sup>) Prior to ATI</b>		
Median(Range)	31(14-53)	34(21-52)
<b>Duration of ART (yrs)</b>		
Median(Range)	3(1-19)	8(2-16)
<b>Duration of ATI (days)</b>		
Median(Range)	121(47-319)	34(8-107)
<b>Peak Plasma Viremia (copies/mL) During ATI</b>		
Geometric Mean(Range)	31,598(416-8,405,097)	229,077(20,922-6,315,485)

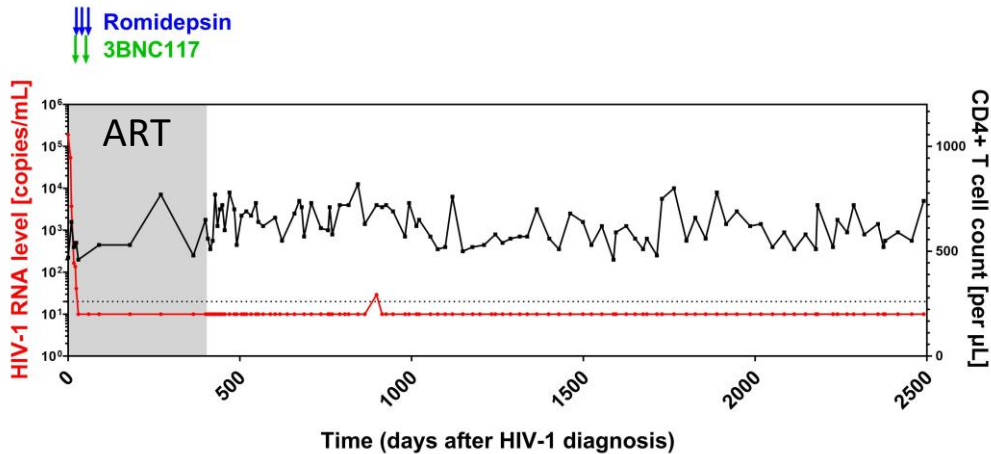


- **Intact provirus** return to the BL levels Post-ATI in the A/E group but not in the Chronic group.
- **Biomarkers** of immune activation and residual pVL remained elevated at Post-ATI compared to the baseline only in the Chronic group.
- It is plausible that the A/E group had a **stronger innate immune response** to HIV leading to a faster decay of the intact HIV DNA reservoir following the re-initiation of ART.



# Immune responses and HIV reservoir evolution from pre-ART to 5 years into post-treatment control

eCLEAR study Gunst et al. 2022. Nat Med



- High proportion of intact proviruses integrated in regions of heterochromatin
- Effector CD4 T-cell activation
- Strong HIV-1 specific CD8 T-cell response



*Thank you!*