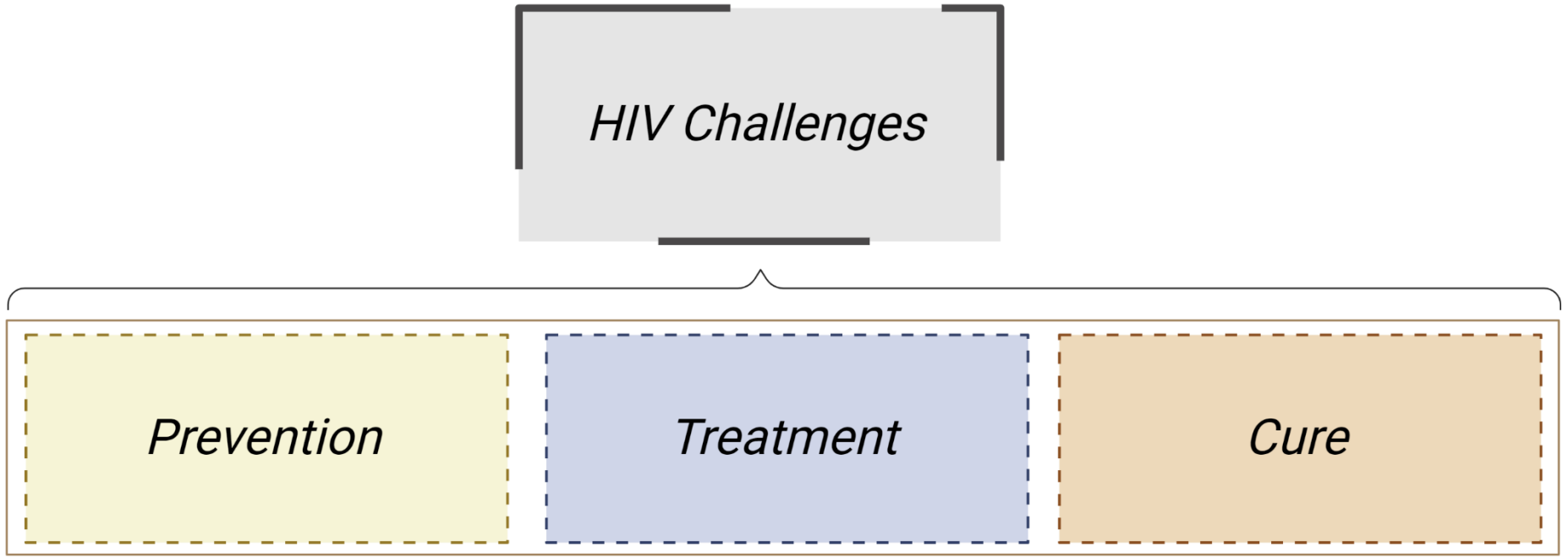
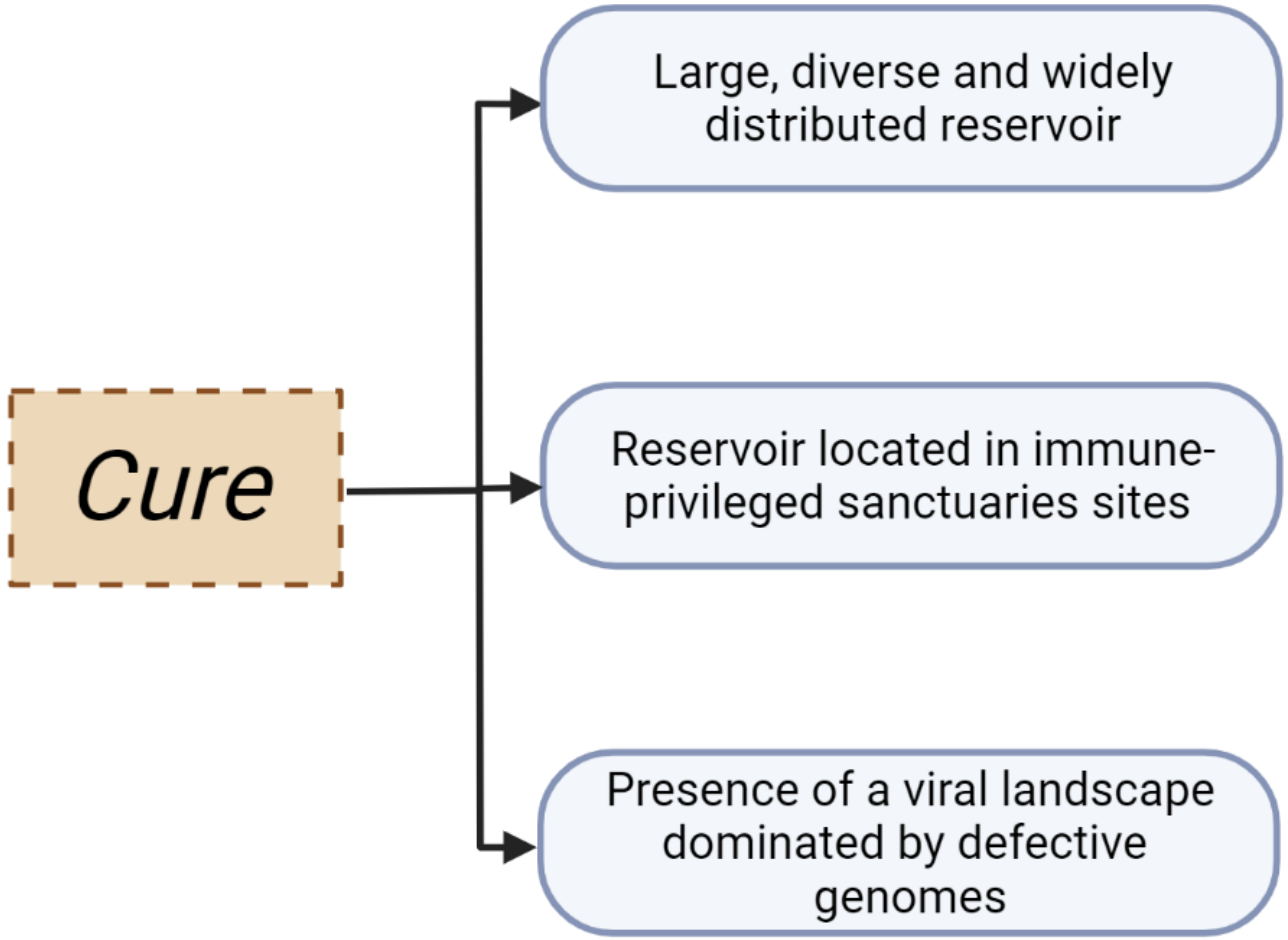
The Immediate Agenda in HIV *Cure* Research

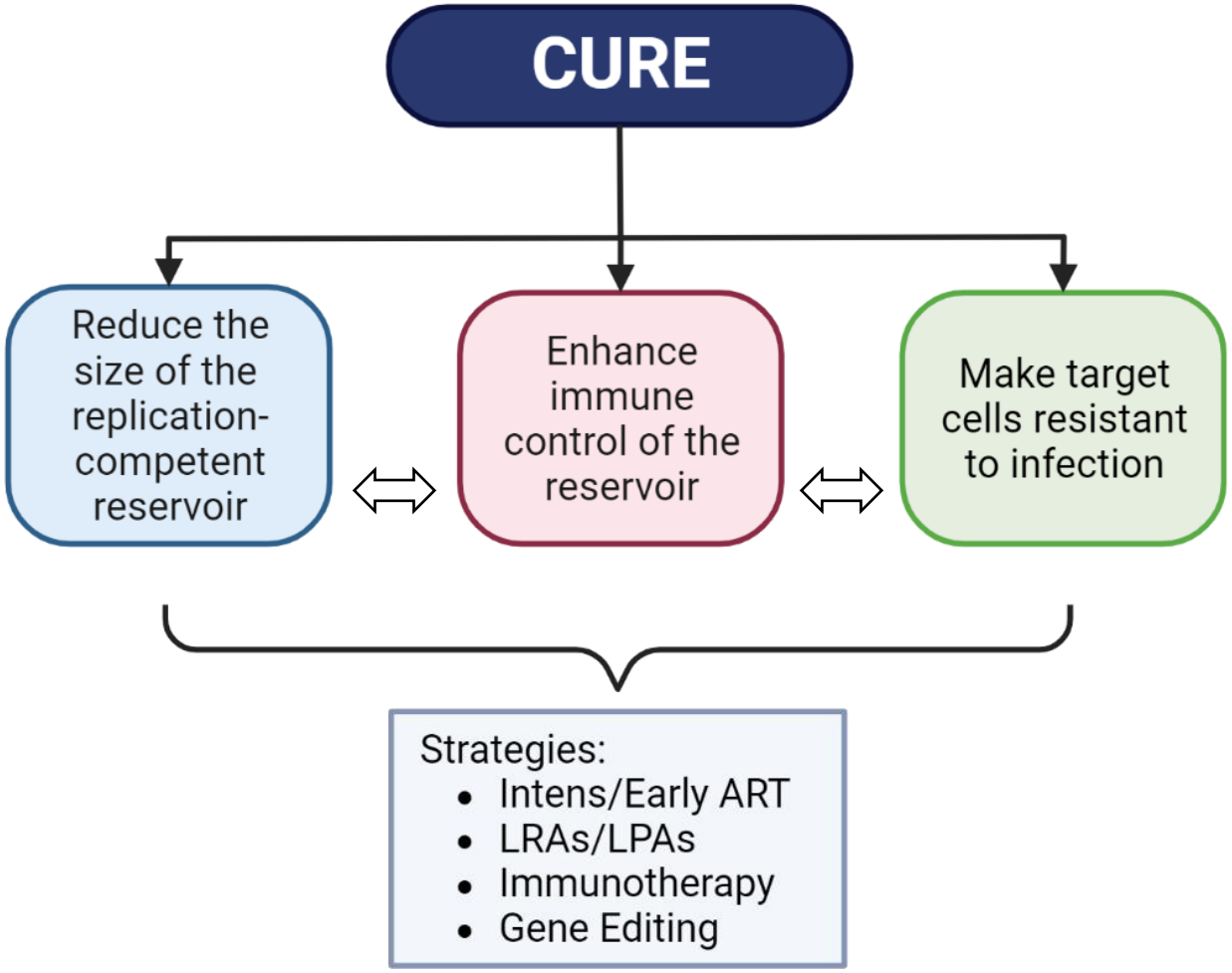
Hot Topics in HIV. 26th October 2023
Vaccines, immune recovery and eradication
Barcelona, 2023



*"The next frontier of HIV medicine will focus on developing **single** one-time prevention or cure interventions that will provide the tools necessary to truly end the epidemic"*

Landovitz et al, Nat Rev Micro 2022


Cure
Large, diverse and widely distributed reservoir
Reservoir located in immune-privileged sanctuaries sites
Presence of a viral landscape dominated by defective genomes


CURE
Reduce the size of the replication-competent reservoir
Enhance immune control of the reservoir
Make target cells resistant to infection
Strategies:
Intens/Early ART
LRAs/LPAs
Immunotherapy
Gene Editing

Outline

Strategies:

- Intens/Early ART
- LRAs/LPAs
- Immunotherapy
- Gene Editing

Considerations for HV Cure Research:

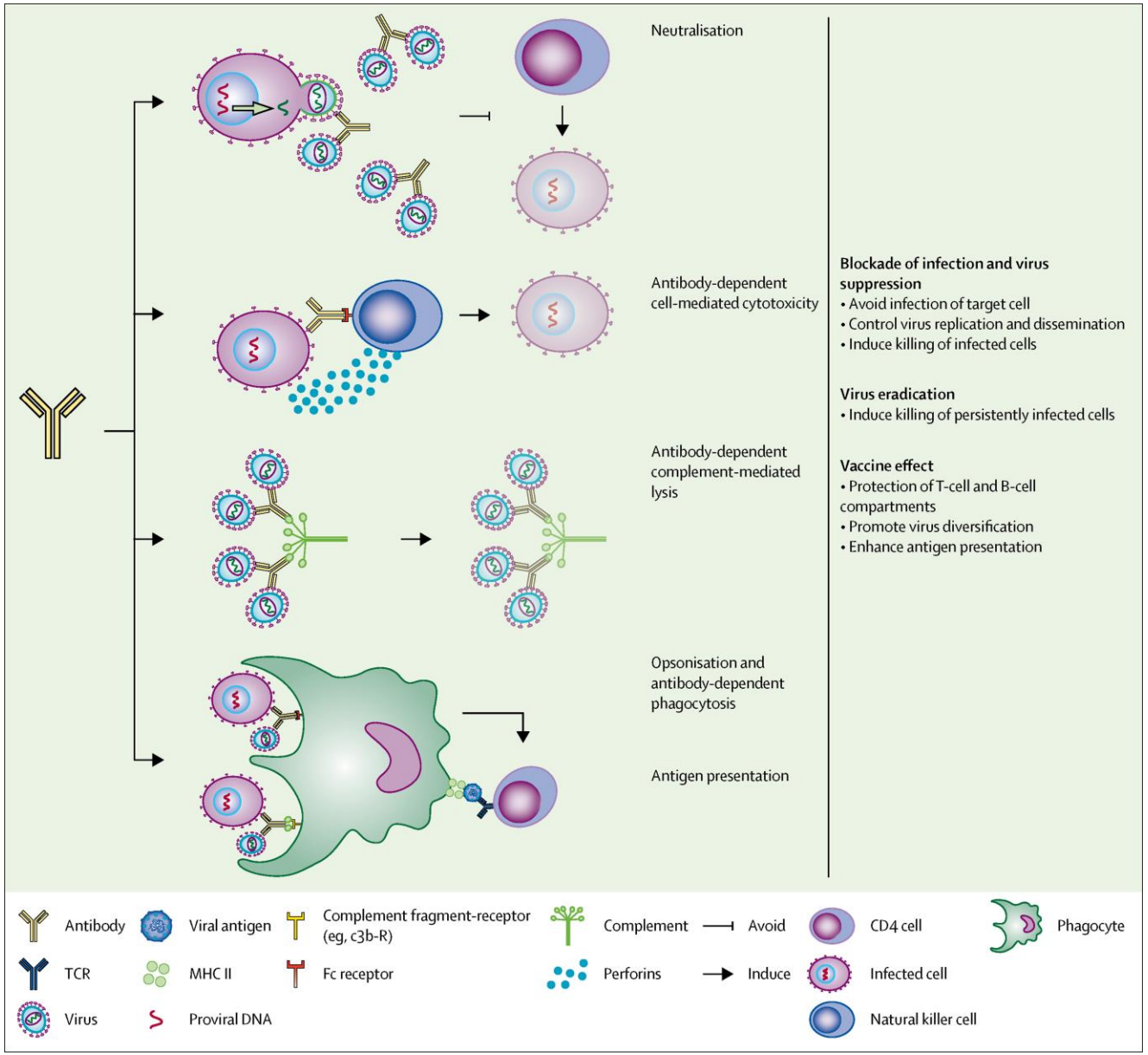
- Tissue Reservoirs
- Biological Sex
- Long-acting ART

Immunotherapy

→ **Induce a sustained**, specific **immune response against HIV** that can effectively eliminate infected cells during ART and control any persistently infected cells after ART interruption (Abs, CAR-T, therapeutic vaccines, innate response enhancers, etc..)

Immunotherapy

Antibodies



Jaworski The Lancet HIV, 2018

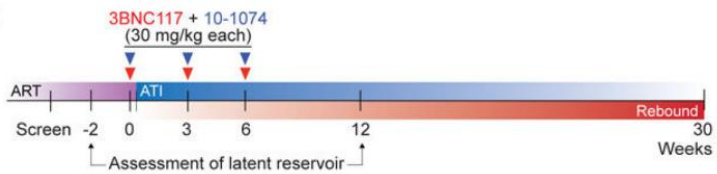
Immunotherapy

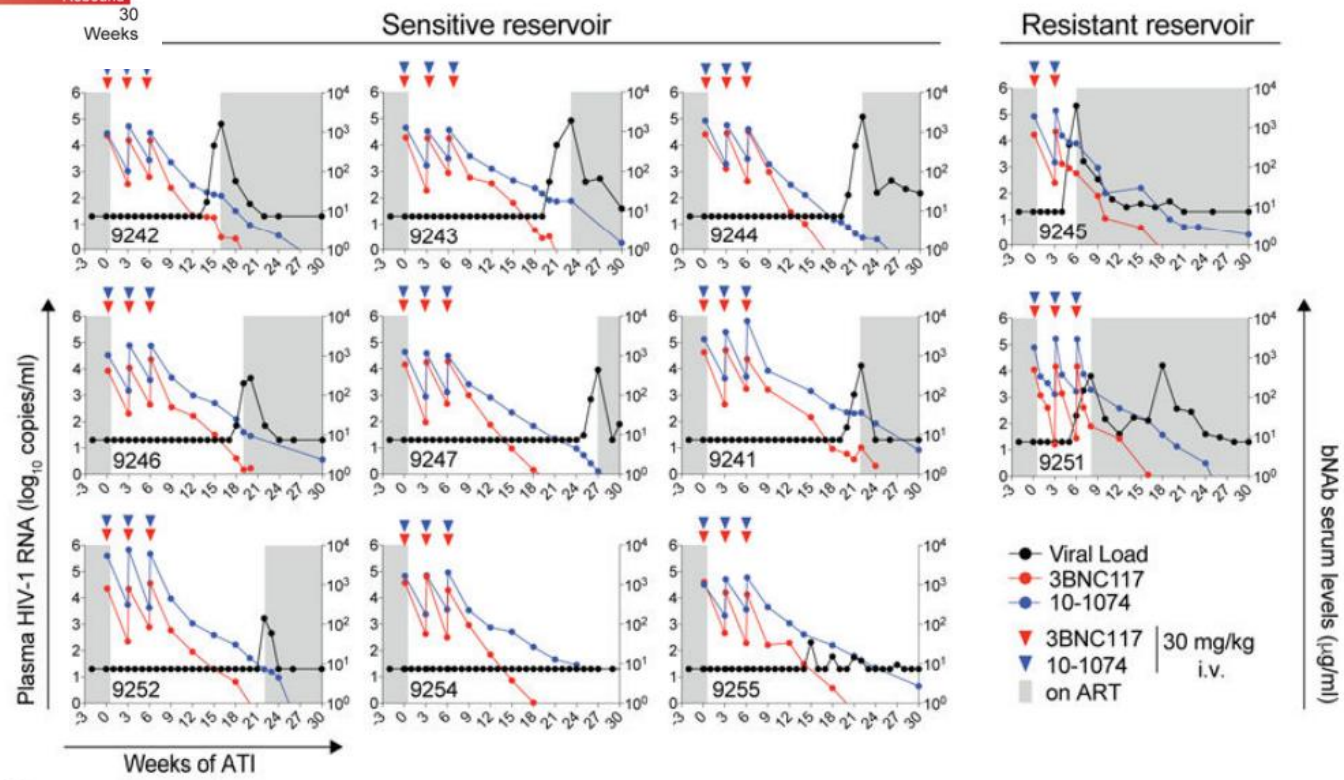
BnAbs

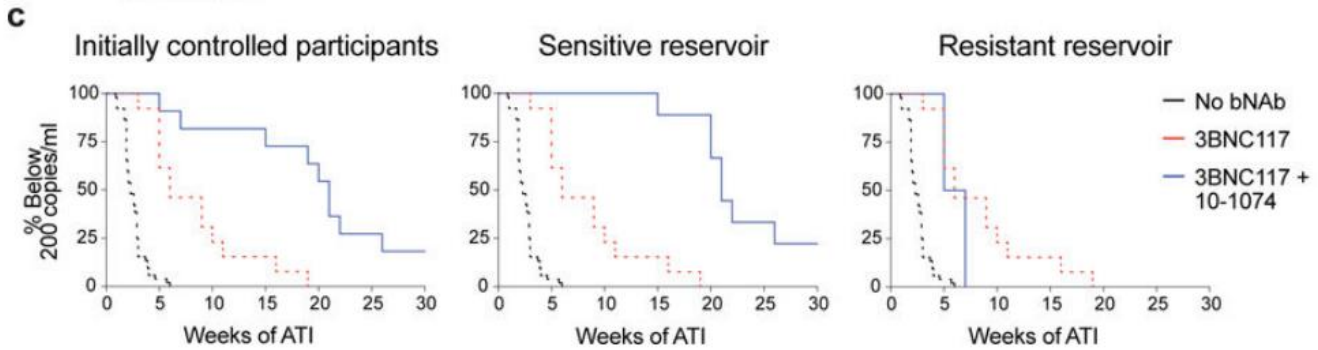
→ Are being developed for **prevention**, **treatment** and **cure**:

- Are able to prevent infection in people with susceptible virus *(Corey NEJM 2021)*
- Delay viral rebound *(Sneller Nature 2022; Mendoza Nature 2018; Gunst Nat Med, 2023)*
- Reduce the reservoir size in ART-people *(Gaebler Nature 2022)*
- Induce a vaccinal effect *(Niessl Nat Med 2020; Rosas-Umbert Nat Comm 2022; Gunst Nat Med, 2022; Gunst Nat Med, 2023)*

Immunotherapy

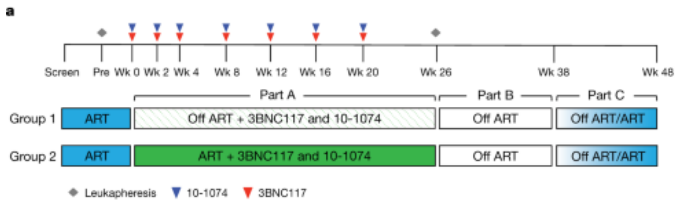


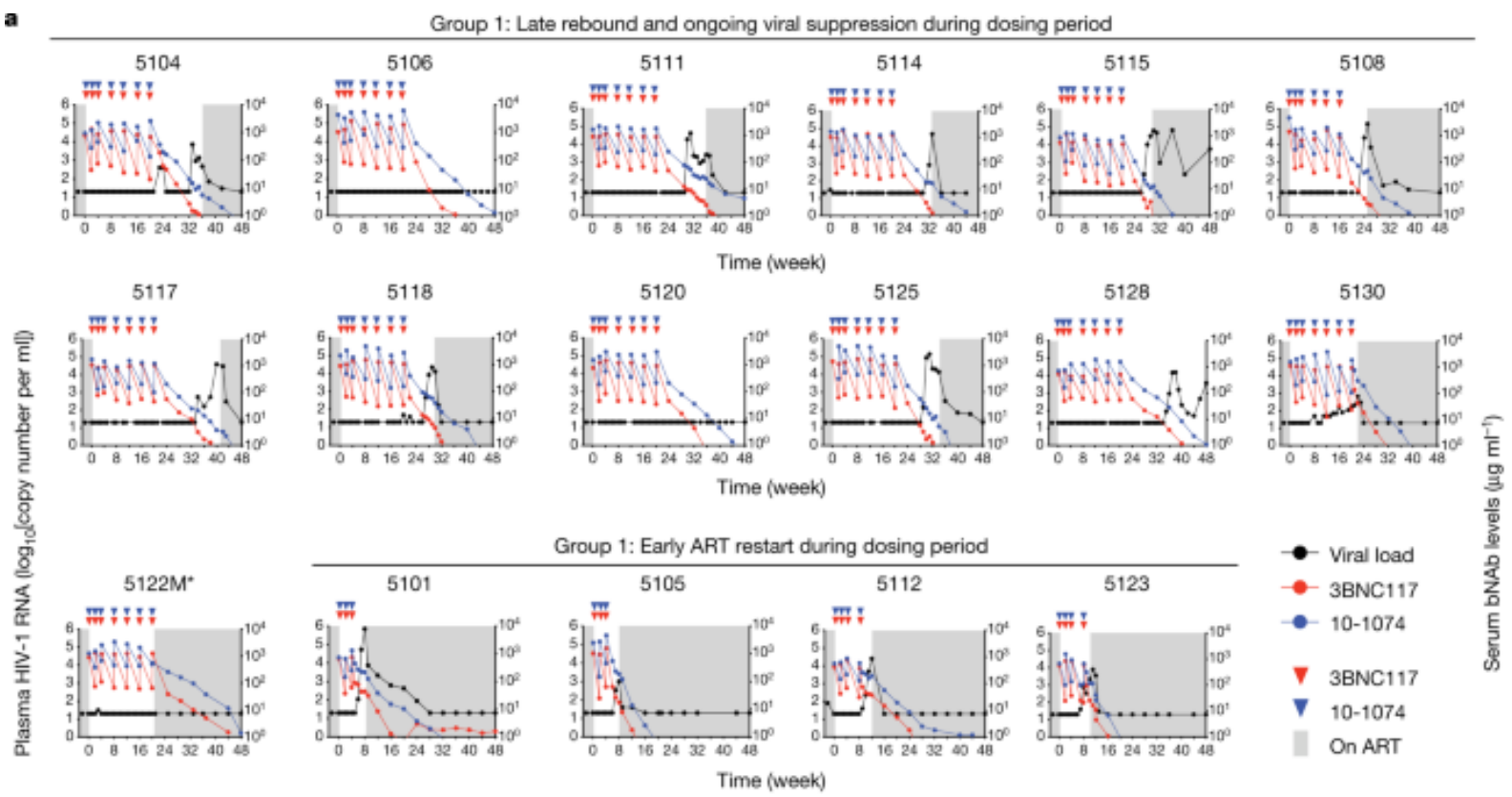


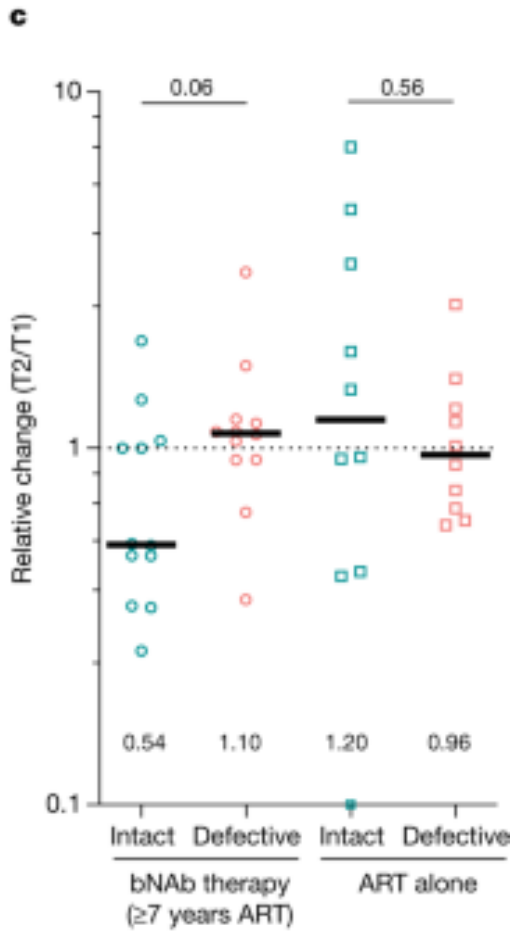


Mendoza et al. Nature 2018

Immunotherapy







Glaebler et al. Nature 2022

Immunotherapy

nNAbs (non-neutralizing Antibodies)

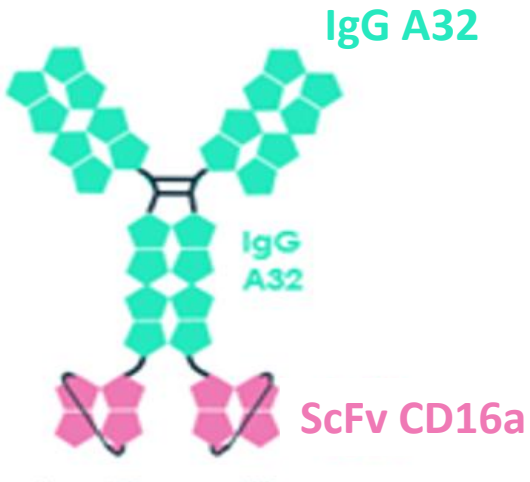
→Can target more conserved regions of HIV *(Moore, J Virol 1994; Tolbert, Structure 2016)*. Implications for the development of resistance mutations

→Potent recruitment of immune cells and mediate ADCC activity *(Ferrari, J Virol 2011)*

→Epitope expressed in very early phase (relevant for viral reactivation) *(Ferrari, J Virol 2011)*

Evaluation of a nNAb bispecific antibody targeting NK cells

Bi-Ab32/16



IgG-scFv
Tetravalent bispec.

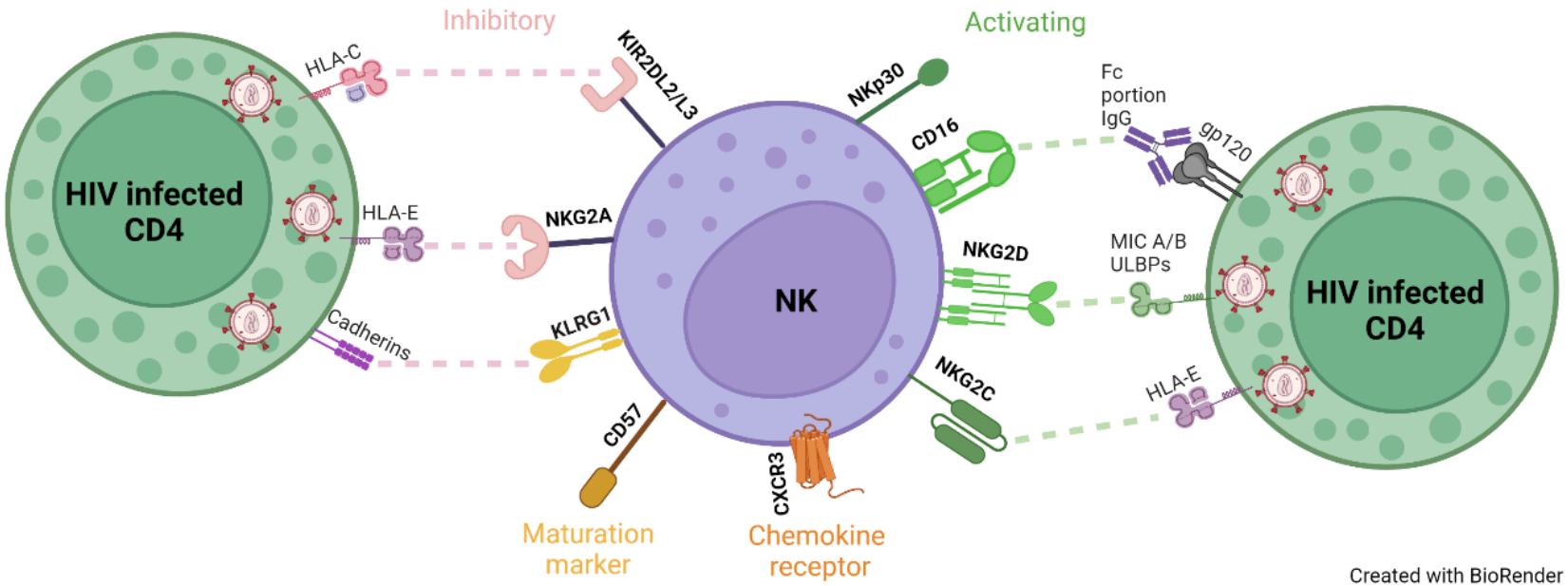
IgG A32 (anti-gp120):

- Non-NAb that targets C1C2 epitope from all viral strains and mediates ADCC
- Correlation with vaccine protection (RV144)
- Highly conserved epitope
- No evidence of escape mutations

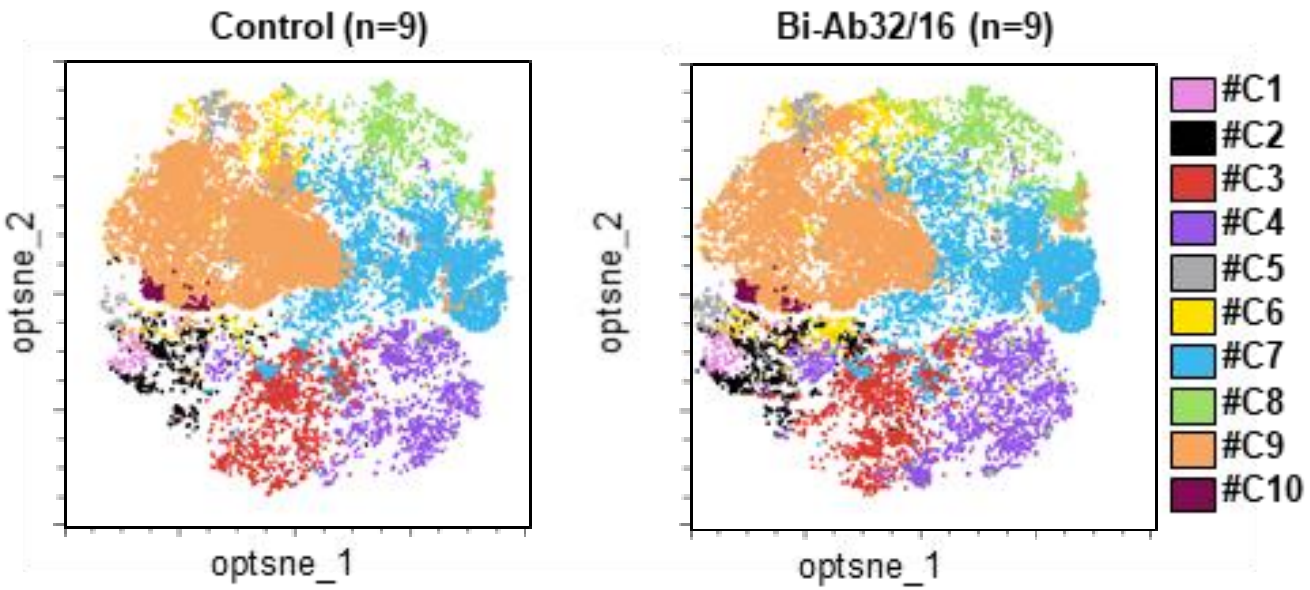
scFv-CD16a:

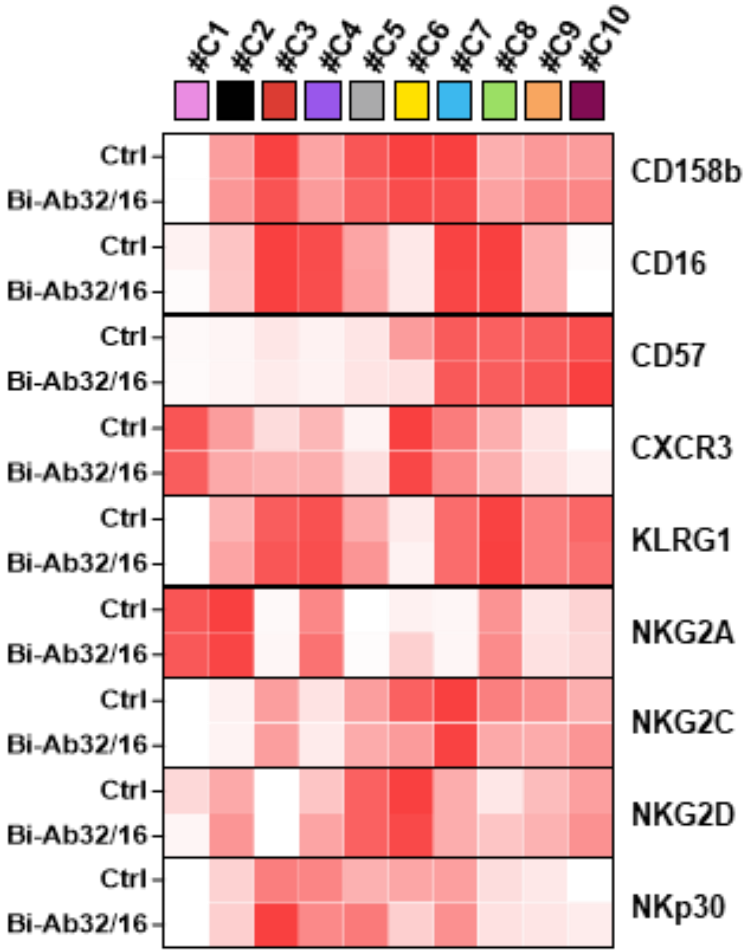
- Expressed mainly on NK and monocytes
- Involved in ADCC
- Recruit a highly cytotoxic NK cell subpopulation
- Strong activation signal

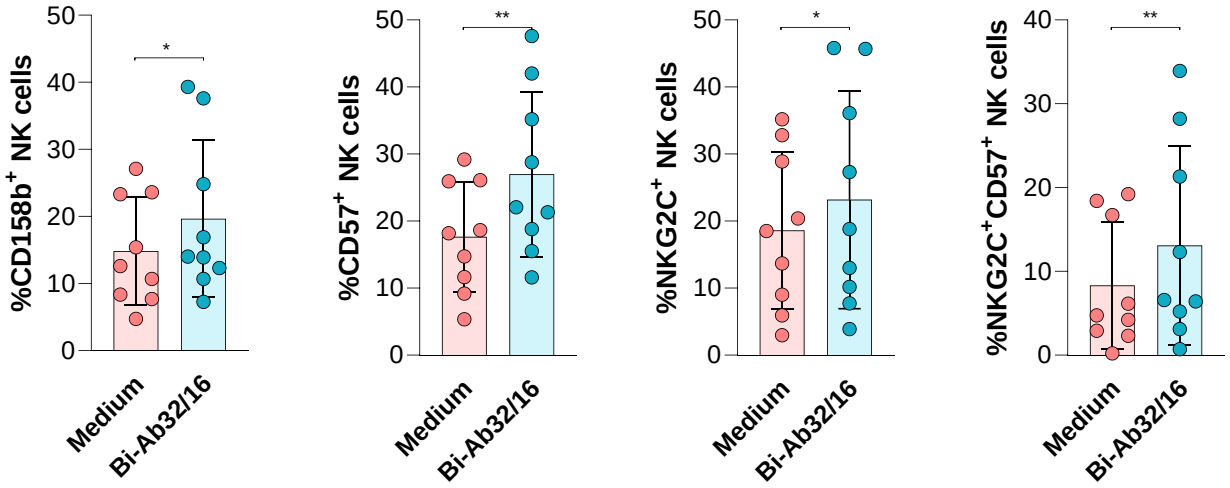
Immunotherapy



Immunotherapy

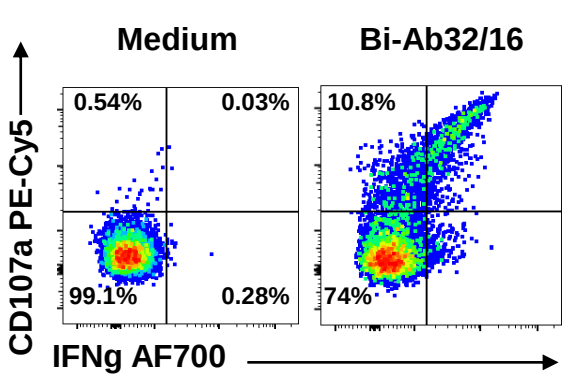


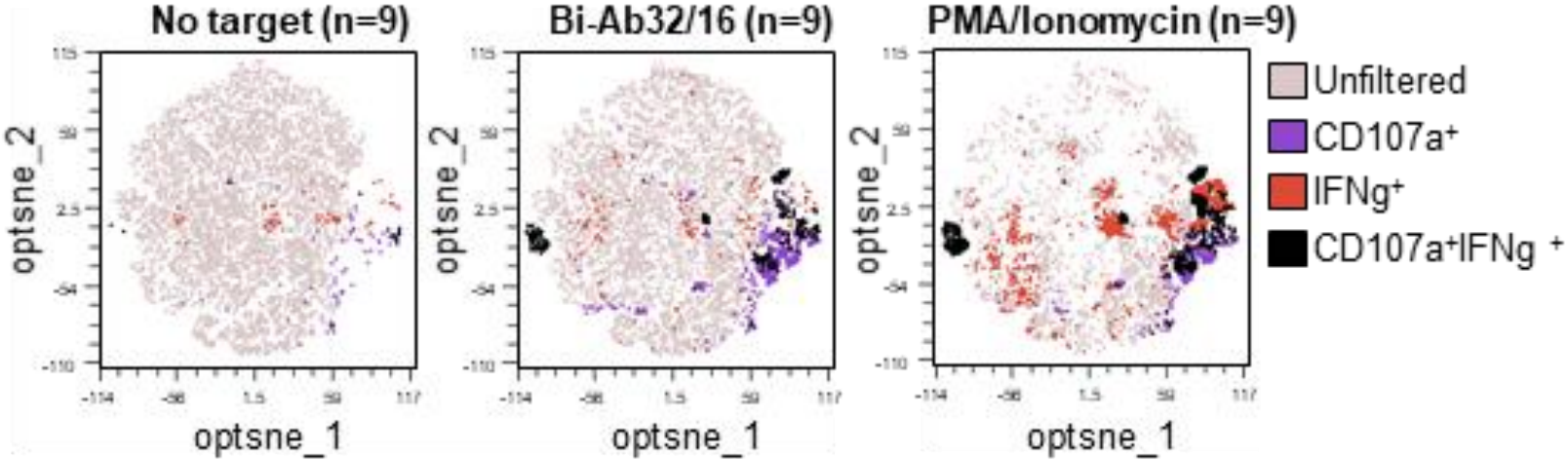


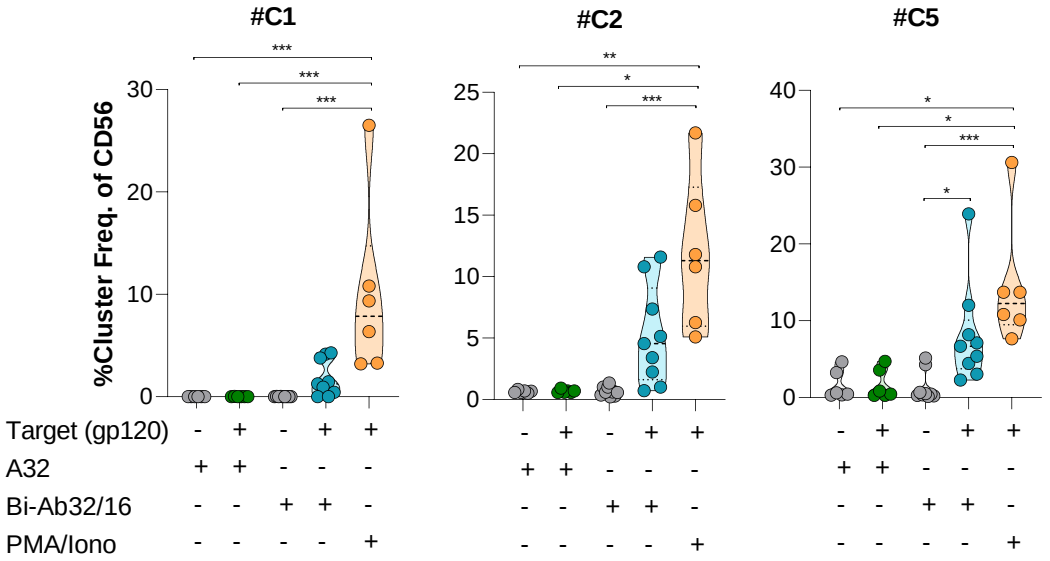


Immunotherapy

Cell activation and functional assessment

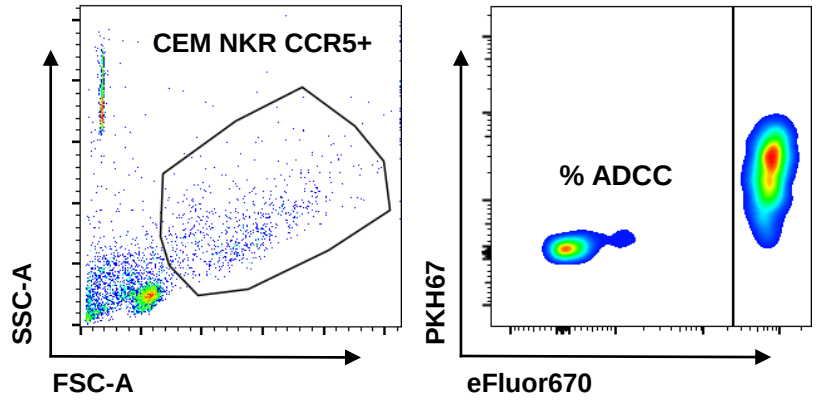






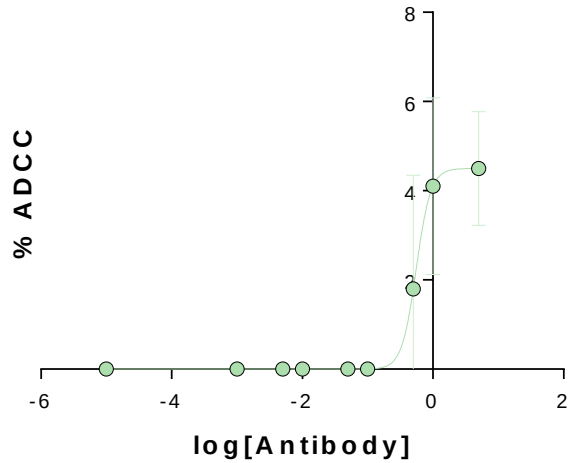
Immunotherapy

NK-mediated cytotoxic response against HIV-expressing cells



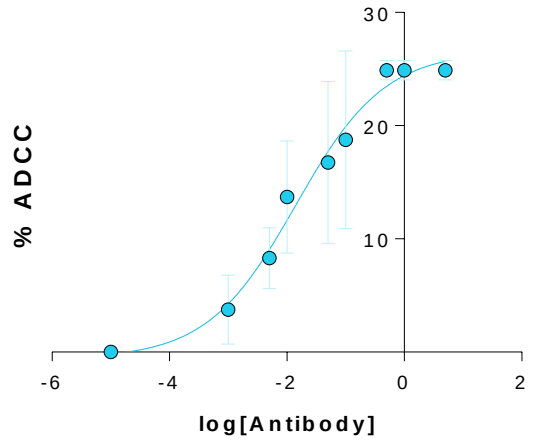
A32

EC_{50} = 0.55 ± 2.55E-5 µg/ml



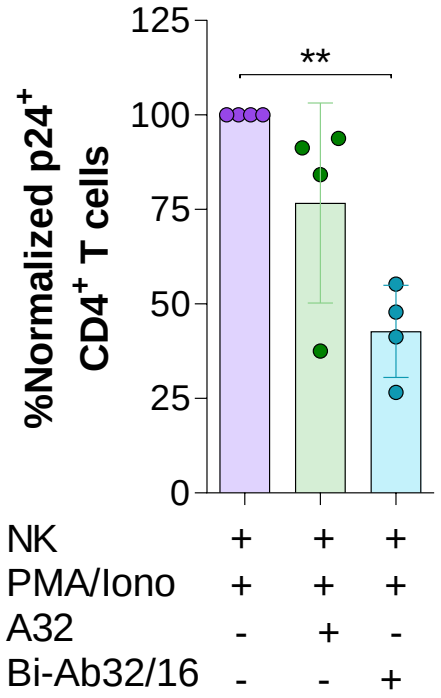
BsAb

EC_{50} = 0.01± 0.003 µg/ml



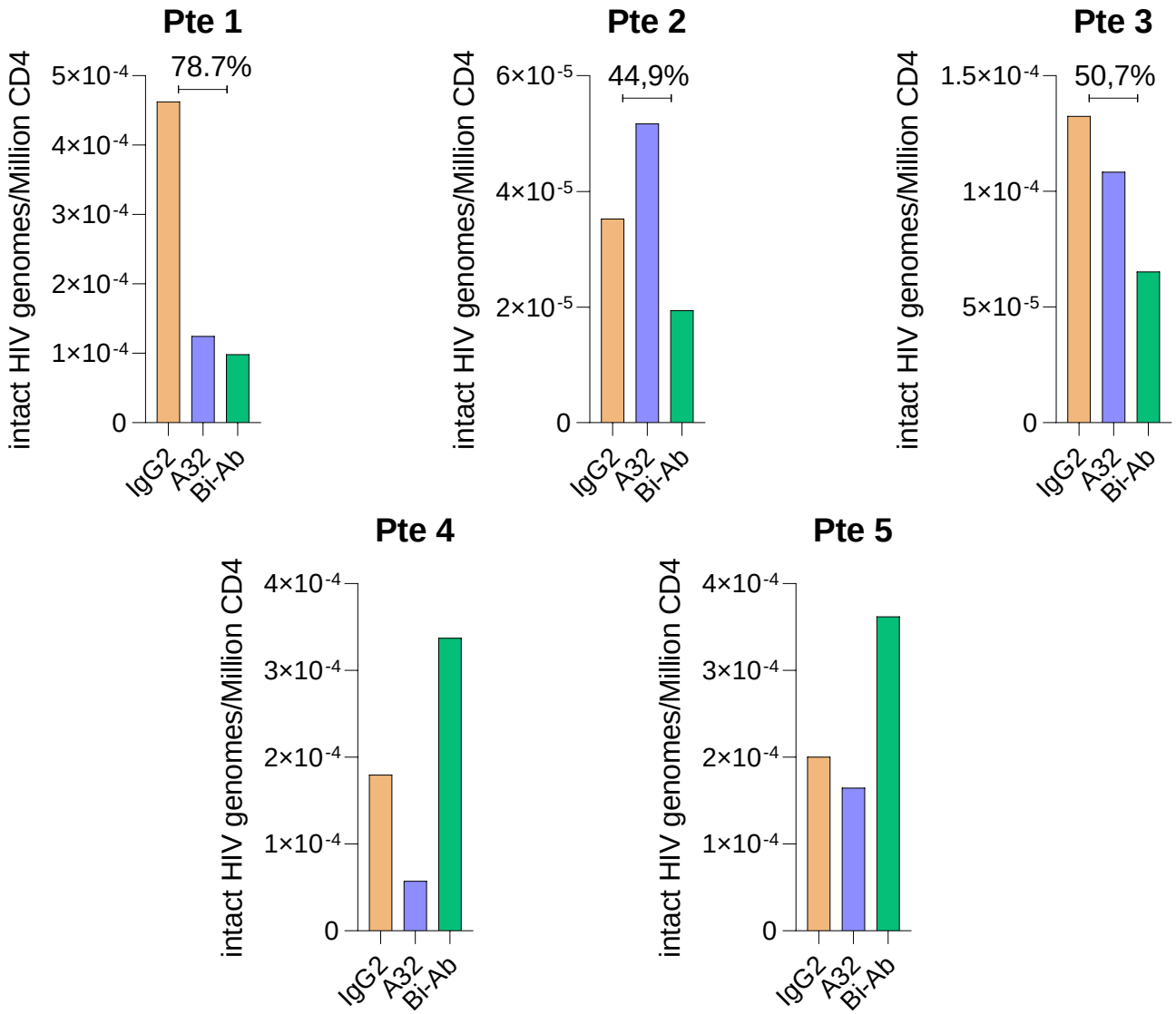
Immunotherapy

BiAb-32/16 promotes NK-mediated cytotoxic response against cells from PLWH after viral reactivation



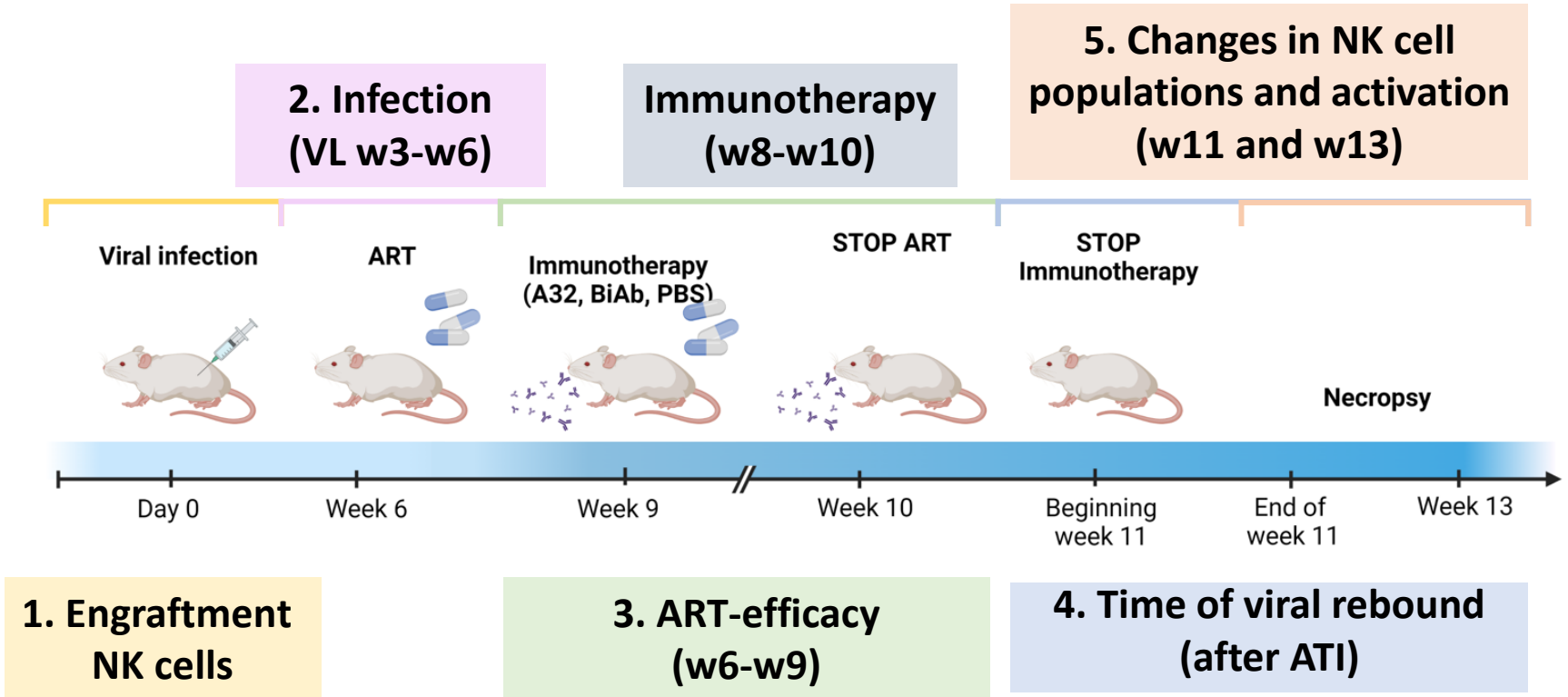
Immunotherapy

Bi-Ab32/16 reduces the intact HIV reservoir in samples from PLWH



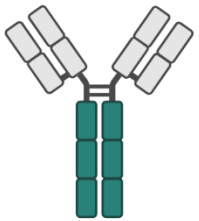
Immunotherapy

- **Animals (n=36)**: CD34 HSC engrafted humanized **NSG-Tg(Hu-IL15)** mice; Sex: F
- **Infection:** Bal strain 10.000 $TCDI_{50}$
- **3 Groups**: Immunotherapy with Bi-Ab32/16 and A32 (500µg/dose, 3 doses/week during 2 weeks), and control arm (PBS)



Immunotherapy

Obstacles for Ab therapy



- ☒ Antibody decay
- ☒ Resistance mutations

- ☑ Multi-epitope targeting
- ☑ Antibody half-life extension
- ☑ Sustained antibody secretion

Immunotherapy

Coming…

ANTIBODIES				
VRC01 (analytical treatment interruption in HVTN 703/HPTN 081 AMP trial participants)	NCT04860323	HIV Vaccine Trials Network	N/A	November 2029
VRC01 (analytical treatment interruption in AMP trial participants)	NCT04801758 (closed to enrollment)	HIV Vaccine Trials Network	N/A	January 2030
GSK3810109A (broadly neutralizing antibody formerly named N6-LS)	NCT04871113 (closed to enrollment)	ViiV Healthcare	Phase IIa	September 2023 CROI 2023, Abstract 520 HIV Glasgow 2022, Abstract O34
10-1074-LS + **3BNC117-LS** in primary HIV infection	NCT04319367	Imperial College London	Phase II	March 2025 IAS HIV Cure & Immunotherapy Forum 2023 HIV Persistence Workshop 2022, Abstracts OP 7.2, PP 8.11 (slides) Trials. 2022 Apr 5;23(1):263
3BNC117-LS + **10-1074-LS**	NCT05300035 (not yet open for enrollment)	French National Agency for Research on AIDS and Viral Hepatitis (ANRS)	Phase II	December 2028
UB-421 (antibody inhibitor of HIV binding to CD4 receptors)	NCT04404049 (not yet open for enrollment)	UBP Greater China (Shanghai) Co., Ltd	Phase II	June 2025
vedolizumab (anti-$\alpha_4\beta_7$ integrin antibody)	NCT03147859	Ottawa Hospital Research Institute	Phase II	December 2023 BMJ Open. 2020;

http://www.treatmentactiongroup org/cure/trials

Immunotherapy

Coming…

VRC07-523LS + **PGT121.414.LS**	NCT05719441 (not yet open for enrollment)	NIAID	Phase II	September 2028
3BNC117-LS-J + **10-1074-LS-J**	NCT06031272 (not yet open for enrollment)	ACTG	Phase I	June 2026
3BNC117-LS + **10-1074-LS**	NCT05612178	NIAID	Phase I	December 2025
AAV8-VRC07 (broadly neutralizing antibody delivered by AAV vector)	NCT03374202 (closed to enrollment)	NIAID	Phase I	August 2026 Nat Med. 28(5):1022-1030. CROI 2022, Abstract 498 CROI 2021, Abstract 160, Webcast CROI 2020, Abstract 41LB, Webcast
SAR441236 (tri-specific broadly neutralizing antibody)	NCT03705169 (closed to enrollment)	NIAID	Phase I	November 2023

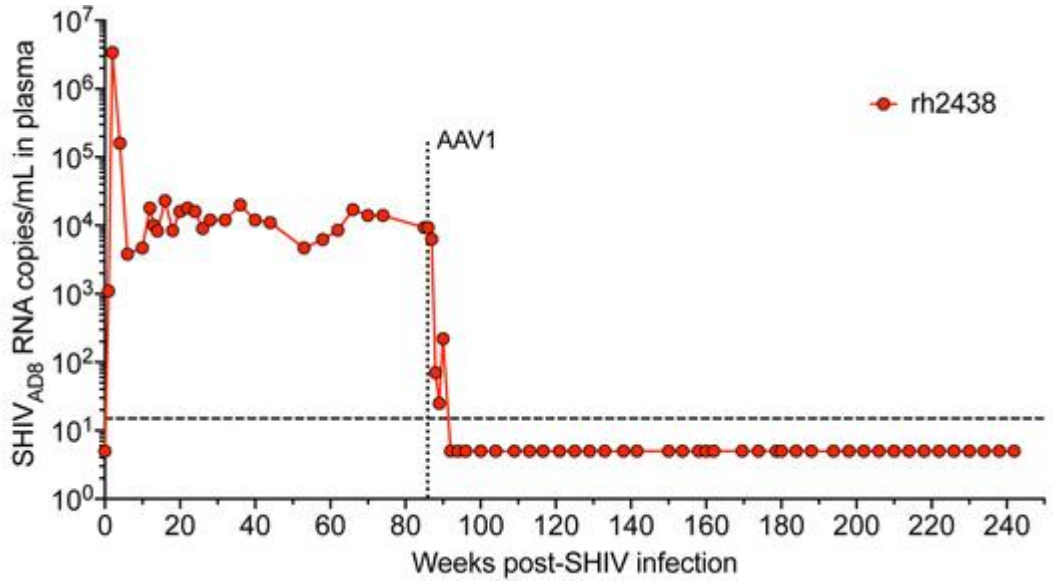
http://www.treatmentactiongroup org/cure/trials

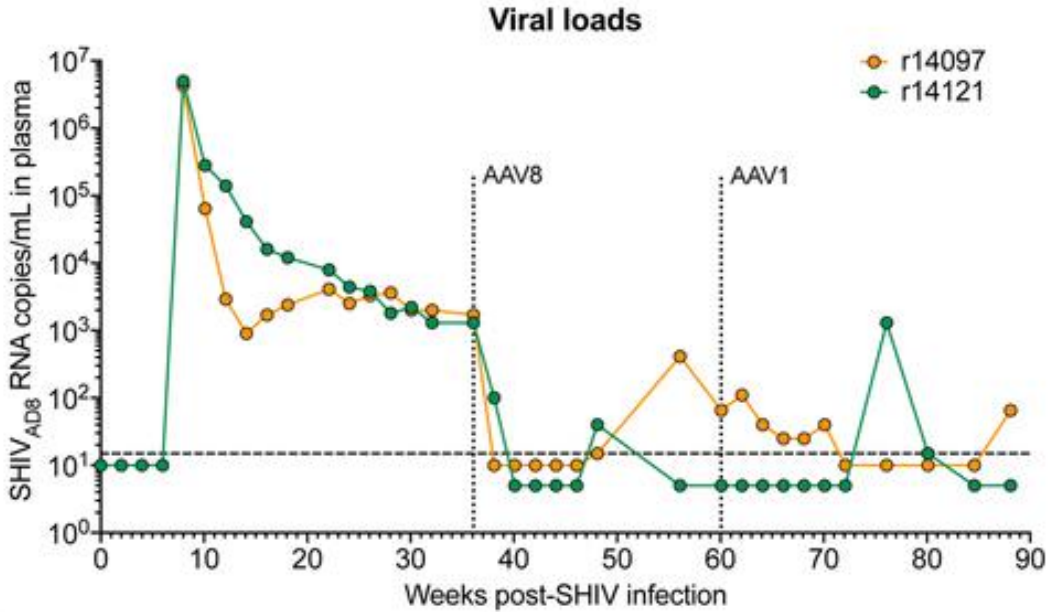
Immunotherapy

Sustained Ab production

→ AAV-delivered mAbs

AAV-encoded mAbs in **non-human primates**





Limitation anti-drug antibodies

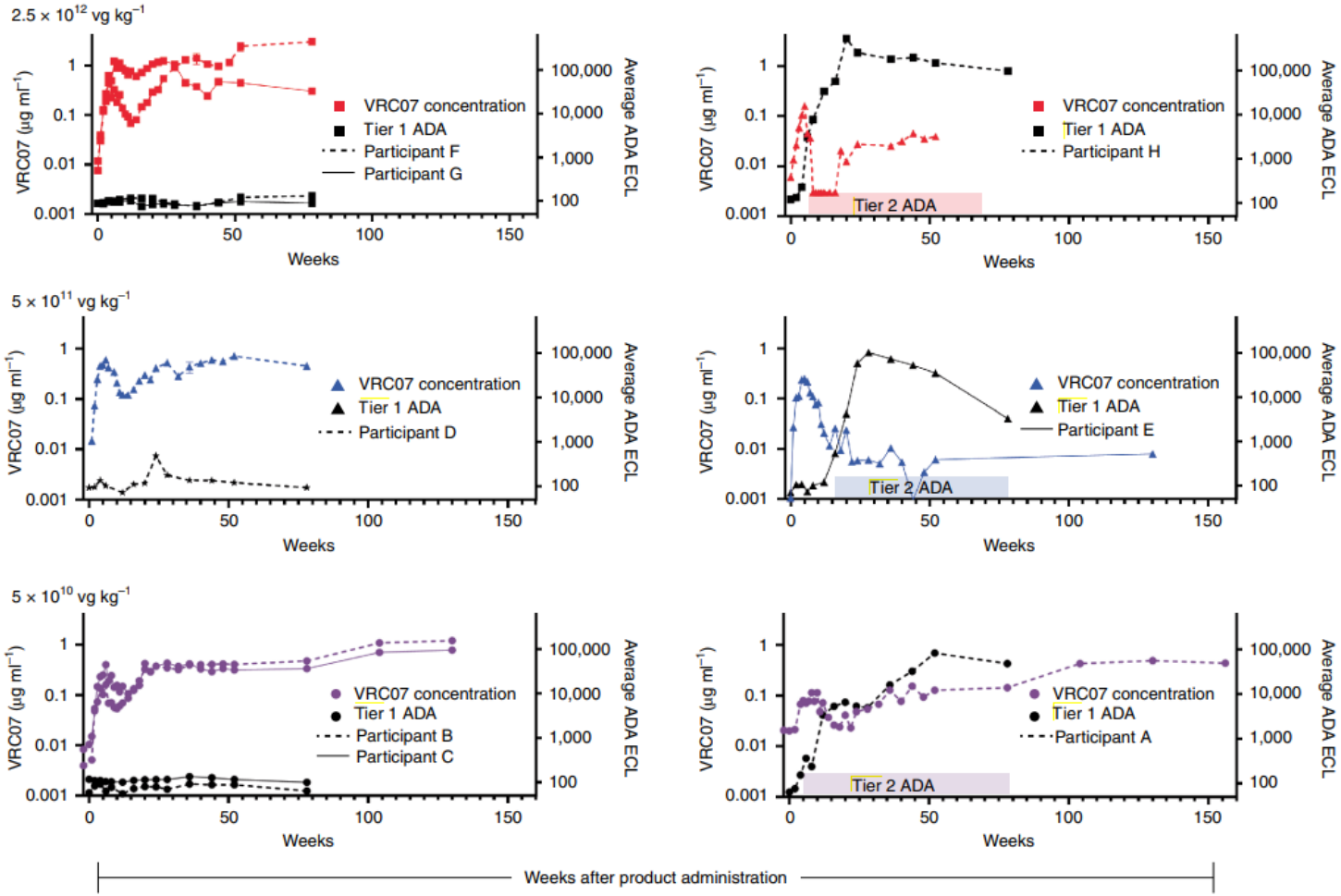
New approximations are being tested to overcome ADA

Martinez-Navio et al., Immunity 2019

Immunotherapy

Sustained Ab production

→ Phase I, IM AAV8-VRC07 in humans

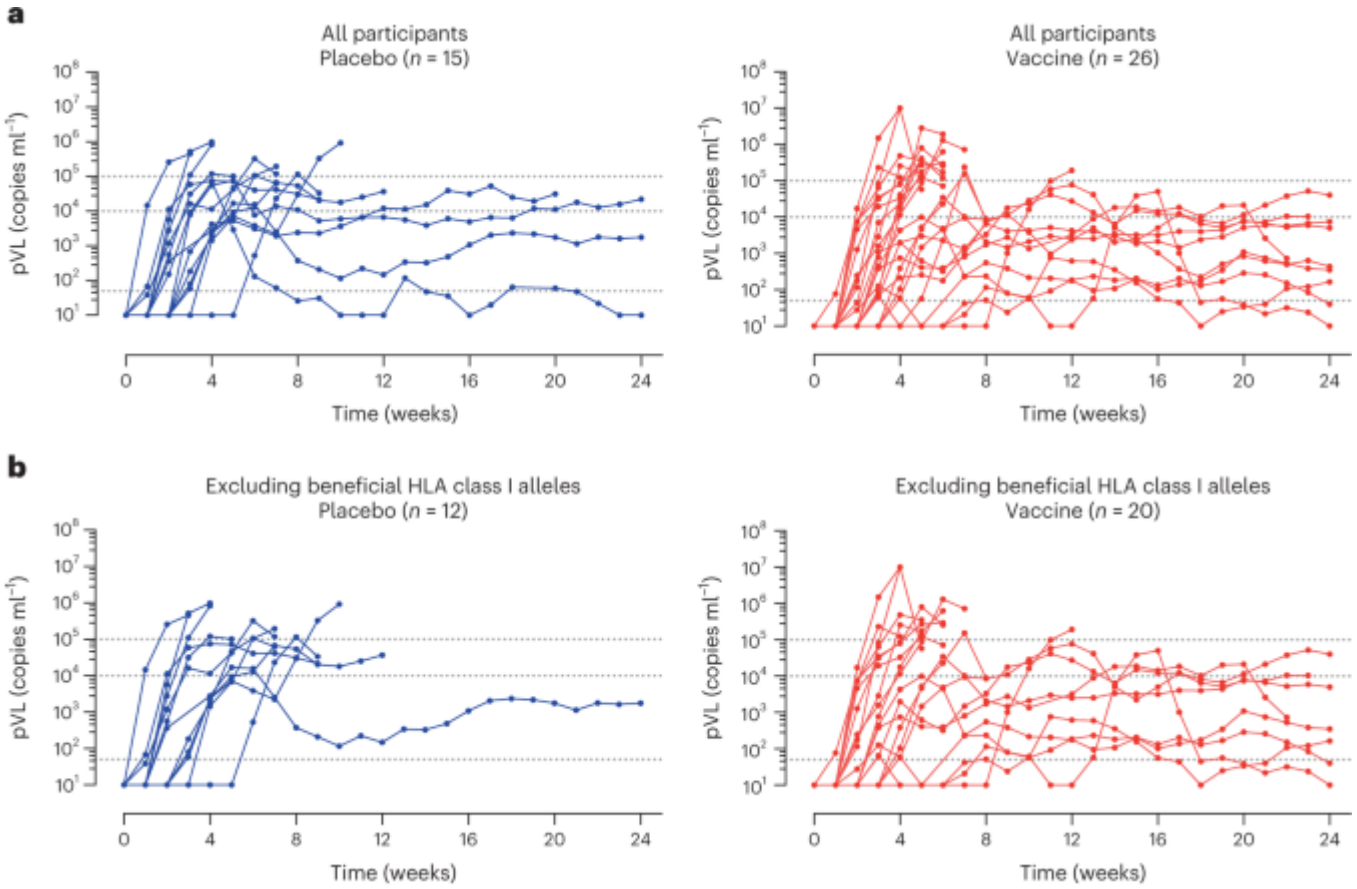


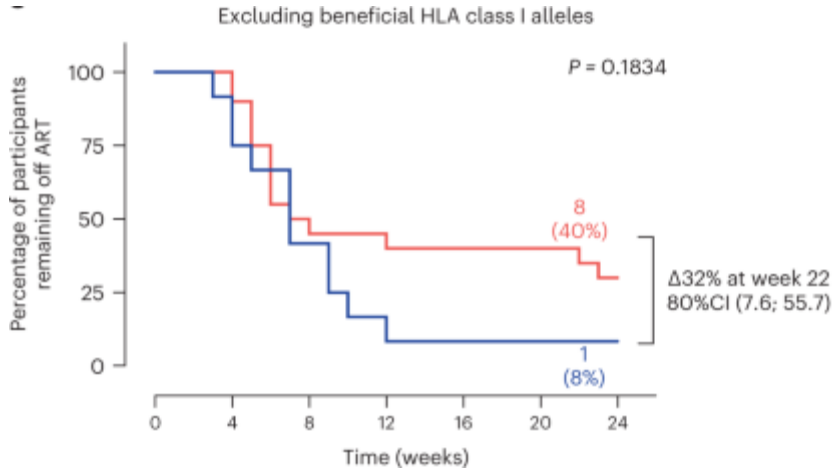
Casazza et al., Nat Med 2022

Immunotherapy

Therapeutic vaccines

→ Therapeutic vaccine strategies that enhance HIV control in the absence of ART





Bailón et al., Nat Med, 2022

Immunotherapy

Therapeutic vaccines

→ More coming

THERAPEUTIC VACCINES				
BELIEVE: BCG vaccination effect on latent reservoir size in treated HIV-1 infection	NCT05004038 (closed to enrollment)	University of Zurich	Phase IIa	January 2024
GS-1966/GS-1144 HIV vaccine regimens	No clinicaltrials.gov entry, #7 on Midway Research Center list	Gilead Sciences	Phase Ib	N/A
426c.Mod.Core-C4b, 3M-052-AF + Alum	NCT06006546 (not yet open for enrollment)	NIAID, HIV Vaccine Trials Network	Phase I	December 2025
ChAdOx1.HIVconsv62–MVA.tHIVconsv4 (C62-M4), ChAdOx1.tHIVconsv1+C62-MVA.tHIVconsv3+M4 (C1C62-M3m4)	NCT05604209	University of North Carolina, Chapel Hill	Phase I	August 2024
ChAdOx1.HTI, MVA.HTI, ConM SOSIP.v7 gp140	NCT05208125 (closed to enrollment)	IrsiCaixa	Phase I	December 2023
DC-HIV04: a1DC + inactivated whole autologous HIV, a1DC + conserved HIV peptides	NCT03758625	Sharon Riddler, University of Pittsburgh	Phase I	March 2025
ICVAX: PD-1-enhanced HIV DNA vaccine	CTR20223007	Immuno Cure BioTech	Phase I	N/A IAS HIV Cure & Immunotherapy Forum 2023
NETI: Trimer 4571 therapeutic vaccination	NCT04985760	NIAID	Phase I	January 2025
Therapeutic vaccine based on aDC1 dendritic cells	NCT05786937 (not yet open for enrollment)	University of Sao Paulo General Hospital	Phase I	December 2023

http://www.treatmentactiongroup.org/cure/trials

Immunotherapy

Therapeutic vaccines

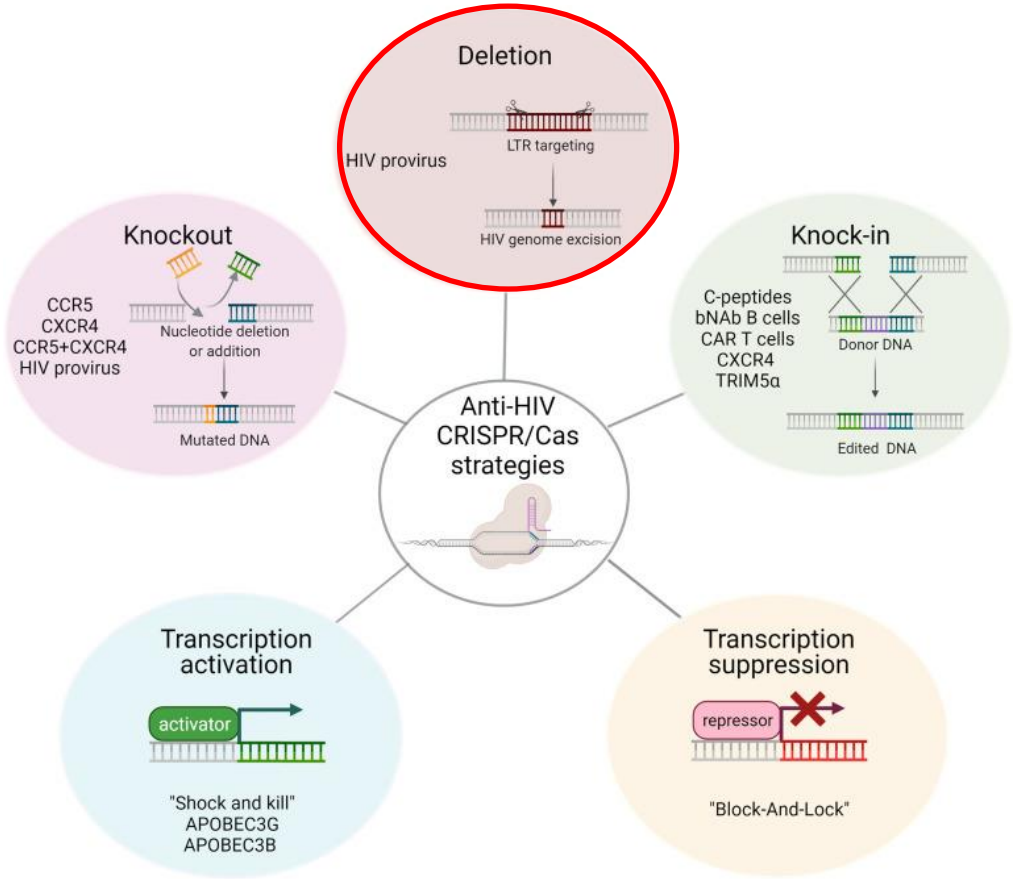
→ Combinations

Ad26.Mos4.HIV, MVA-BN-HIV, PGT121, PGDM1400, VRC07-523LS (therapeutic vaccines, broadly neutralizing antibodies)	NCT04983030	Boris Juelg, MD PhD	Phase I/IIa	April 2026
IMPAACT P1115 v2.0: Very early intensive treatment of HIV-infected infants to achieve HIV remission (ART +/– VRC01)	NCT02140255	IMPAACT	Phase I/II	December 2031 Strategies for an HIV Cure 2023, Abstract PP05 CROI 2022, Abstract 31
panobinostat + pegylated interferon-alpha2a	NCT02471430 (closed to enrollment)	Massachusetts General Hospital	Phase I/II	December 2023 CROI 2022, Abstract 357 CROI 2020, Abstract 341
Therapeutic conserved element DNA vaccine (**IL-12 adjuvanted p24CE**), MVA vaccine boost (**MVA/HIV62B**), TLR9 agonist (**lefitolimod**), broadly neutralizing antibodies (**VRC07-523LS + 10-1074**)	NCT04357821 (closed to enrollment)	UCSF	Phase I/II	December 2024 Strategies for an HIV Cure 2023, Abstract PP66 CROI 2023, Abstract 435
FT538 +/- vorinostat	NCT05700630 (not yet open for enrollment)	Masonic Cancer Center, University of Minnesota	Phase I	August 2024
HVRRICANE: HIVIS DNA + MVA-CMDR vaccines +/- TLR4 agonist	NCT04301154	PENTA Foundation	Phase I	October 2023
N-803 (recombinant human super agonist interleukin-15 complex) +/- **VRC07-523LS + 10-1074**	NCT04340596	NIAID	Phase I	April 2026
N-803, 3BNC117-LS, 10-1074-LS	NCT05245292	Rockefeller University	Phase I	December 2025
VRC07-523LS, PGDM1400LS, N-803, Ad26.Mos4.HIV, MVA-HIV, A244d11gp120/ALFQ	NCT05769569 (not yet open for enrollment)	Henry M. Jackson Foundation for the Advancement of Military Medicine	Phase I	July 2025

http://www.treatmentactiongroup.org/cure/trials

Gene Therapy

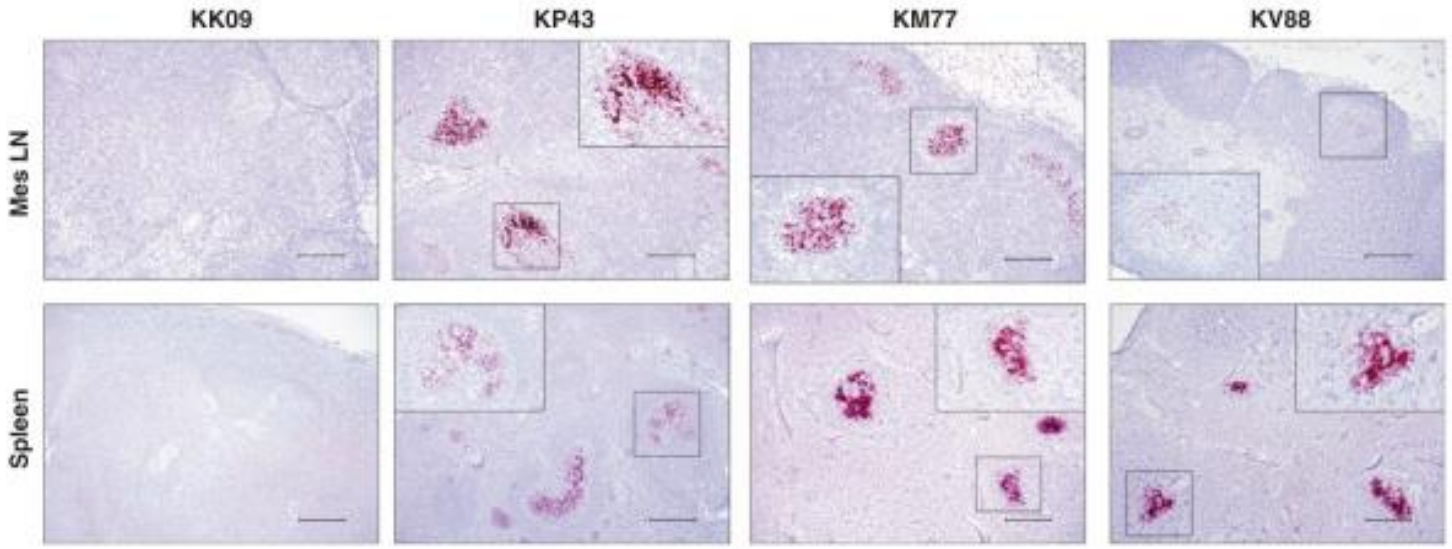
Gene-based and cell-based therapies

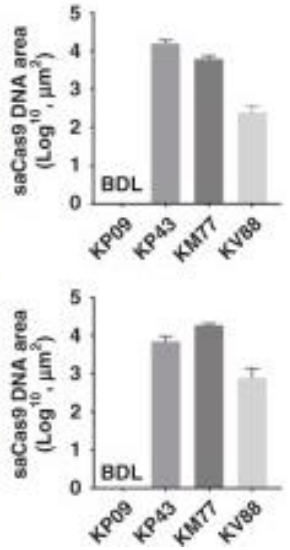


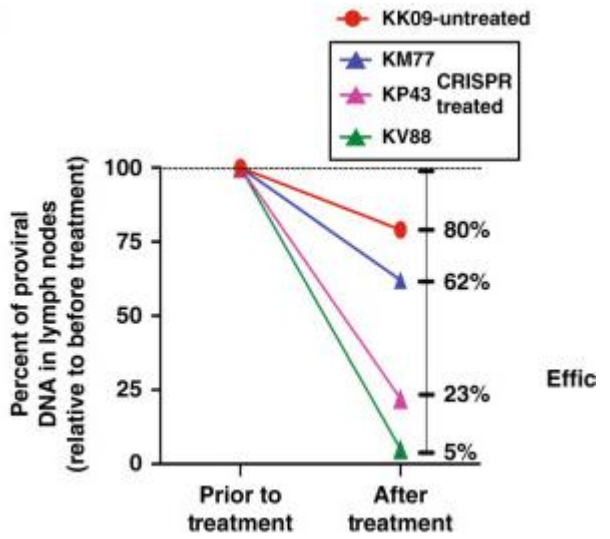
Alexandra Maslennikova et al, Front Cell Infect Microbiol.2022

Gene Therapy

→ AAV9-CRISPR/Cas9 gene editing construct designed for eliminating proviral DNA (non-human primates)







Clinical trials are ongoing: Excision Biotherapeutics → First in-human trial Phase I/IIa. EBT-101 is a HIV-1-specific CRISPR)/Cas9

Mancuso et al., Nature 2020

Gene Therapy

GENE THERAPIES				
EBT-101 (CRISPR/Cas9 targeting HIV provirus)	NCT05144386	Excision BioTherapeutics	Phase I/IIa	March 2025
LVgp120duoCAR-T cells	NCT04648046	Steven Deeks, UCSF	Phase I/IIa	December 2027
Cal-1: Dual anti-HIV gene transfer construct	NCT02390297 (closed to enrollment)	Calimmune	Phase I/II	October 2031 CROI 2020, Abstract 338
SB-728-T (autologous T cells gene-modified to disrupt CCR5 receptor expression)	NCT03666871 (closed to enrollment)	Case Western Reserve University	Phase I/II	February 2024
An ATI study to evaluate the impact of **AGT103-T** to suppress HIV replication in the absence of ART	NCT05540964 (enrolling by invitation)	American Gene Technologies International Inc.	Phase I	July 2025
CD4 CAR + SB-728mR modified T cells	NCT03617198 (closed to enrollment)	University of Pennsylvania	Phase I	December 2027 CROI 2022 (James L. Riley)
Chimeric Antigen Receptor (CAR)-T cell therapy	NCT03240328	Guangzhou 8th People's Hospital	Phase I	December 2030 J Clin Invest. 2021 Aug 10;150211.
EBT-101 (long-term follow-up study)	NCT05143307 (enrolling by invitation)	Excision BioTherapeutics	Phase I	April 2037
Long-term follow-up of HIV+ participants exposed to **SB-728-T** or **SB-728mR-T**	NCT04201782 (enrolling by invitation)	Sangamo Therapeutics	Phase I	June 2035
Long-term follow-up of study participants treated with **AGT103-T**	NCT05529342 (enrolling by invitation)	American Gene Technologies International Inc.	Phase I	September 2038
SB-728mR-HSPC (autologous hematopoietic stem/progenitor cells modified at the CCR5 gene)	NCT02500849 (closed to enrollment)	City of Hope Medical Center	Phase I	December 2023

http://www.treatmentactiongroup.org/cure/trials

Outline

Strategies:

- Intens/Early ART
- LRAs/LPAs
- Immunotherapy
- Gene Editing

Considerations for HV Cure Research:

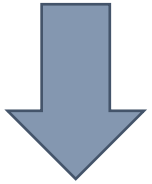
- Tissue Reservoirs
- Biological Sex
- Long-acting ART

Tissue Reservoirs Studies

→ The **gastrointestinal** tract and the **lymph nodes** constitute main anatomical sites in which HIV establishes persistence, mainly during acute infection and when ART is initiated

→ Sample availability from people with HIV (PWH) limits their study

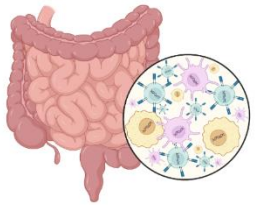
→ New tools are needed



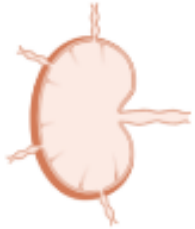
Development of Latency Models in Human Tissues

Tissue Reservoirs

Intestine
(mainly colon)



Tonsil



Cervix

"la Caixa" Foundation

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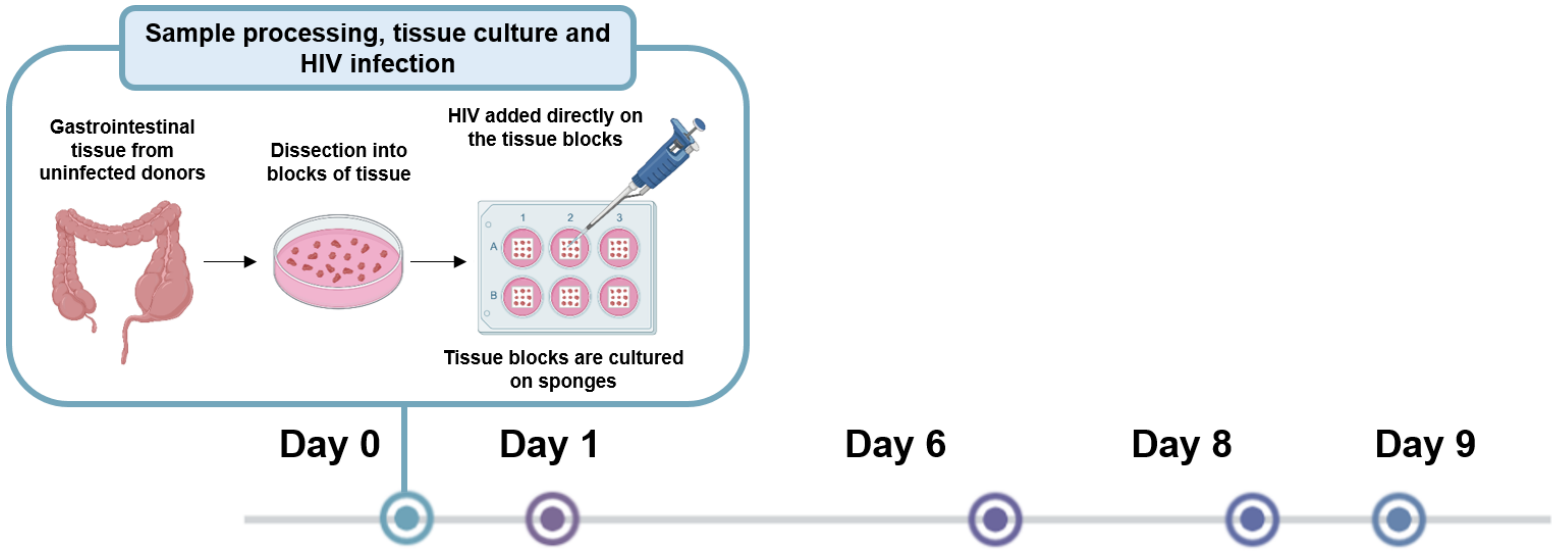
PI: Enrique Martin-Gayo (Universidad Autónoma de Madrid)
PI: Meritxell Genescà (Vall d' Hebron Research Institute)
PI: Julia G. Prado (IrsiCaixa AIDS Research Institute)

Tissue Reservoirs

Experimental design



Tissue Reservoirs

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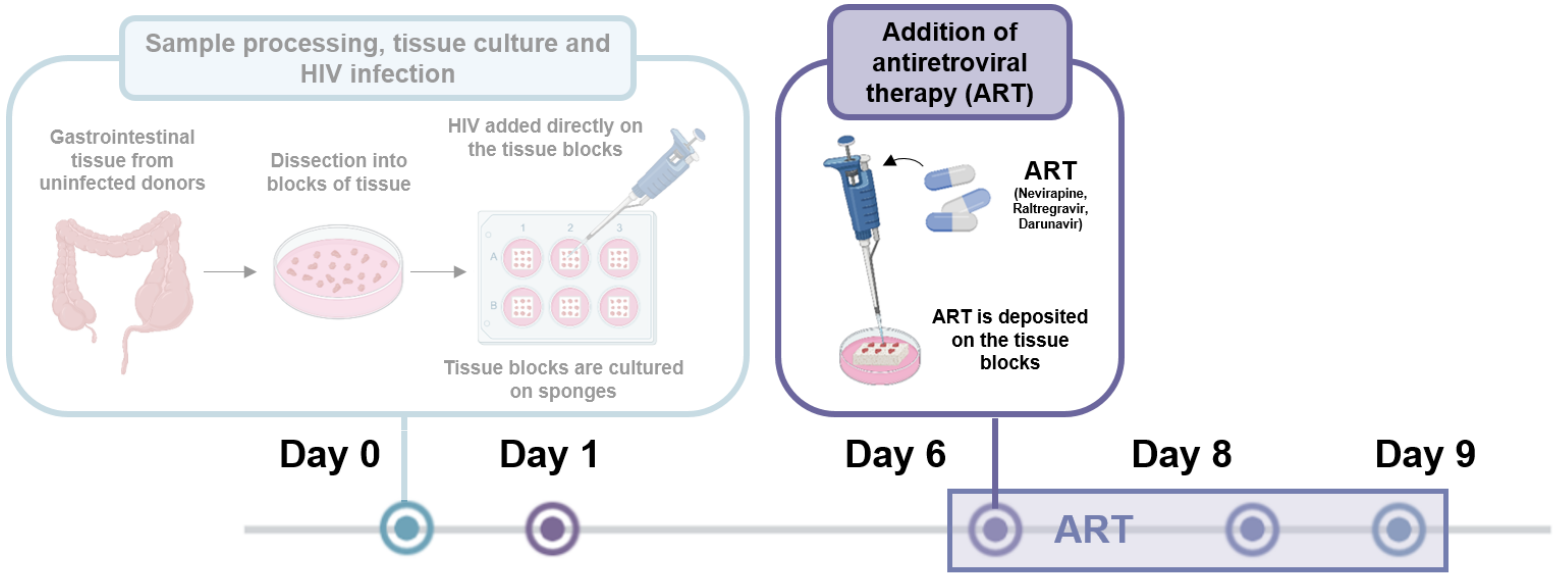
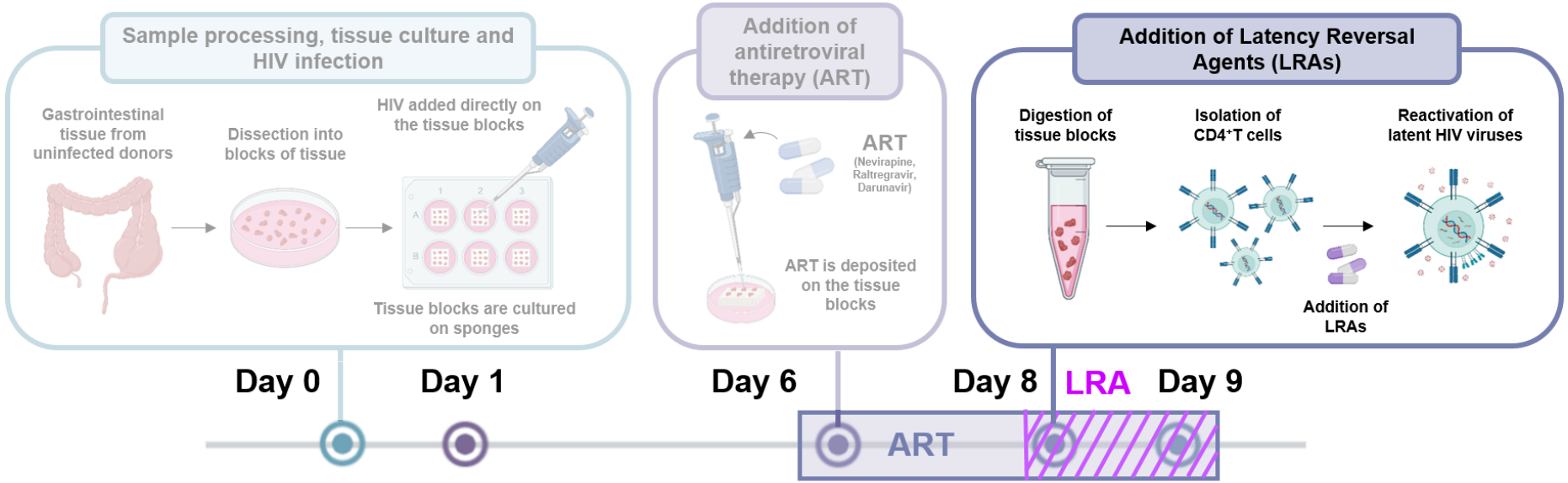


Tissue Reservoirs

Experimental design



Tissue Reservoirs

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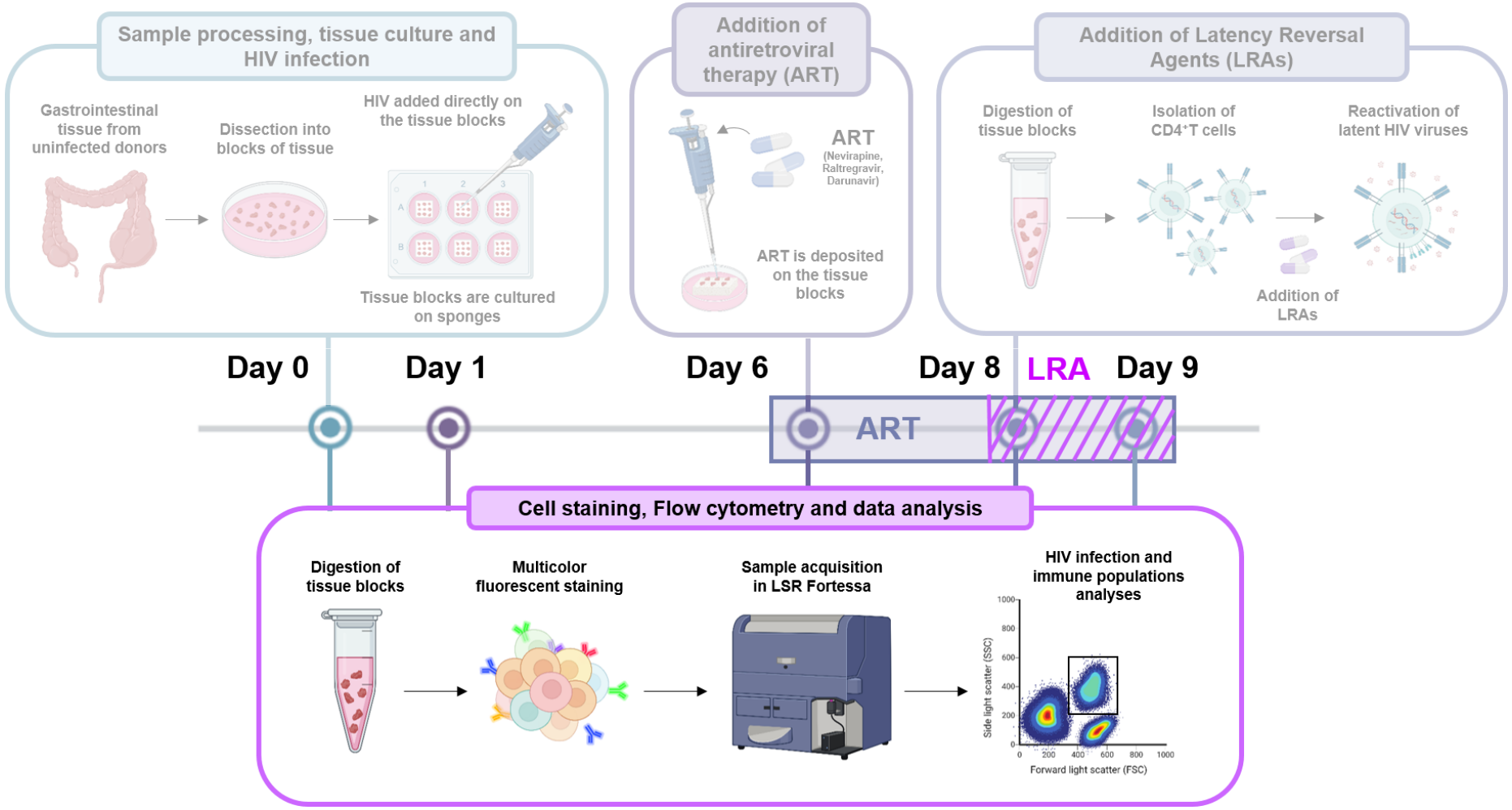

Tissue Reservoirs

- We have developed **tissue models of HIV persistence** to:
- Study the heterogeneity of the HIV-reservoir cells
- Investigate the effects of LRAs on different key CD4+ T cell subsets
- Explore innate immunity within tissues
- Develop new strategies aimed at enhancing local immune responses

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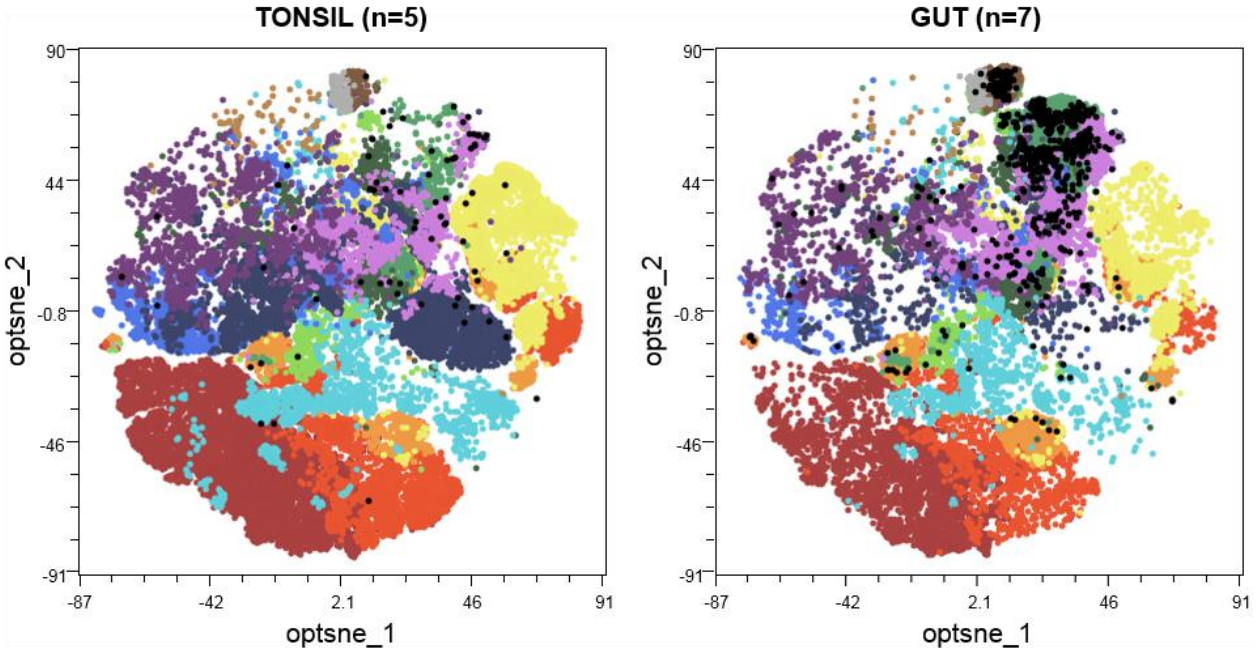

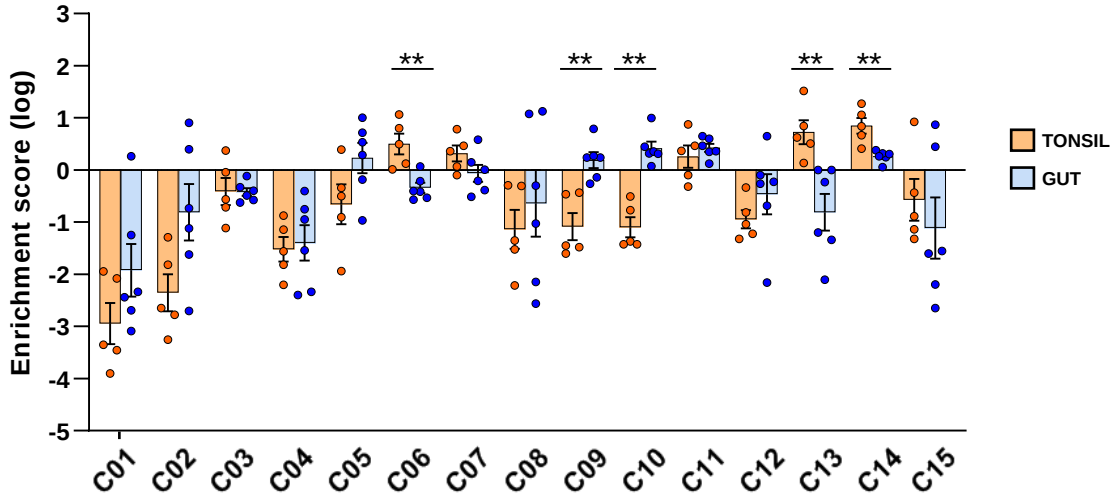

- **C06: $T_{EM\text{-}CD69+CD49a+}$:** $CXCR5^{-}$ $PD1^{-}$ $CD45RO^{+}$ $CCR7^{-}$ $CD69^{+}$ $CD103^{-}$ $CD49a^{+}$ $CD127^{mid}$
- **C09: $T_{EM\text{-}CD69+\text{-}CXCR5+}$:** $CXCR5^{+}$ $PD1^{-}$ $CD45RO^{+}$ $CCR7^{-}$ $CD69^{+}$ $CD103^{-}$ $CD49a^{-}$ $CD127^{-}$
- **C10: $T_{FH\text{-}EM\text{-}CD69+}$:** $CXCR5^{+}$ $PD1^{+}$ $CD45RO^{+}$ $CCR7^{-}$ $CD69^{+}$ $CD103^{-}$ $CD49a^{-}$ $CD127^{-}$
- **C13: $T_{NA\text{-}CD69+\text{-}CXCR5+}$:** $CXCR5^{+}$ $PD1^{-}$ $CD45RO^{-}$ $CCR7^{+}$ $CD69^{+}$ $CD103^{-}$ $CD49a^{-}$ $CD127^{-}$
- **C14: $T_{EM\text{-}CD69+\text{-}CD103+\text{-}CD49a+}$:** $CXCR5^{-}$ $PD1^{-}$ $CD45RO^{+}$ $CCR7^{-}$ $CD69^{+}$ $CD103^{+}$ $CD49a^{+}$ $CD127^{+}$

Tissue Reservoirs

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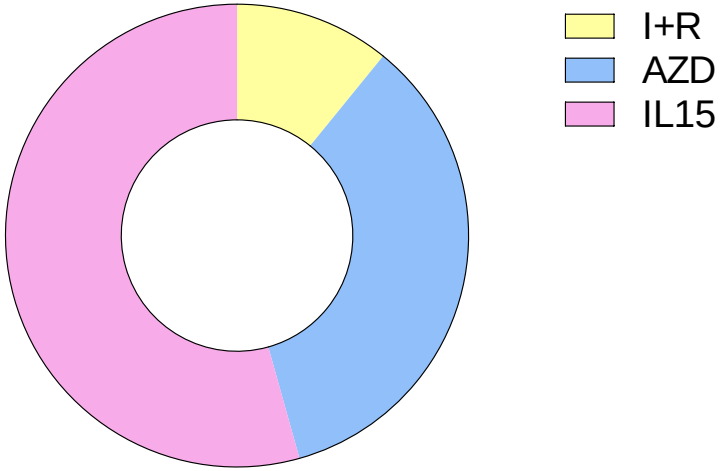
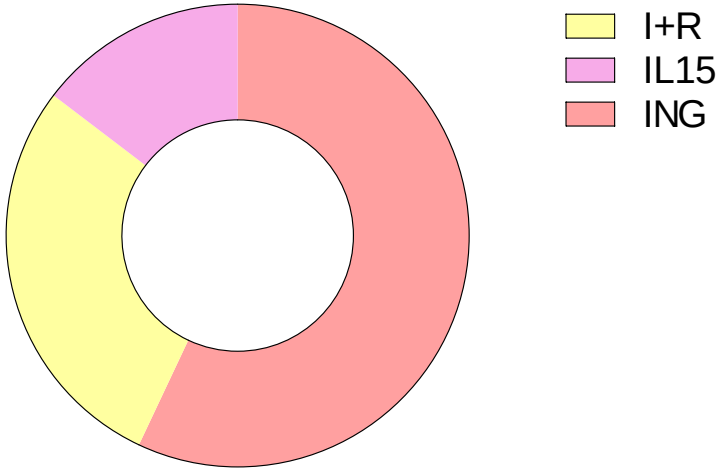
Tissue Reservoirs

The **effect of different LRAs** was evaluated in the CD4⁺ T subsets: Ingenol (ING), Romidepsin (RMD), ING + RMD, Panobinostat (PNB), AZD5582 (AZD) and IL-15

Gut total CD4 LRAs



Tonsil total CD4 LRAs



Innate Immunity

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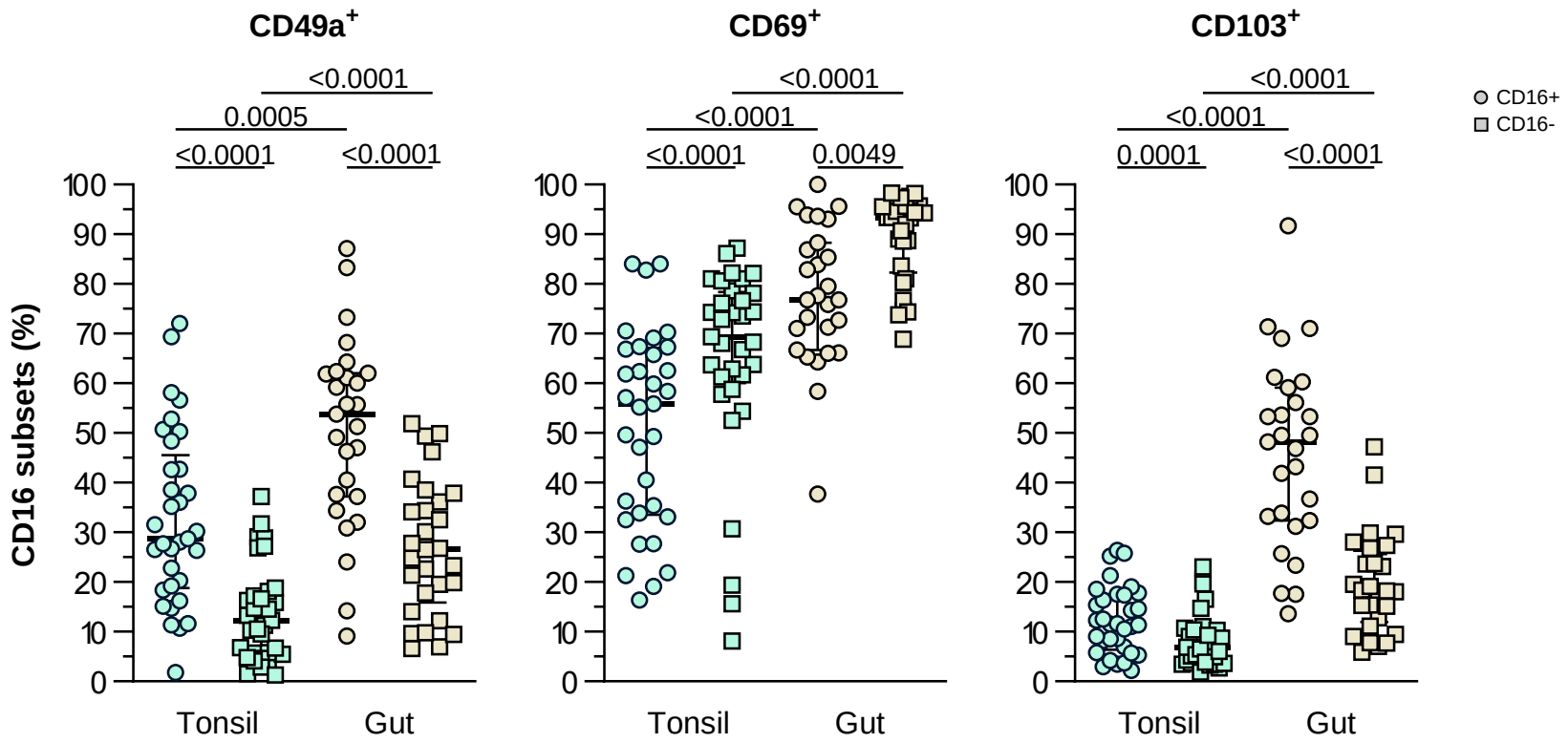
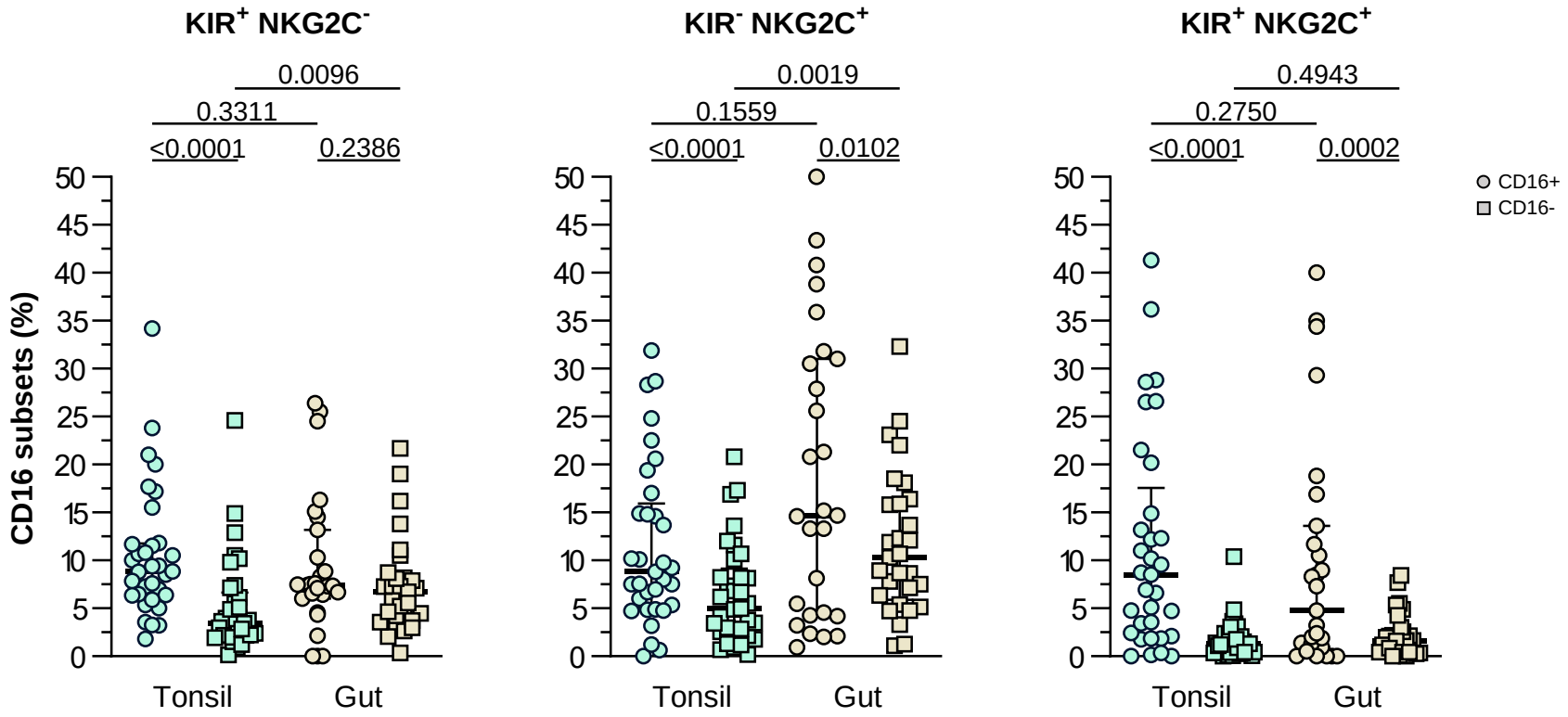
- **Explore innate immunity within tissues**
- Develop new strategies aimed at enhancing local immune responses

Innate immunity in tissues



→ Gut NK have more resident markers, including CD69, CD103 and CD49a, than tonsil NK cells

Innate immunity in tissues

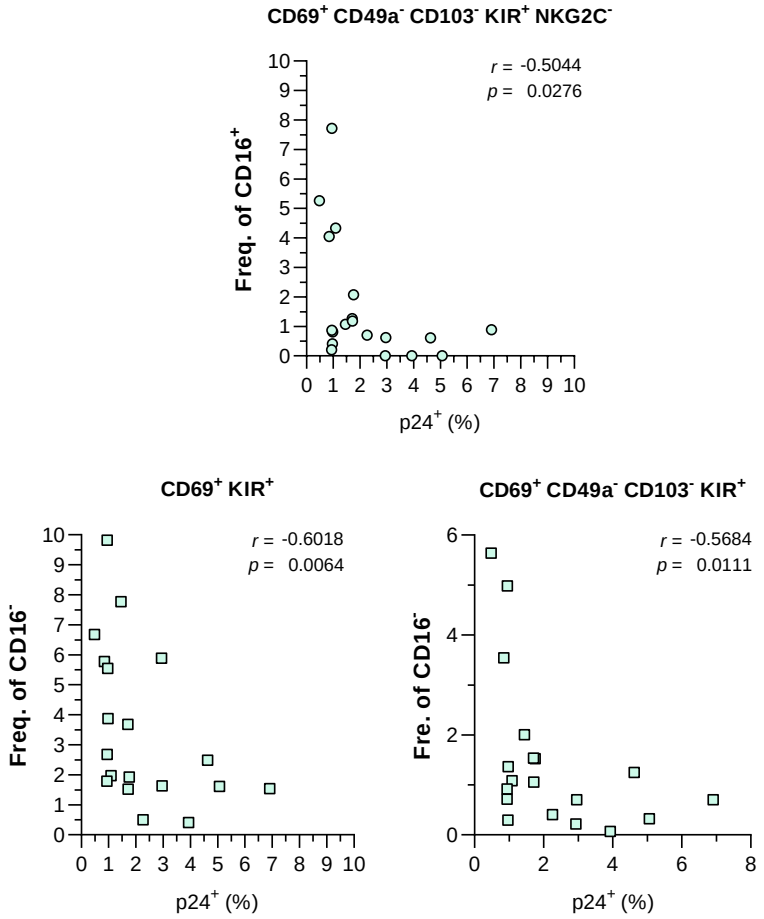


→ Gut tissue have more KIR+ and NKG2C+ (memory-like) NK cells, specially on the CD16- population, than tonsil NK cells

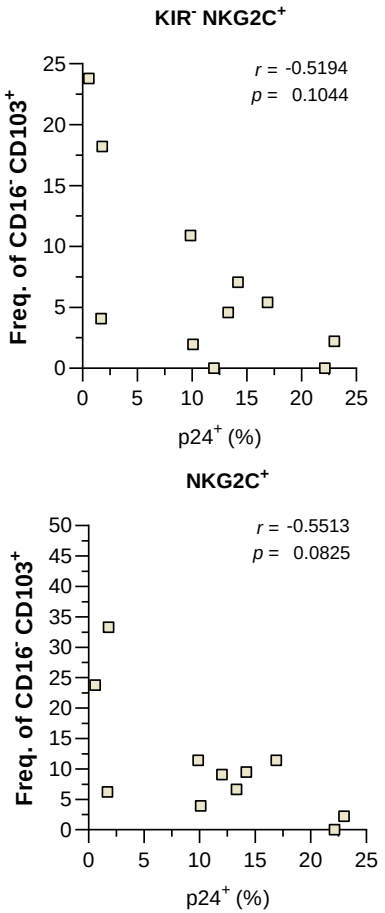
Innate Immunity

Innate immunity in tissues

Tonsil NKs



Gut NKs



→ In tonsils, CD69+CD49-KIR+ NK cells are associate with lower level of HIV-infection

→ In gut, CD103+KIR+ and NKG2C+ NK cells are associate with lower level of HIV-infection

Outline

Strategies:

- Intens/Early ART
- LRAs/LPAs
- Immunotherapy
- Gene Editing

Considerations for HV Cure Research:

- Tissue Reservoirs
- Biological Sex
- Long-acting ART

Considerations for HIV Cure Research

Biological Sex

→Women have lower set-point HIV RNA levels during primary infection *(Sterling et al., NEJM 2001)*

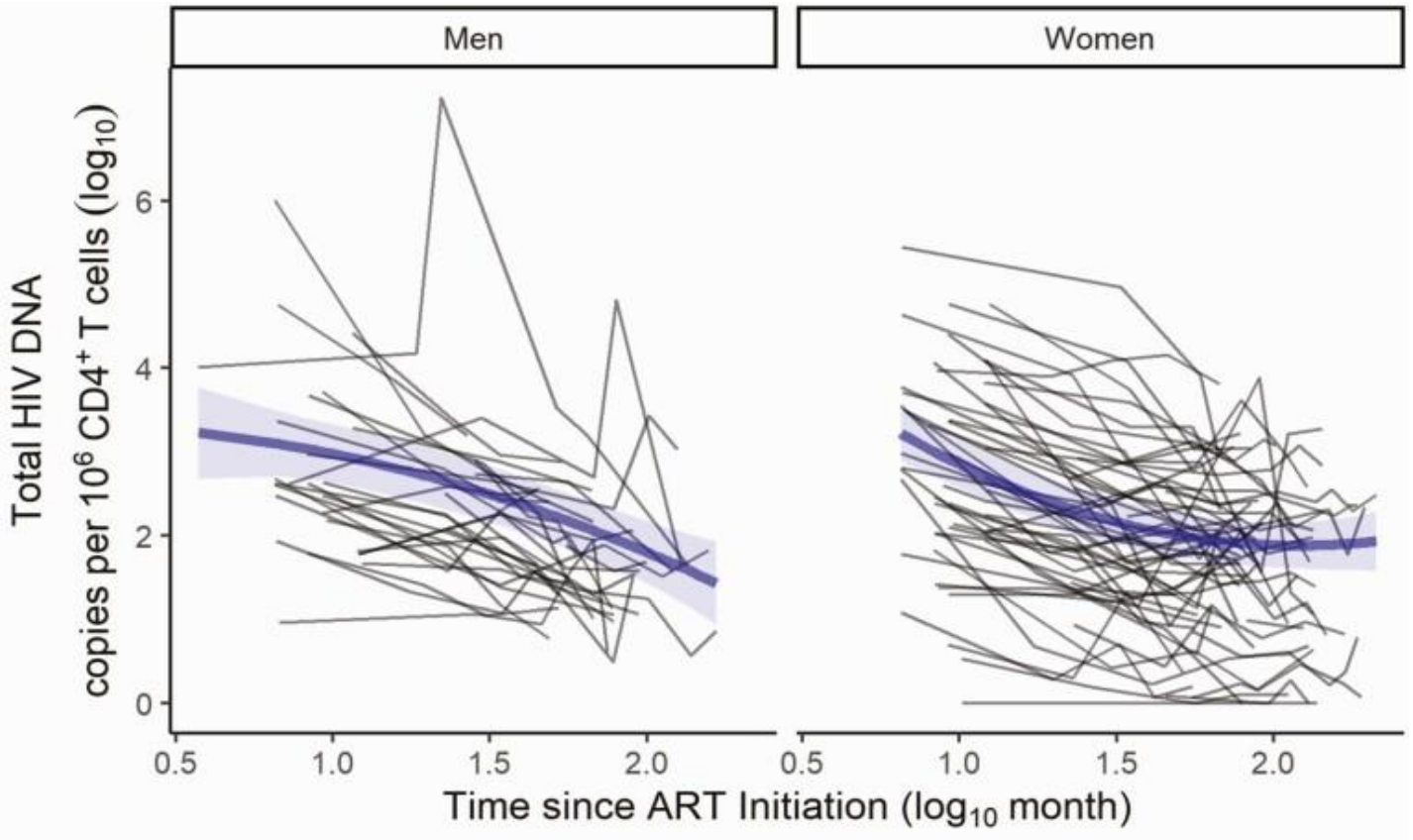
→Higher activation of interferon-stimulated genes *(Sterling et al., JID 2013; Griesbeck et al., J Immunol 2015)*

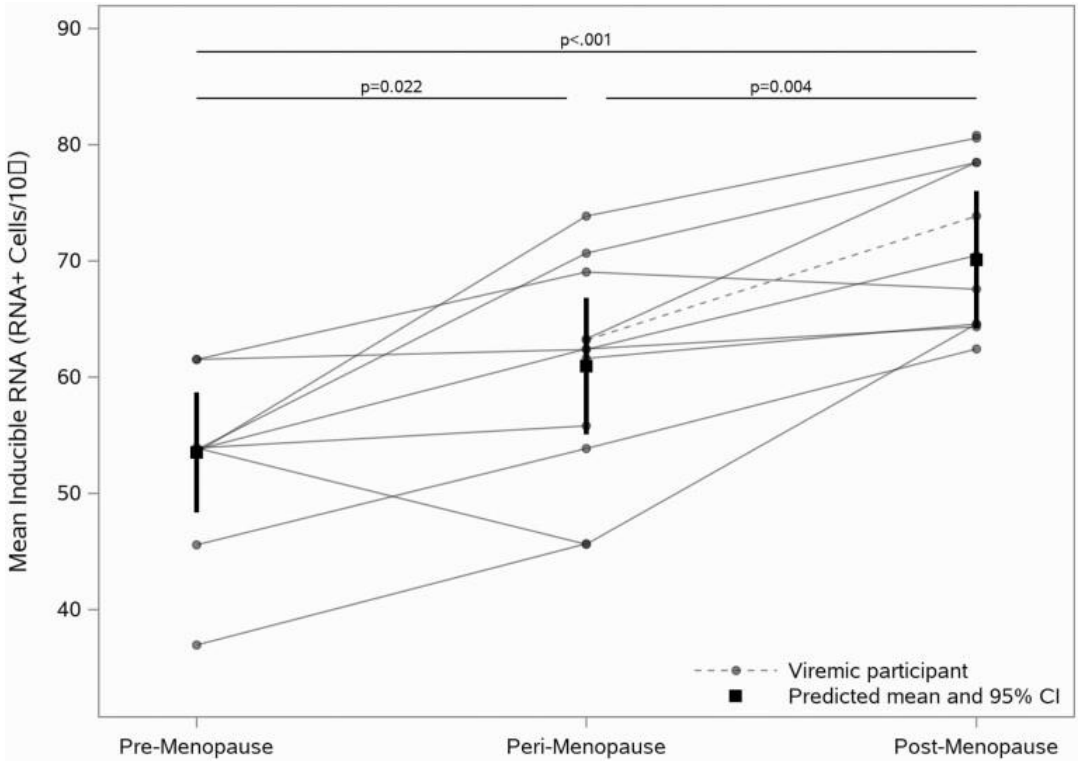
→Accelerated disease progression at a given viral load *(Griesbeck et al., AIDS 2001)*

→Proinflammatory effects of persistent interferon α production *(Addo et al., JID 2014)*

Considerations for HIV Cure Research

Biological Sex





Gianella et al, Clin Inf Dis 2022

Considerations for HIV Cure Research

Remaining questions

→Is the selection and evolution of the HIV reservoir equal between both sexes?

→Are proviral reservoir size, composition, and integration site profile similar between women and men?

→Is the activity of immune modulators and LRAs the same between both biological sexes?

Outline

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Considerations for HV Cure Research:

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Considerations for HIV Cure Research

Long-acting ART

- Long-acting drugs will complicate the (rapid) treatment interruption, necessary to evaluate cure strategies
- Possible selection of resistance mutation during the period of drug decay
- Need to cover the “decay period” with daily drugs
- Need to monitor drug levels during “remission” period

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