



VIII JORNADAS DOCENTES

Viernes 23 y sábado 24 de septiembre

¿El futuro es la inmunoterapia?

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CONTENT

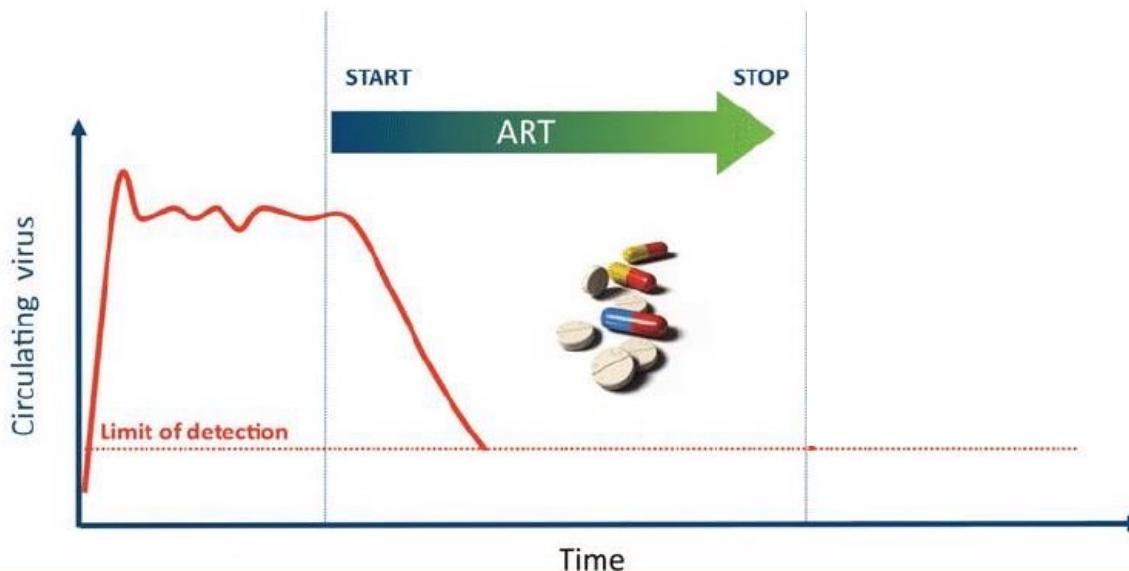
- Immunotherapy definition
- Objective & TPP: HIV eradication vs Functional Cure
- Current strategies being studied alone or in combination
 - Therapeutic vaccines
 - Immunomodulators
 - bNAbs
- Conclusions

Immunotherapy is any treatment with a mechanism of action is the activation/amplification or suppression/reduction of an immune response.

- Examples:
 - *BCG vaccine for the treatment of vesical cancer*
 - *Monoclonal antibodies against CD20 (rituximab/ocrelizumab) for autoimmune and hematological diseases*
 - *Monoclonal antibodies against immune Checkpoint suchs as PD1 (pembrolizumab) for lung cancer*
 - *Cancer therapeutic vaccines*
 - *Etc.*

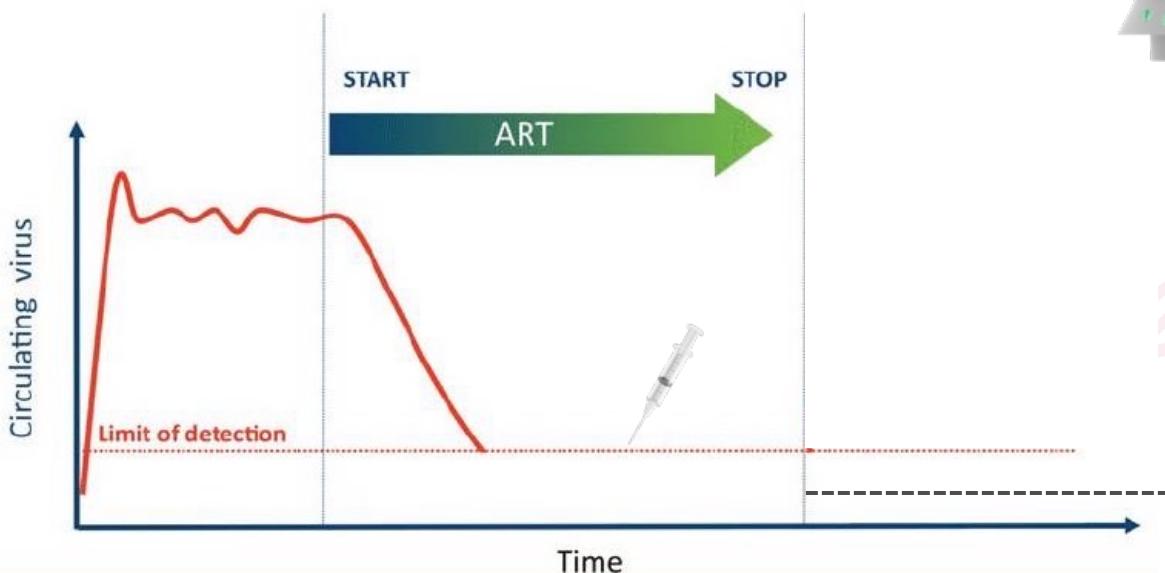
OBJECTIVES

- ART effectively blocks active viral replication but does not eliminate viral reservoir.
- There is residual replication and inflammation → aging / comorbidities.
- Virus rebounds fast upon ART interruption

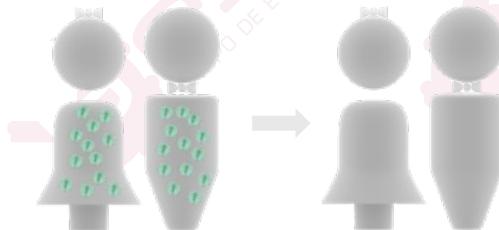


OBJECTIVES

- Can we achieve an absence of viral rebound?



HIV Eradication
Sterilizing cure



Hütter, AIDS 2011
Tebas, NEJM 2014

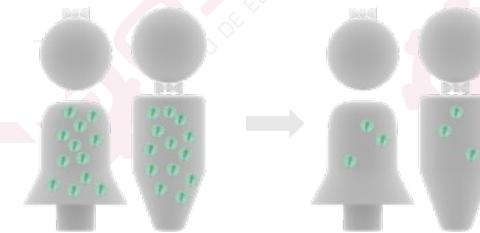
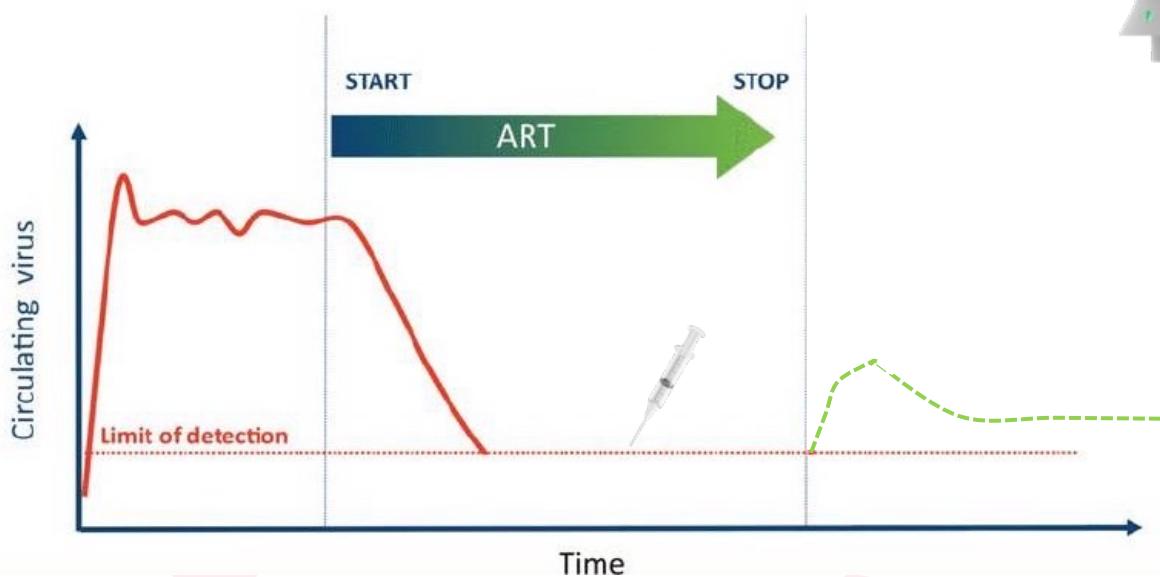
Duarte & Salgado, Lancet HIV 2015
Gupta, Nature 2019
Gupta, Lancet HIV 2020



OBJECTIVES

- Or contain viral rebound to low levels (=VC, EC, EEC, PTC)?

HIV remission
Functional cure



Shepperd, AIDS 1993
Buchbinder, AIDS 1994
Casado Sci Rep 2020
Esperanza

Sáez-Cirion, PLoS Path 2013





Multi-stakeholder consensus on a target product profile for an HIV cure



Sharon R Lewin*, Timothy Attoye, Cathy Bansbach, Brian Doeble, Karine Dubé, Mark Dybul, Devi SenGupta, Adam Jiang, Rowena Johnston, Rosanne Lamplough, Joseph M McCune, Gary J Nabel, Thumbi Ndung'u, John Pottage, David Ripin, James F Rooney, Izukanji Sikazwe, Moses Nsubuga, Mitchell Warren, Steven G Deeks*, on behalf of the Sunnylands 2019 Working Group

	Minimum	Optimum (→ similar to ART!!)
Target Population	>16 and <65, ART suppressed, CD4 >500	All PLWH
Clinical Efficacy	pVL < 200 (transmission threshold) in >20% of individuals. Relapse rate <10%/year Remission duration >2years	pVL <50 In >90% individuals Relapse rate <2%/year Remission duration >3 years or complete eradication of virus, including the rebound-competent reservoir, as detected by a diagnostic assay
Safety & tolerability	No SAEs, Low frequency of reversible G3 (depending of efficacy)	No G3 or 4
Protection from reinfection	None	Full
Etc.		



Allo- HSCT Complex procedure:

- Bone Marrow Transplant from a CCR5 delta32 donor
- High mortality
- Only for certain onco/hematological disorders
- Graft vs HIV mechanism behind?

Spontaneous control in the absence of ARV or after very early-ARV initiation :

- Low – extremely low viral reservoir
- Limited diversity – low evolution
- Integration in silenced sites
- Strong CTL response

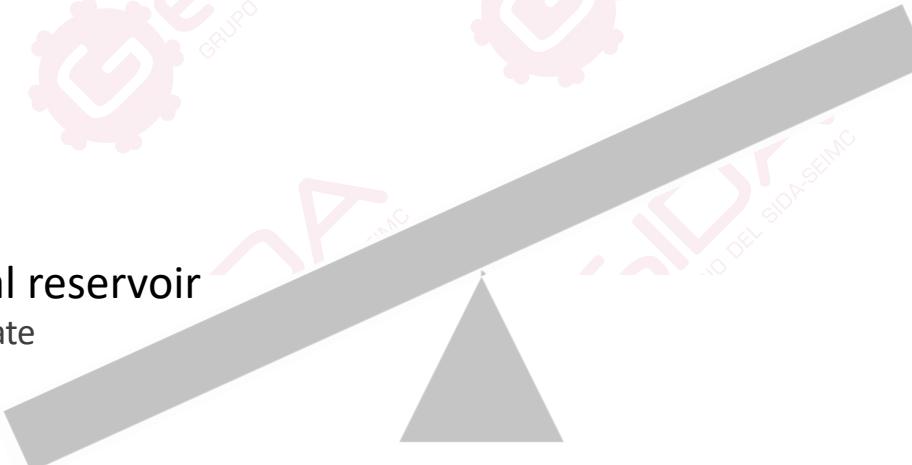
&



VIRUS

Reduce or Silence viral reservoir

- Reverse Latency & eliminate
- Limit Persistence
- Limit Evolution
- Lock the reservoir



IMMUNE

Enhance Immune system

- Effective killing to escaped variants
- Able to sensor reactivated cells
- Reversion of T-cell exhaustion





**nature
medicine**

REVIEW ARTICLE

<https://doi.org/10.1038/s41591-021-01590-5>

 Check for updates

Research priorities for an HIV cure: International AIDS Society Global Scientific Strategy 2021

Steven G. Deeks¹✉, Nancie Archin², Paula Cannon^{1b}³, Simon Collins⁴, R. Brad Jones⁵,
Marein A. W. P. de Jong⁶, Olivier Lambotte⁷, Rosanne Lamplough⁸, Thumi Ndung'u^{9,10,11},
Jeremy Sugarman¹², Caroline T. Tiemessen^{1b}¹³, Linos Vandekerckhove^{1b}¹⁴, Sharon R. Lewin^{1b}^{15,16,17}✉
and The International AIDS Society (IAS) Global Scientific Strategy working group*

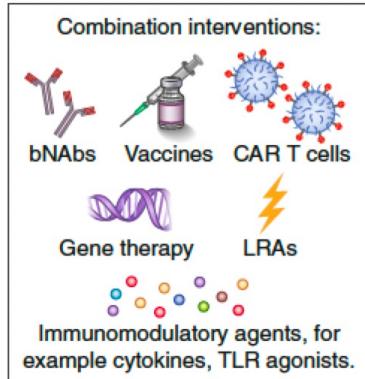
Deeks, Nat Med 2022



IMMUNOTHERAPIES

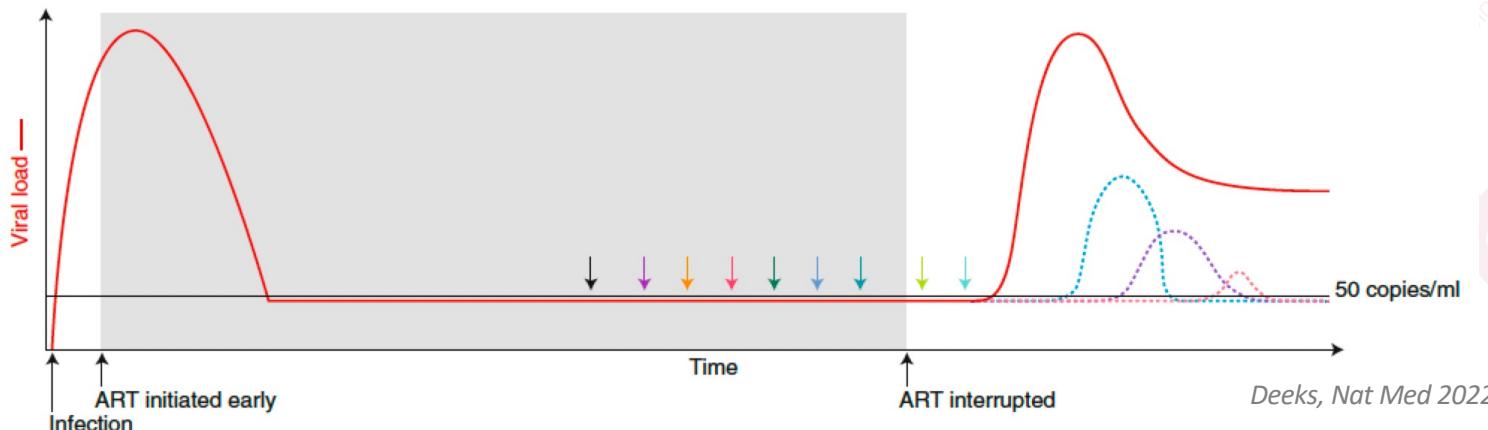
ART during acute or early HIV infection, leading to:

- Reduced inflammation and immune activation
- Limited viral diversification
- Preserved functional immune responses
- Lower reservoir burden and complexity



ART interruption followed by:

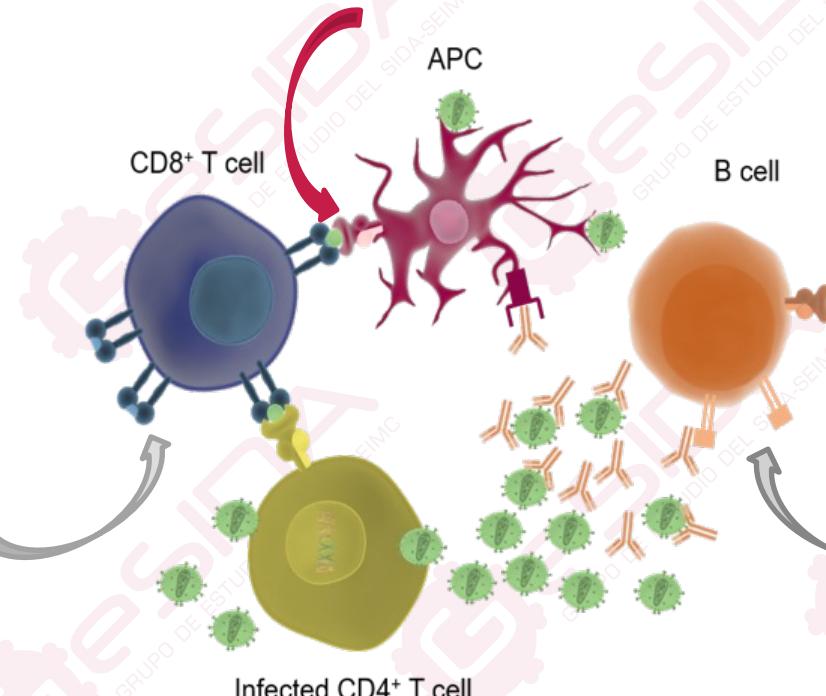
- Regular monitoring for HIV RNA in plasma
- Additional monitoring: immune responses, reservoir size and composition



IMMUNE TARGETS

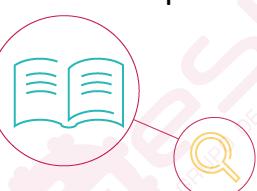


Immune modulators to improve / enhance immune response
→ Checkpoint inhibitors / TLR agonists

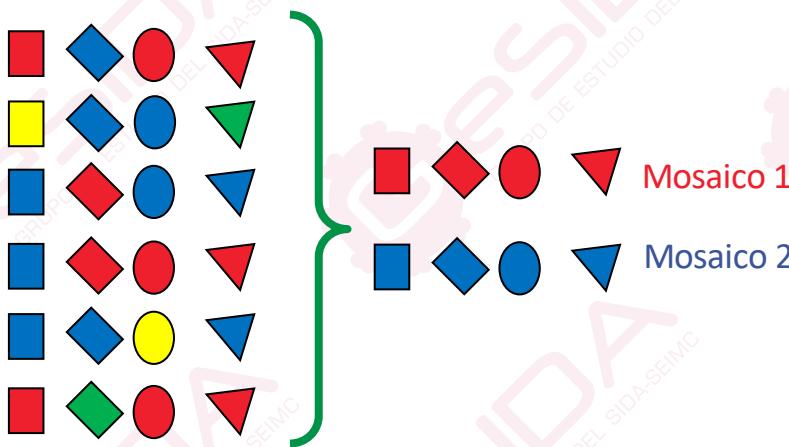


CD8 T cell mediated killing
of infected cells
→ Therapeutic vaccines

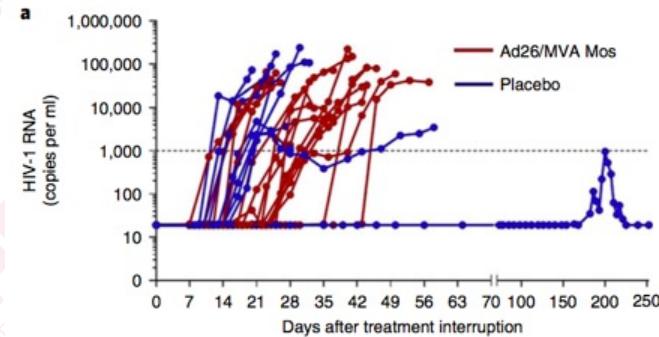
Generation of Ab able to
neutralize new virions.
→ bNAb



1. Include **more diversity** in the vaccine design



- **Janssen (NCT03307915)**
 Viral vectors : Ad26.Mos4.HIV + MVA-Mosaic
 Ad26.Mos4.HIV + Clade C gp140 + Mosaic gp140



Colby, Nat Med 2020





2. **CONSERVED elements / Networked Residues** from the virus in the vaccine design

Conserved elements from Gag-p24

p24CE1/2 + p55^{gag}

Conserved elements from different HIV proteins
HIVconsv → tHIVconsv3 y tHIVconsv4

Networked residues from different HIV proteins defined
by the web of structural interactions between residues
Role in viral replicative fitness? → limit viral evolution & escape

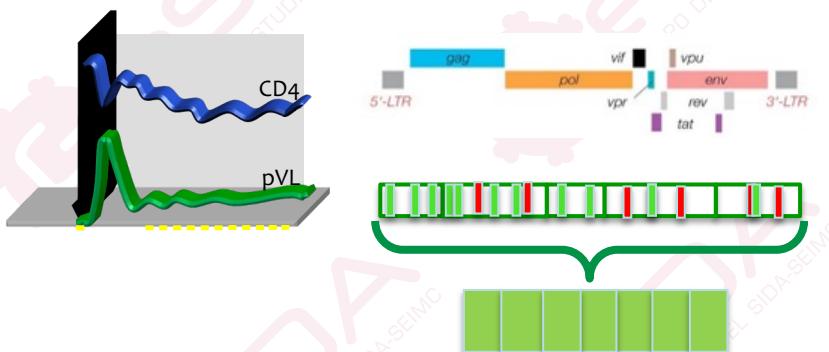
- **NIAID (NCT03560258)** ACTG A5369
- Vector DNA

- **University of Oxford (NCT03844386)**
- Viral vectors: ChAdOx1, MVA

- **Ragon (Boston)**, Ghaia Gt, et al, Science 2019
- Not in CT yet



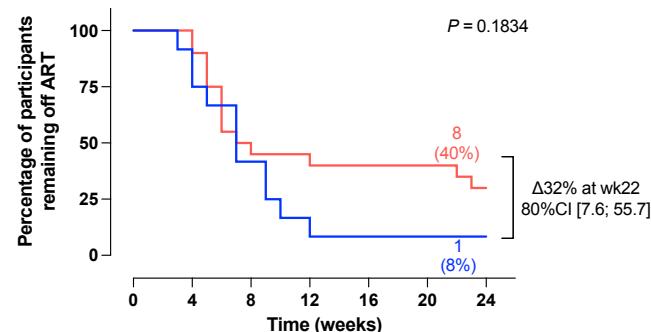
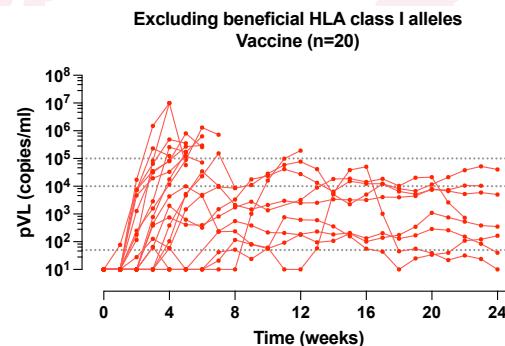
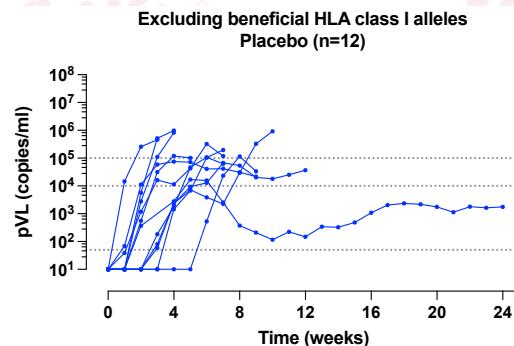
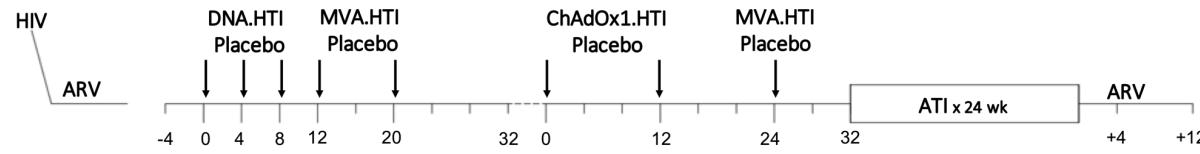
3. Include **ONLY regions** for which immune response is associate to better **viral control in humans**



26 regions (Gag, Pol, Nef, Vif) : HTI vaccines

- IrsiCaixa / AELIX Therapeutics
- DNA + ChAdOx1 + MVA
- *Preclinical: mRNA*

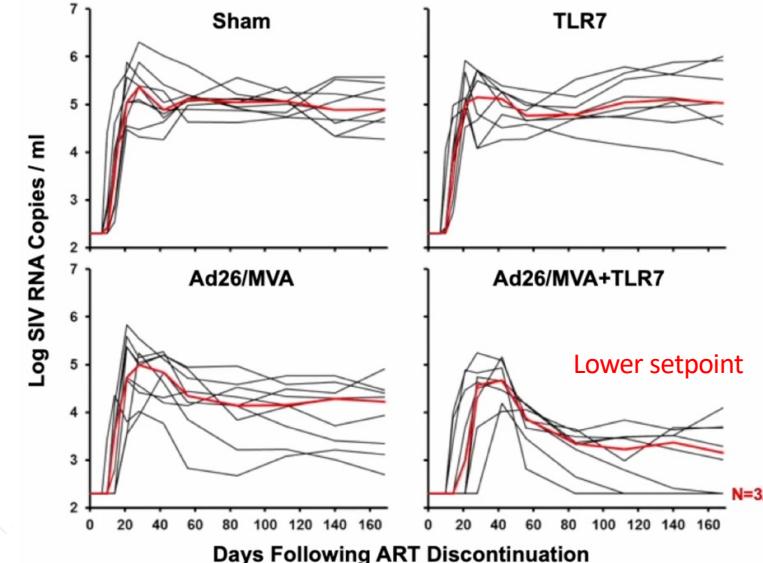
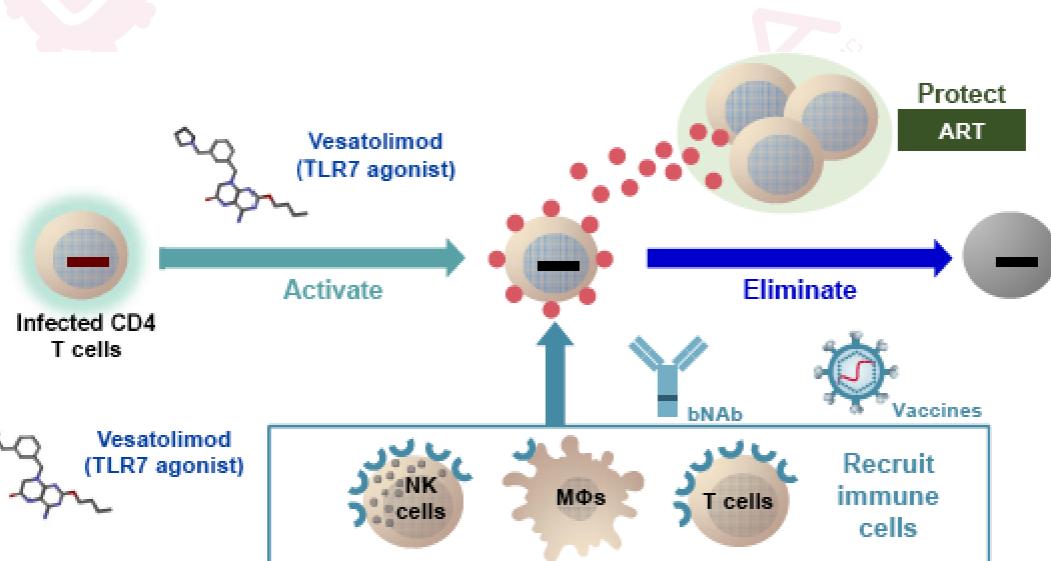
- AELIX-002 (NCT03204617)**
 - DNA + ChAdOx1 + MVA
 - 45 early treated
 - ATI
 - Completed



Mothe, CROI 2021
Bailon, Nat Med 2022 (accepted)

- **AELIX-002 (NCT03204617)**
 - DNA + ChAdOx1 + MVA
 - 45 early treated
 - ATI
 - Completed
- **AELIX-003 (NCT04364035)**
 - ChAdOx1 + MVA + **Vesatolimod**
 - 60 early treated
 - **ATI**
 - **Ongoing (Q4 2022)**
- **BCN03 (NCT05208125)**
 - ChAdOx1 + MVA + **SOSIP**
 - 30 chronics
 - **ATI**
 - **Ongoing (Q4 2023)**

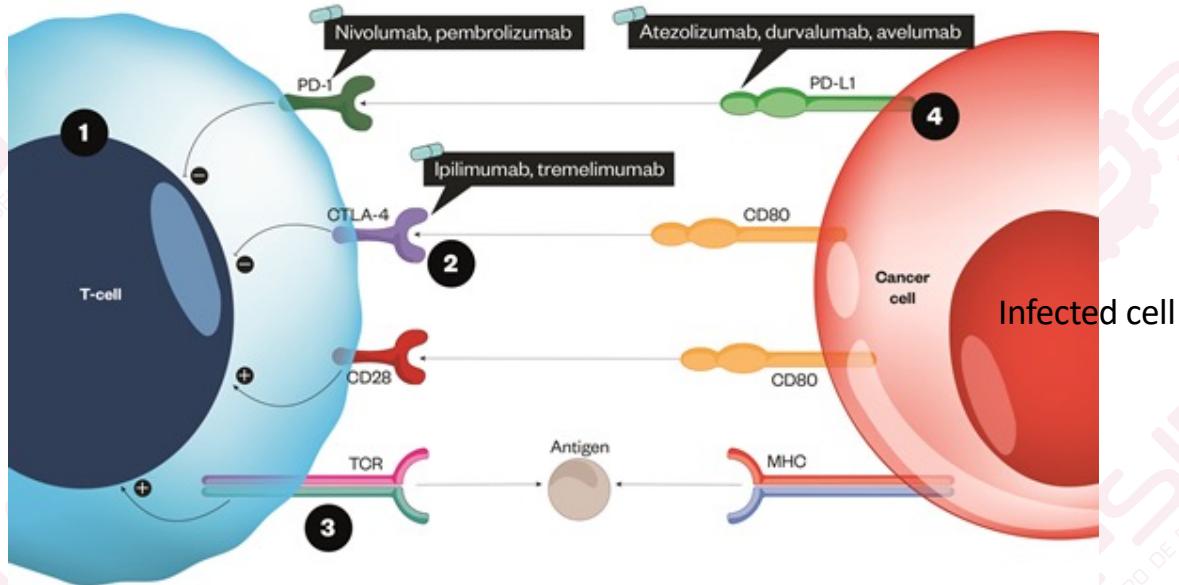
TLR AGONISTS



Borducchi, Nature 2016



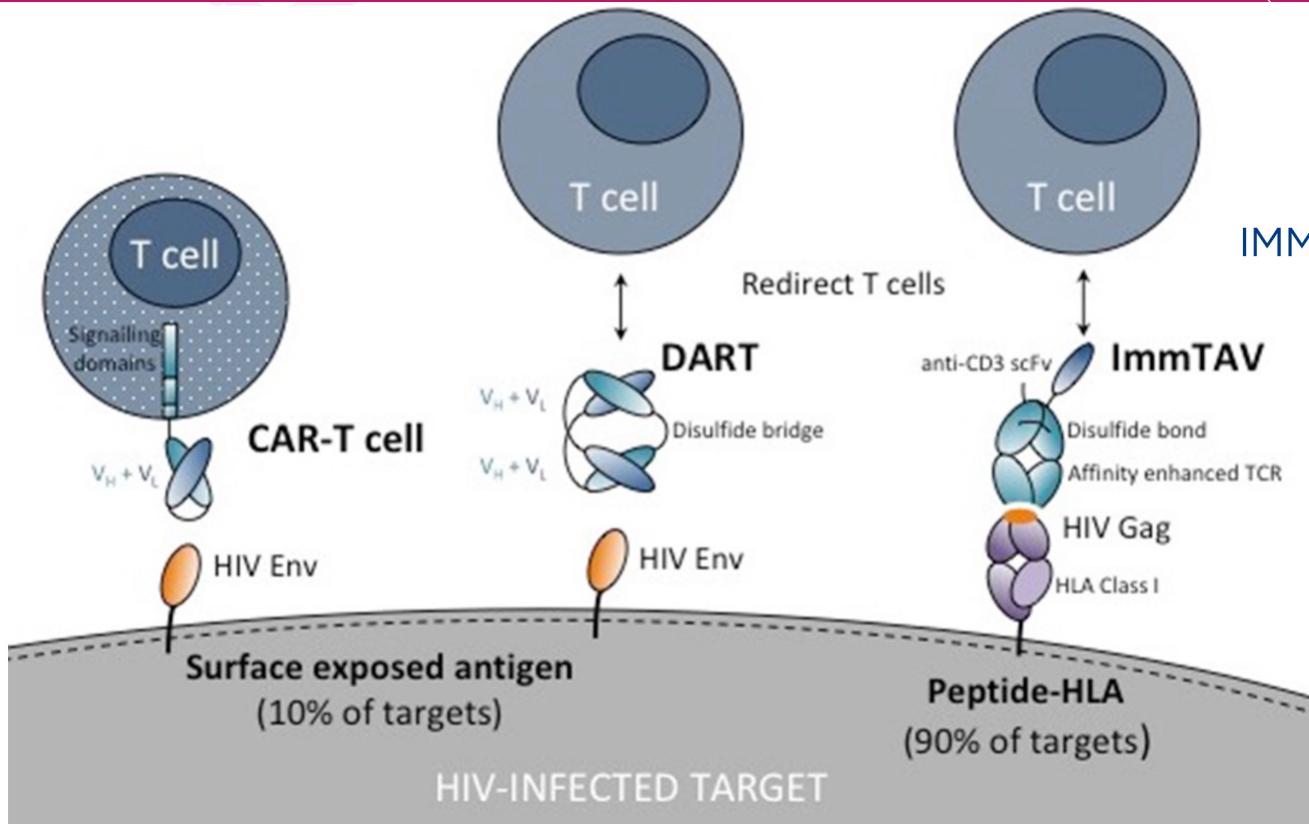
IMMUNE CHECKPOINT BLOQUERS



irAEs Risk

→ so far only being studied in HIV individuals with cancer that require specific treatment.

CAR-T cells, DART, ImmTAV



IMMUNOCORE



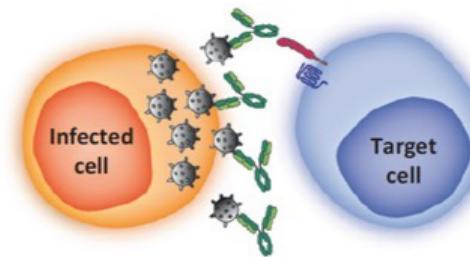
Cell-free viral neutralization



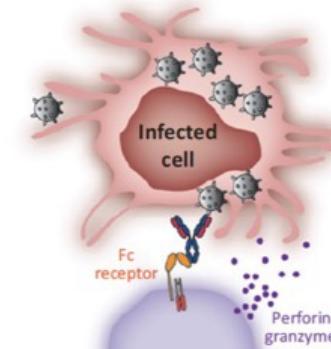
CD4
CCR5

Target
cell

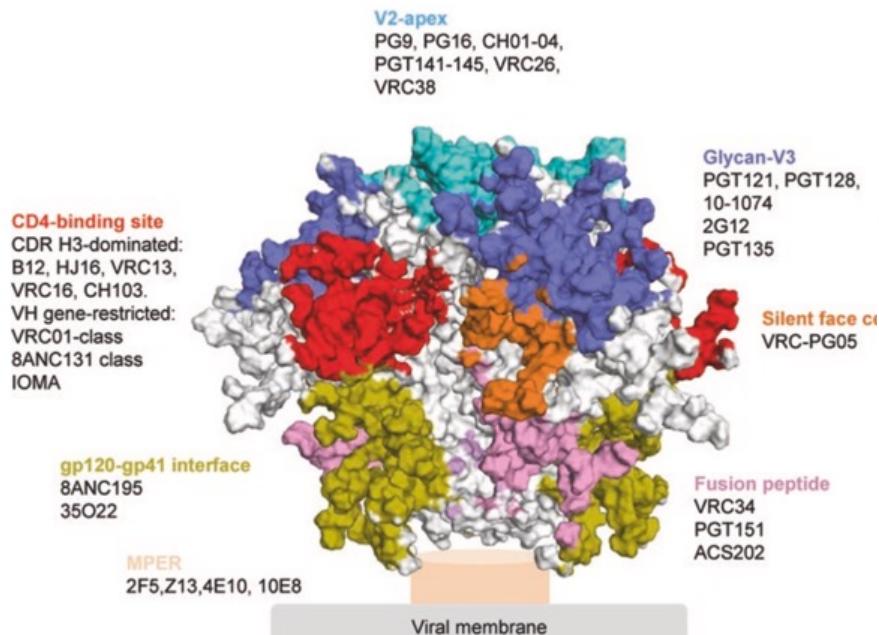
Inhibition of cell-to-cell viral spread



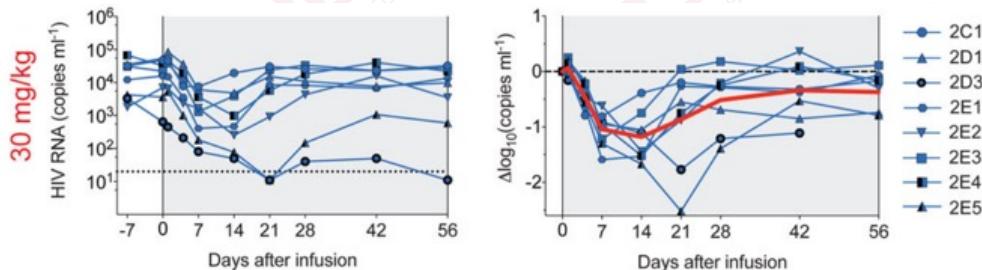
Fc-dependent antiviral activity



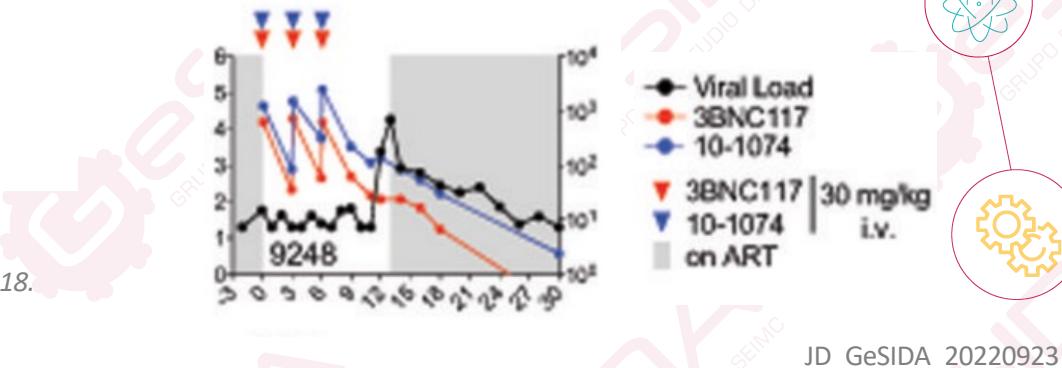
Infected
cell
Fc
receptor
Perforin,
granzymes
Effector
cell



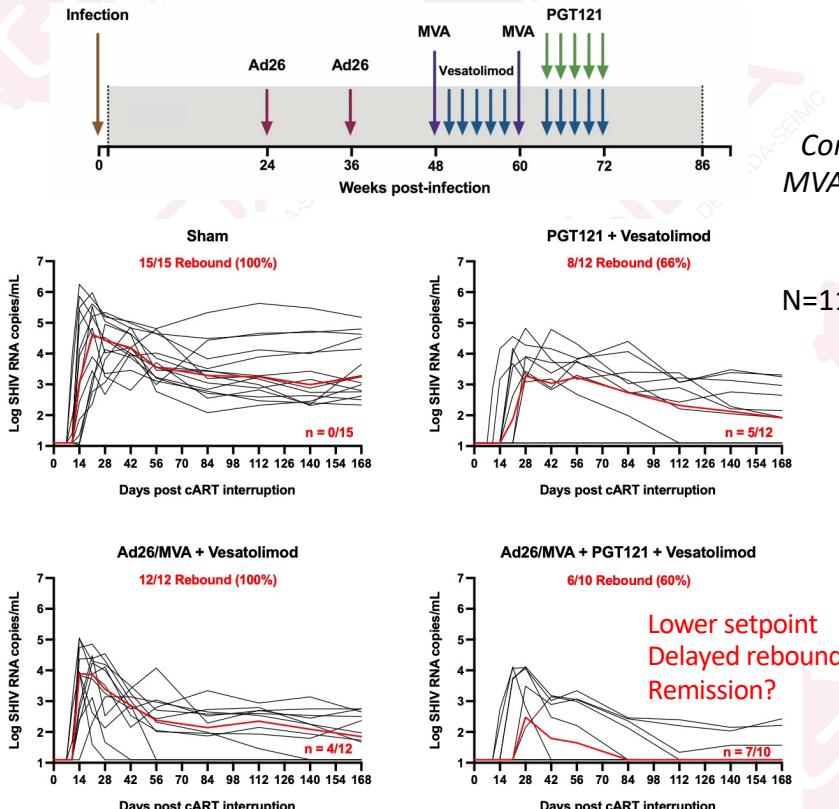
3BNC117 monotherapy(naïve) → fast resistance but also pre-existing
→ Assays to measure sensitivity not yet well developed



→ Combinations / Bi or Tri-specific / Long acting / AAV for delivery



COMBINATIONS



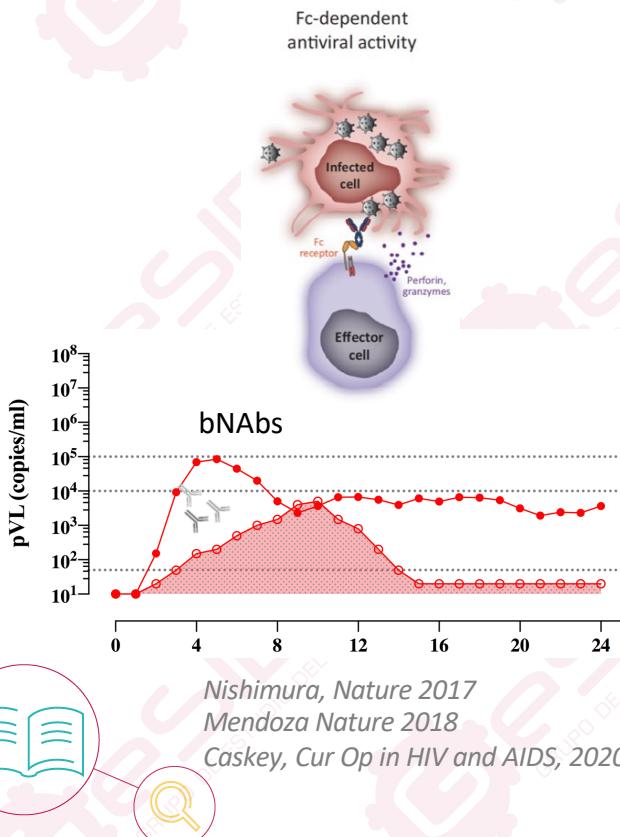
NCT04357821

Combinatorial Therapy With a Therapeutic Conserved Element DNA Vaccine, MVA Vaccine Boost, TLR9 Agonist and Broadly Neutralizing Antibodies: a Proof-of-concept Study Aimed at Inducing an HIV Remission

N=11 (single arm, open) Not yet recruiting

1. IL-12 adjuvanted p24CE DNA prime (p24CE/IL-12) at Weeks 0 and 4
2. IL-12 adjuvanted DNA boost (p24CE plus p55gag) at Week 12
3. MVA/HIV62B (MVA62B) boost at Week 20
4. VRC07-523LS and 10-1074 at week 24
5. TLR9 agonist (lefilolimod) between Weeks 24 and 33 (10 doses)
6. ATI with single dose of VRC07 and 10-1074 at Week 34

VACCINAL EFFECT



- **eCLEAR (NCT03041012)**

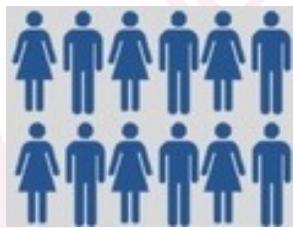
- RMD + 3BNC117
- 60 Naïve individuals
- ATI
- Completed, Rosas-Umbert , CROI 2022

- **BCN03 (NCT05208125)**

- ChAdOx1 + MVA + SOSIP
- 30 chronics
- ATI
- **Ongoing (Q4 2023)**

- **RIO (NCT04319367)**

- 10-1074-LS and 3BNC117-LS before and during ATI
- 72 early treated
- ATI
- **Ongoing (2024)**



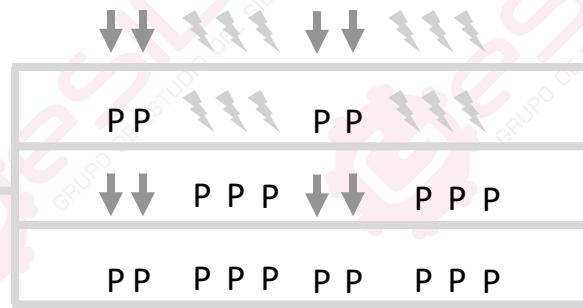
POPULATION



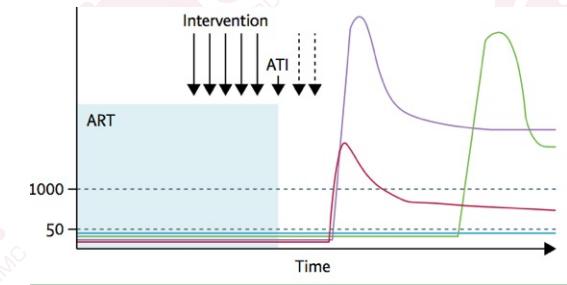
Bailon, Alarcon-Soto, Benet. Current Opinion 2022 (accepted)

Screening

Randomization



TRIAL DESIGN



ATI ENDPOINTS

CONCLUSIONS

- Immunotherapies for an HIV cure are still in a very early stage clinical development.
- Promising results in the NHP when combining therapeutic vaccines +/- immunomodulators have not yet been translated in human CT
- New HTI therapeutic vaccines promising results as T cell backbones
- Combination strategies at early clinical testing
- Safety concerns of ICI in HIV field with risk of irAEs?
- Still absence of correlates of control or remission → crucial to improve CT design and make ATI safer
- TPP for an HIV cure needs to reach same safety and effectiveness than current ART



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