Vaccines for Prevention & Vaccines for Treatment

Hot Topics in HIV

Vaccines, immune recovery and eradication

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Conflicts of interest

BM is co-inventor of the HTI T-cell immunogen (PCT/EP2013/051596) on clinical development

BM has received consulting fees from AELIX Therapeutics SL & AbbVie, and for scientific communications from Gilead, Janssen & ViiV Healthcare

Preventive & Therapeutic Vaccines

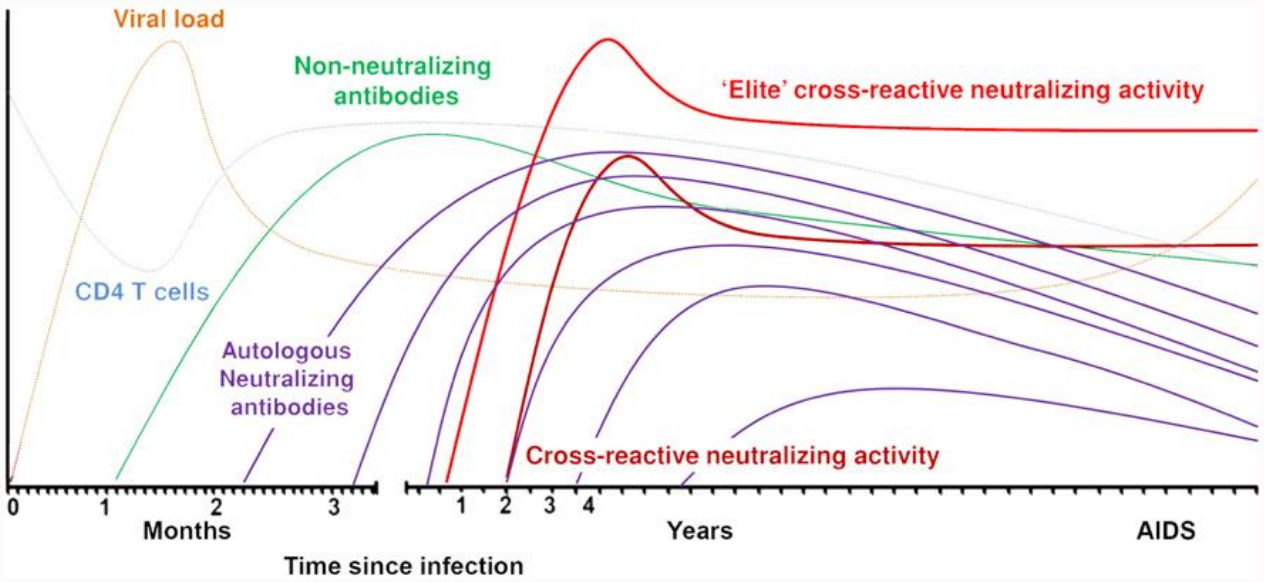
Studies/Clinical Trials in PWH
can inform Preventive Vaccines

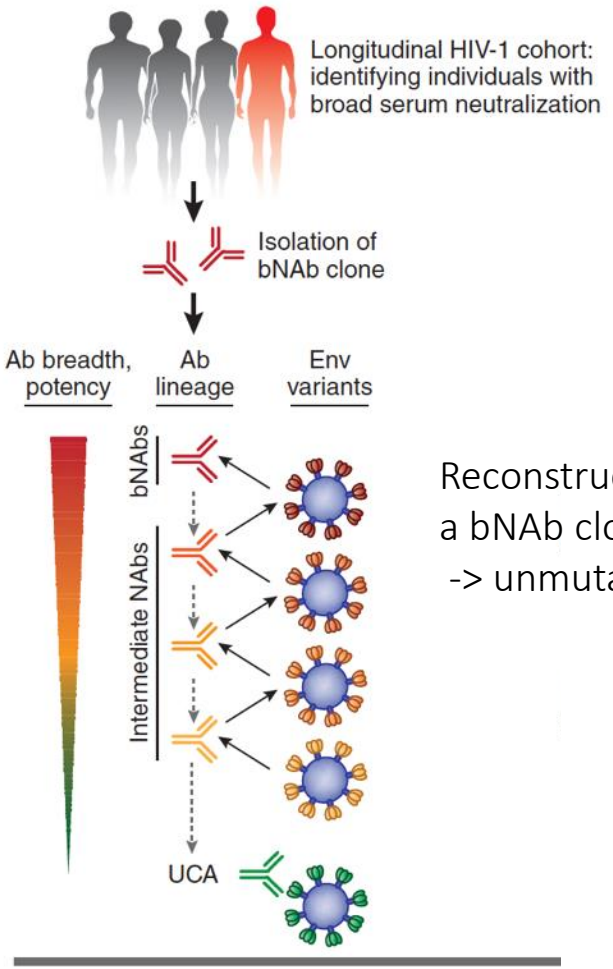
Advances in Prevention inform
Therapeutic Vaccines

Vaccines inducing both B & T cells
will be needed for both
Prevention & Cure Strategies

Vaccines for Prevention

- Current bNAb vaccine development is driven by immunobiology of PWH who make bNAbs.





■ BEDSIDE TO BENCH

Tracking the development of broadly neutralizing antibodies

Henning Gruell & Florian Klein

Reconstruct the development of a bNAb clone
-> unmutated common ancestor (UCA)

Euler & Schuitemaker, Front Immu 2012; Gruell & Klein, Nat Med 2014;

Vaccines for Prevention

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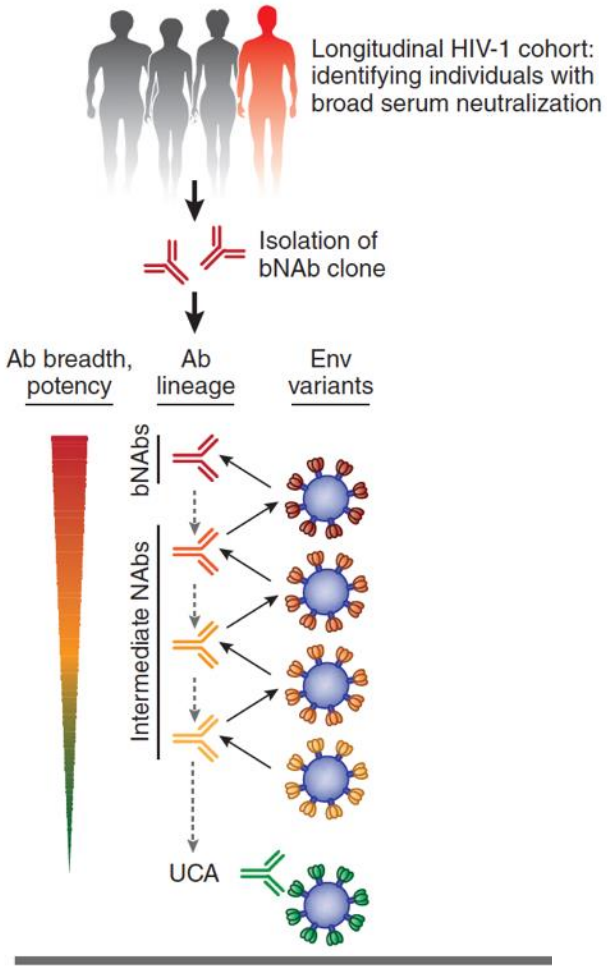
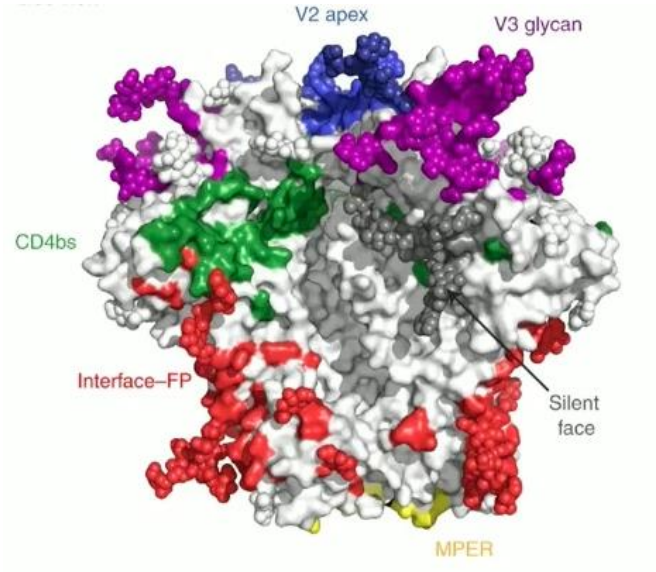




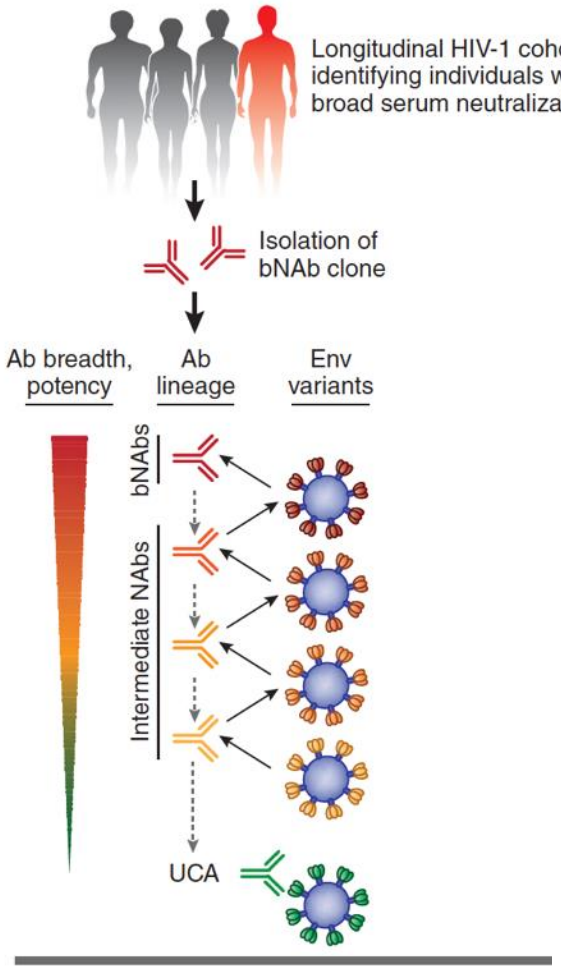
Unique properties across 6 classes of bNAbs:

- Rare germ-line precursors
- Extensive somatic hypermutation & CDR length
- Can take years to develop, few bNAbs described weeks after acute/early HIV

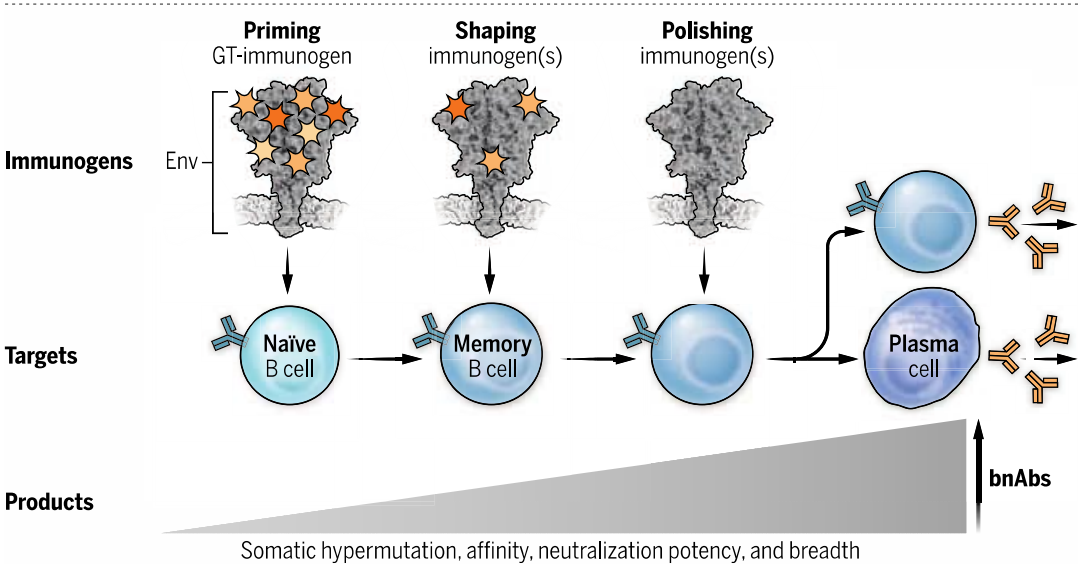
Gruell & Klein, Nat Med 2014; Sok and Burton, Nat Immunology 2018

Vaccines for Prevention

- Current bNAb vaccine development is driven by immunobiology of PWH who make bNAbs.



➔ **Reverse vaccinology** : 'Germ-line' targeting immunogens to engage the UCA, initiate B cell maturation towards bNAb development



Gruell & Klein, Nat Med 2014; Sanders & Moore, Science 2024

Vaccines for Prevention

Tackling the viral diversity will need to go along with an HIV-specific ‘ready-to-go’ immune response able to eliminate virus harboring cells and abort infection or induce viral control in those breakthrough infections

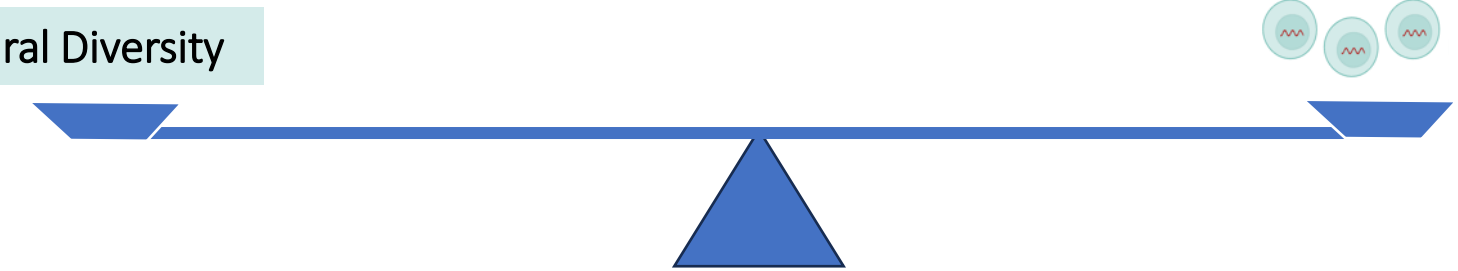
bNAbs

- Passive infusion to 2-3 different epitopes : **AMP trials**
- bNAb inducing vaccines : Germ-line targeting approaches

T-cells

Immune Response

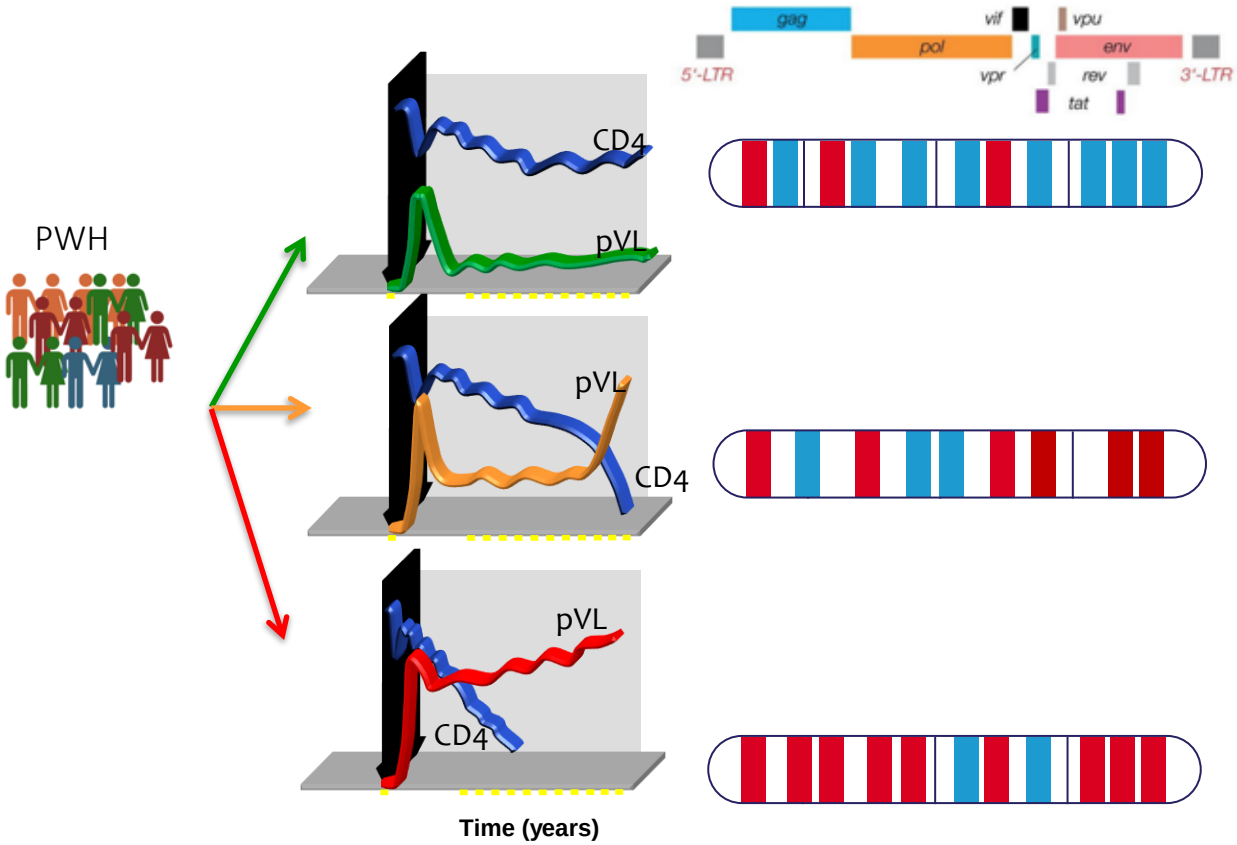
- Cover diversity
- Cytotoxicity / functionality
- Location : at site of infection
- NK function / CD4 T help
- MHC-E restricted?



Mgodi, JAIDS 2021; Corey NEJM 2021; Huang, EbioMedicine, 2021

Vaccines for Treatment (HTI)

- The HIVACAT T-cell immunogen (HTI) driven by human immune data : designed to redirect T-cell immune responses to HIV beneficial regions of HIV identified by high resolution screening in > 1,000 untreated PWH with variable viral loads.



- Functional avidity
- Suppressive Capacity
- HLA coverage
- Conservation
- Subtypes

Mothe B, et al. J Transl Med. 2011; Mothe B. Plos One 2012; Mothe B, J Transl Med. 2015;

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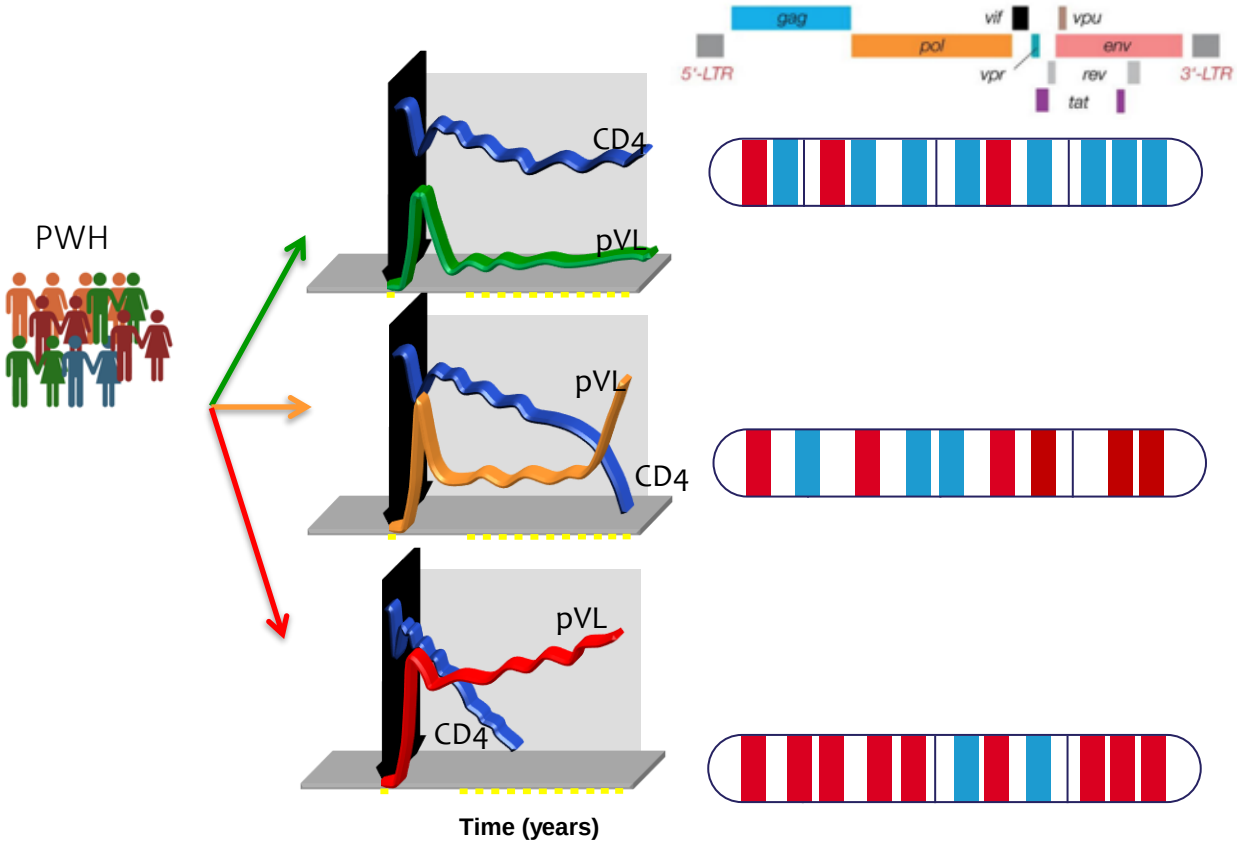
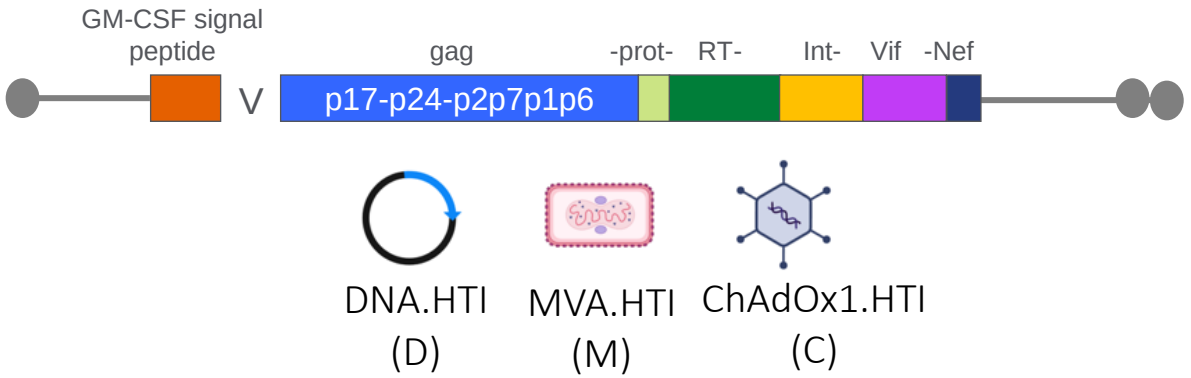


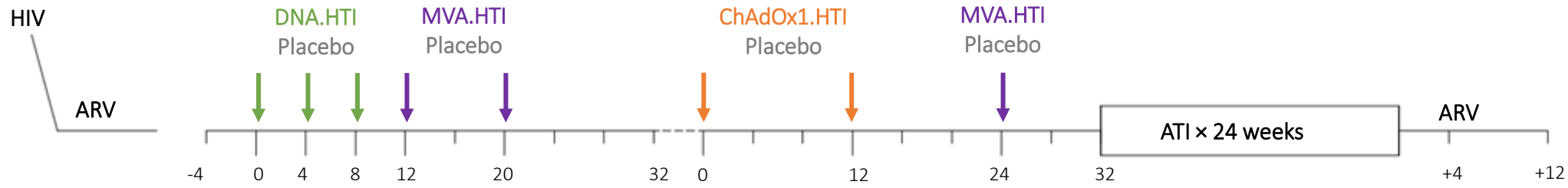


Mothe B, et al. J Transl Med. 2011; Mothe B. Plos One 2012; Mothe B, J Transl Med. 2015;

HTI vaccines

AELIX-002
NCT03204617

- RCT, placebo controlled
- DDDMM – CCM
- N = 45, 2:1 randomization
- Completed



nature medicine

Article

https://doi.org/10.1038/s41591-022-02060-2

Safety, immunogenicity and effect on viral rebound of HTI vaccines in early treated HIV-1 infection: a randomized, placebo-controlled phase 1 trial

- HTI vaccines safe & highly immunogenic in early –ART
- Both CD4 and CD8 T cells induced
- Polyfunctional T cells
- Good coverage of pre-ART (reservoir) viruses
- Ex-vivo viral inhibition to autologous virus

✓ Frequencies of HTI-specific T cells associated with improved viral control (longer time off ART and lower pVL)

✗ No differences reduction in total or intact proviral DNA

Bailón L, Nat Med 2022

Functional Cure (ART-free remission)

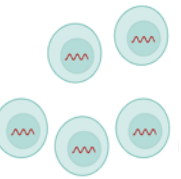
Tackling the viral reservoir will need to go along with a boosted immune response able to eliminate virus harboring cells and contain virus rebound

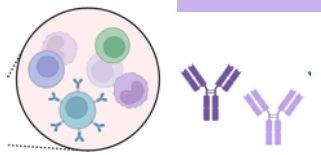
Immune Response

APPROACHES

- Early ART (limit size & diversity)
- Reverse Latency (Ag expression)
- Block & Lock (induce stemness)

Viral Reservoir



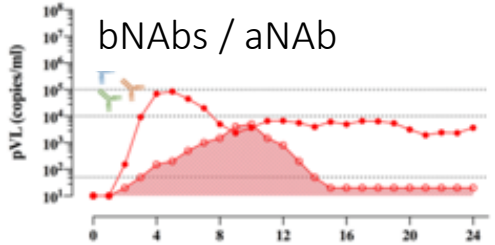


APPROACHES

- Increase breadth / Depth
- Escape coverage
- Specificity / Dominance patterns
- Increase cytotoxicity / functionality
- Reverse exhaustion
- Migration (B cell follicle)
- Enhance NK function / CD4 T help

→ T cell vaccine backbone

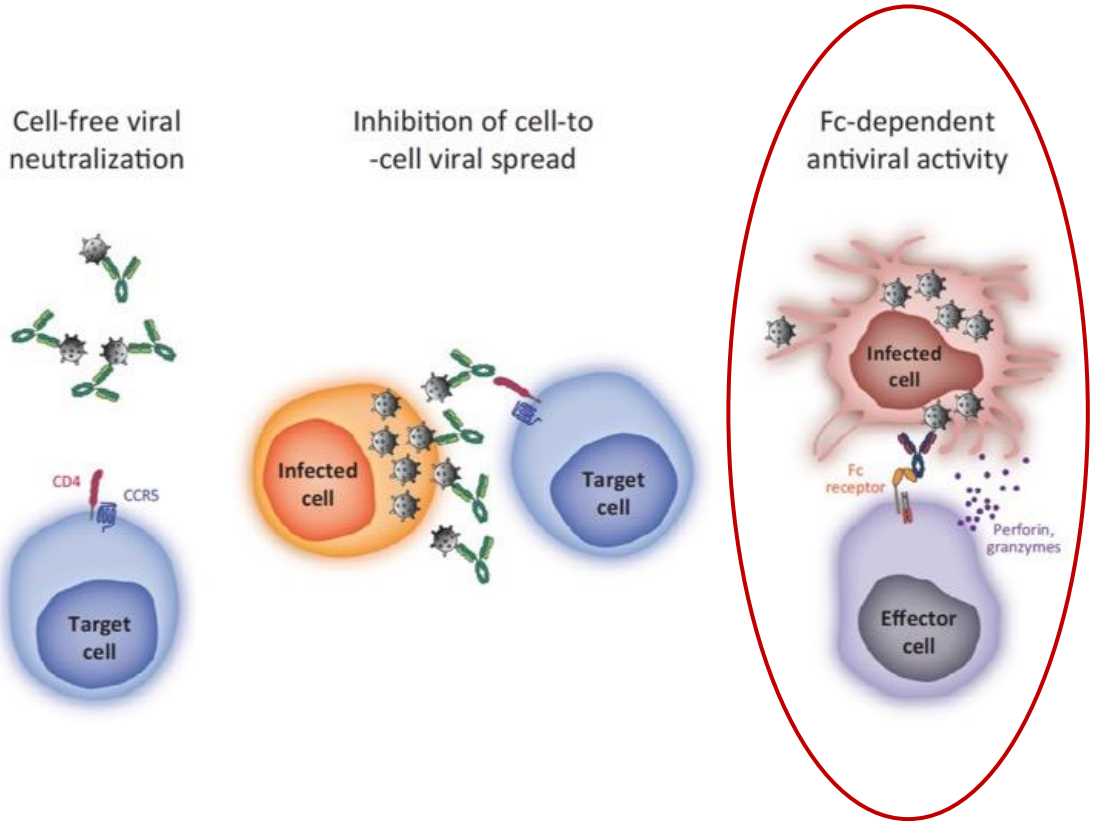
bNAbs / aNAb

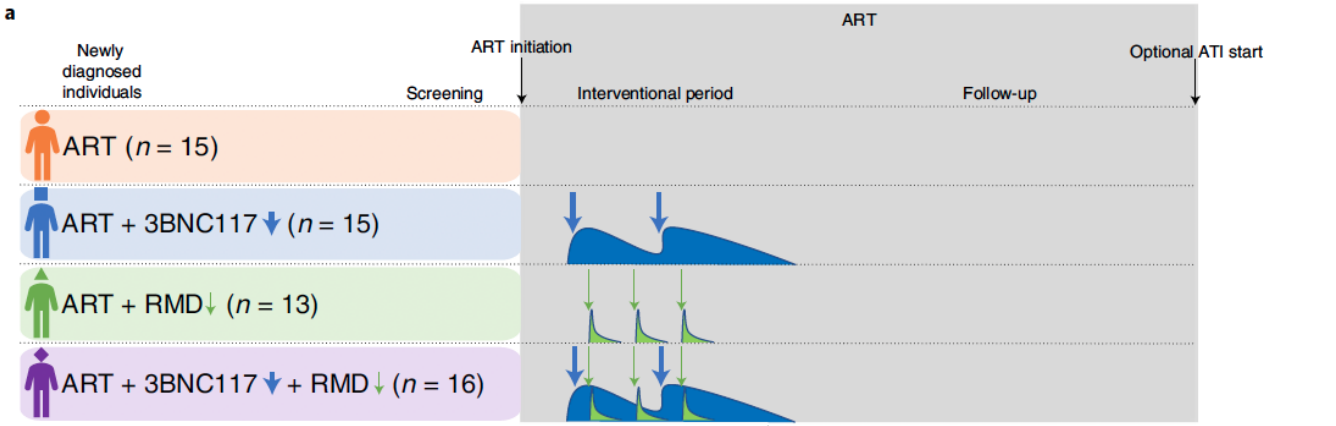


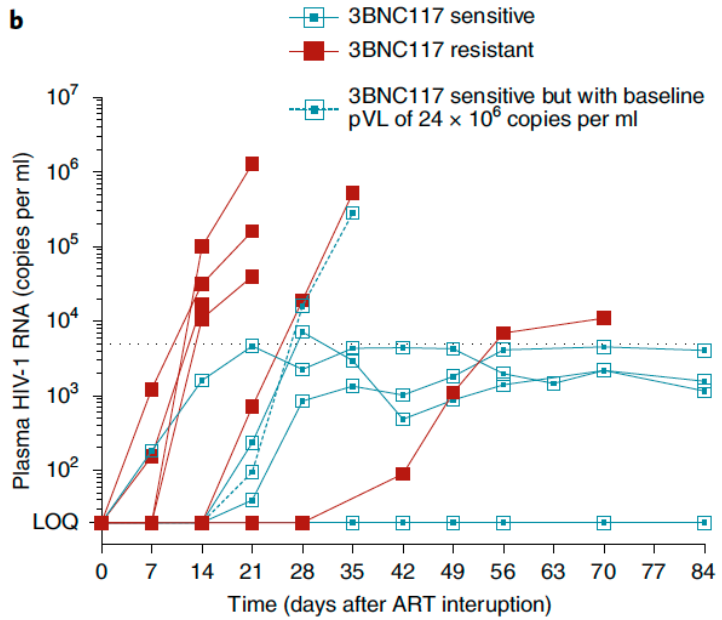
Capture released viruses and slow down viral recrudescence to 'facilitate' CTL to work (in addition to potential vaccinal effect)

Sneller M, et al, Nat Med 2022, Gaebler C, Nat Med 2022; Gunst J, Nat Med 2022; Rosas-Umbert, Nat Commun 2022

bNAbs (not only bN) – vaccinal effect





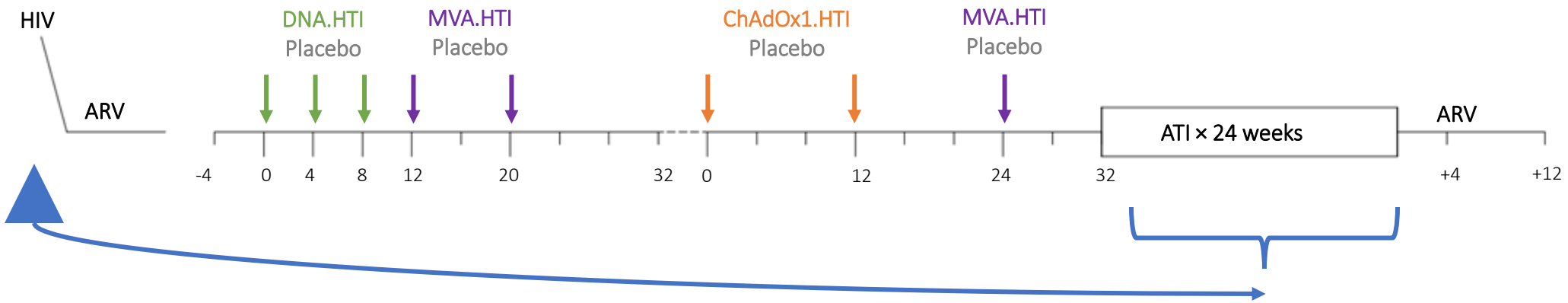


Mouquet, Trends Immunol 2014; Sneller M, et al, Nat Med 2022, Gaebler C, Nat Med 2022; Gunst J, Nat Med 2022; Rosas-Umbert, Nat Commun 2022

Role of Ab in AELIX-002?

KINATI: humoral responses triggered during the ATI?

Same as pre-ART?



AELIX-002 NCT03204617
RCT, placebo controlled
DDDMM – CCM
N = 45, 2:1 randomization
Completed

Cristina Peligero –TUPE002LB (ongoing work, PI20/0139) -

KINATI substudy

What humoral responses were triggered during the ATI? Same as pre-ART?

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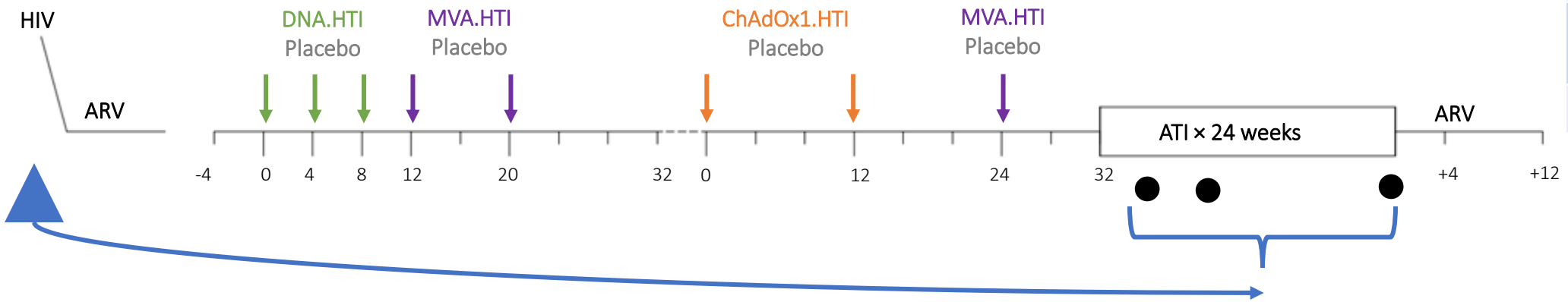

Pre-ART : closest time to ART initiation during acute/early HIV

ATI-Rc : closest time to viral recrudescence (pVL >50 & <500)
ATI-Peak : closest time to peak viremia
ATI-End : last timepoint of ATI at ART resumption

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KINATI substudy

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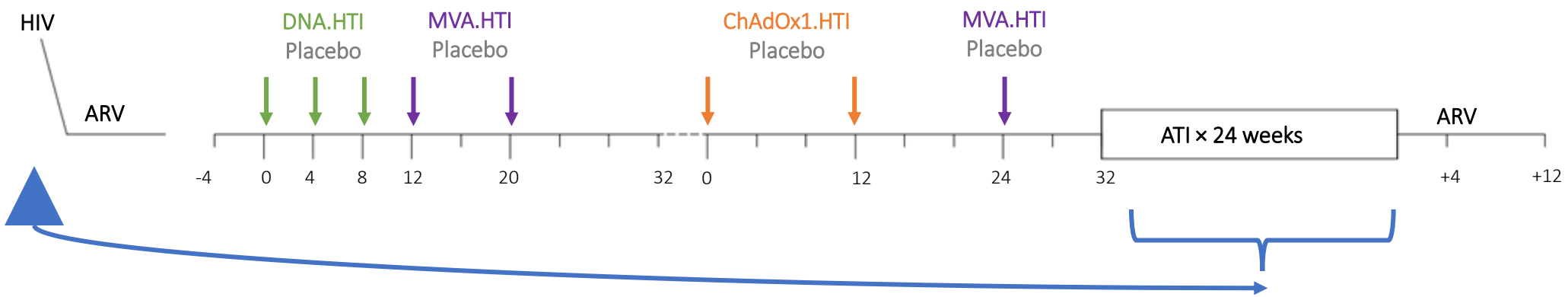

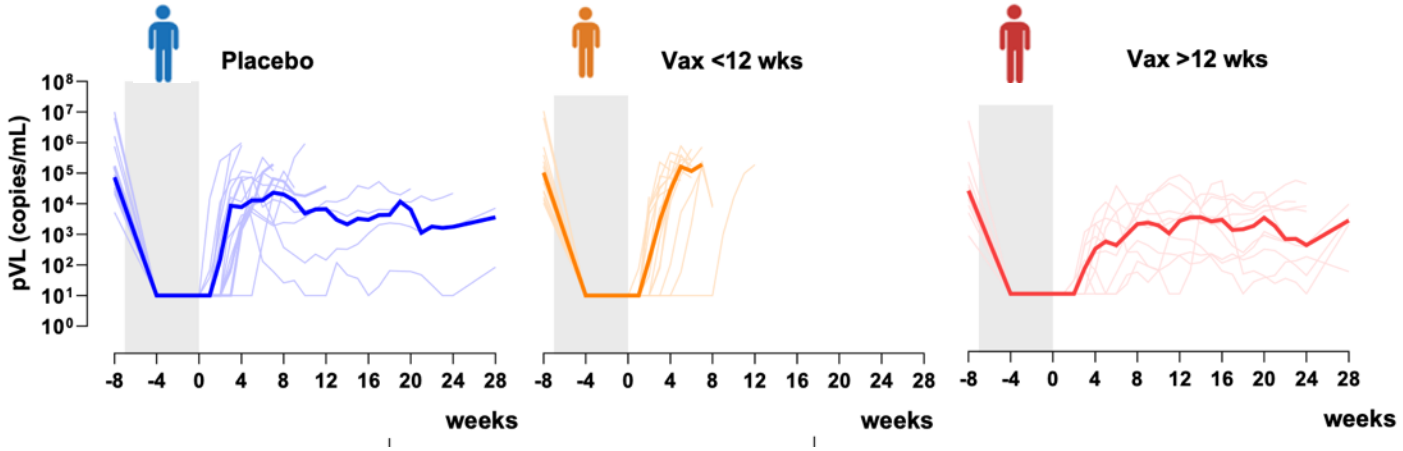

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KINATI – B cells

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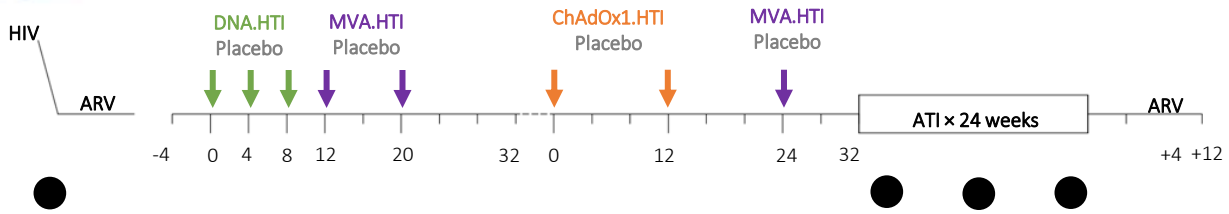
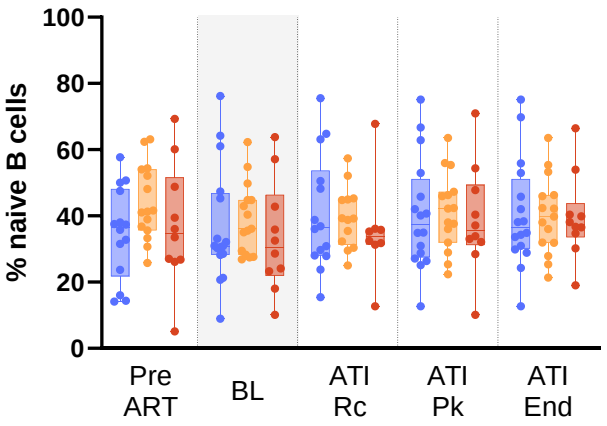
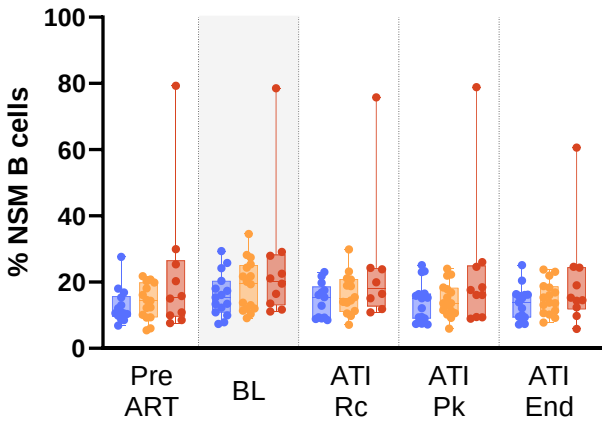
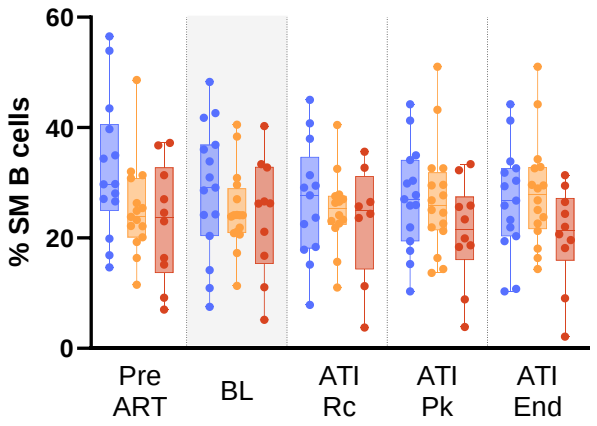
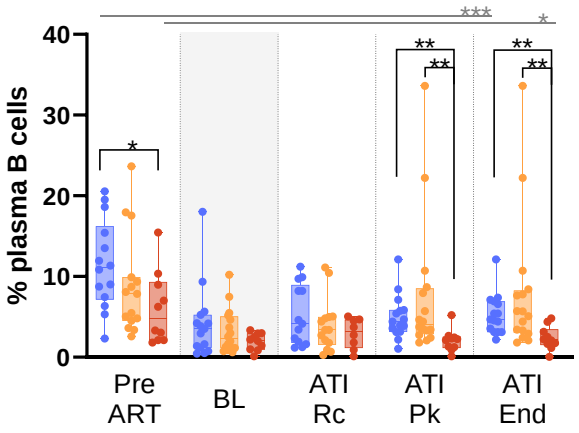


Placebo Early resumer (<12w off ART) Late resumer (>12w off ART)





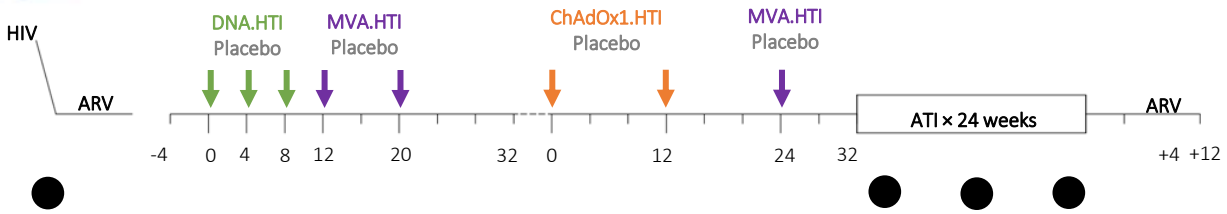




- Plasma B cells are reduced upon ART suppression, that increase after ATI but to a lesser extent than preART
- Lower frequencies of plasma B cells at the end of ATI in those that remain off ART >12 weeks

Cristina Peligero –TUPE002LB (ongoing work, PI20/0139) -

KINATI – B cells



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RCT, placebo controlled
DDDMM – CCM
N = 45, 2:1 randomization
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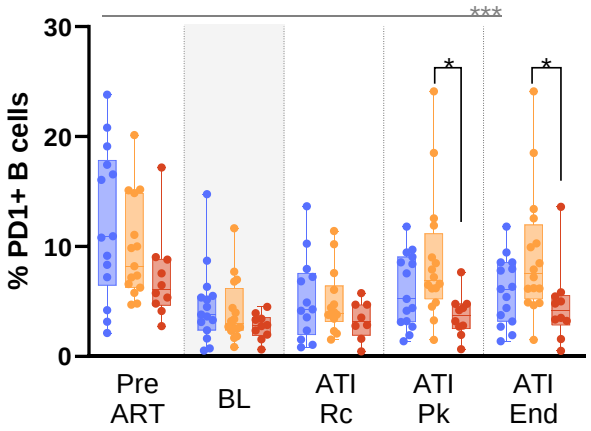
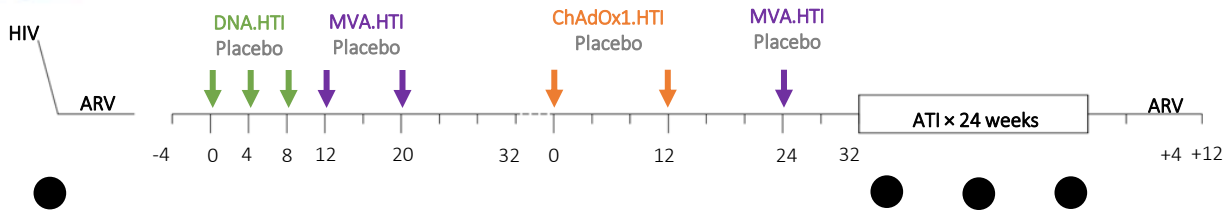


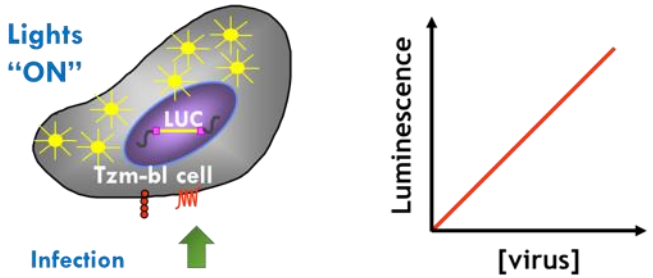
- Lower frequencies of activated B cells at the end of ATI (vs pre-ART), specially in those that remain off ART >12 weeks
- Levels of activation at the End of ATI highly correlated with pre-ART levels

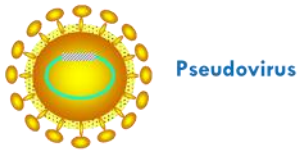
Cristina Peligero –TUPE002LB (ongoing work, PI20/0139) -

KINATI - aNAbs

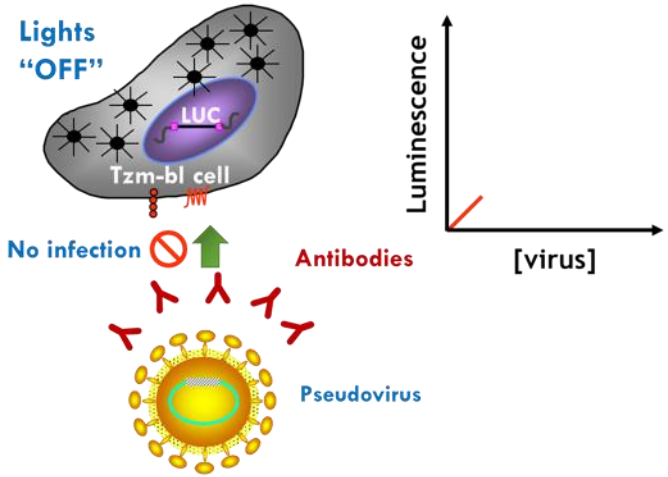


Days since HIV acquisition
63 (6, 140)





ISOLATE	CLADE	TIER
NL4.3	B	1
TRO.11	B	2
CE1176	C	2
25710	C	2
398F1	A	2
CNE8	CRF01	2



+ Autologous pre-ART HIV
(n=39 participants)

AELIX-002
NCT03204617

RCT, placebo controlled

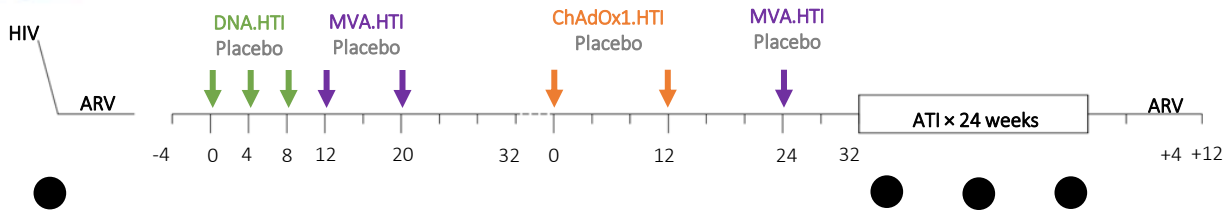
DDDMM – CCM

N = 45, 2:1 randomization

Completed

Edwards Pradenas, Anna Pons-Grifols, Julià Blanco

KINATI - aNAbs



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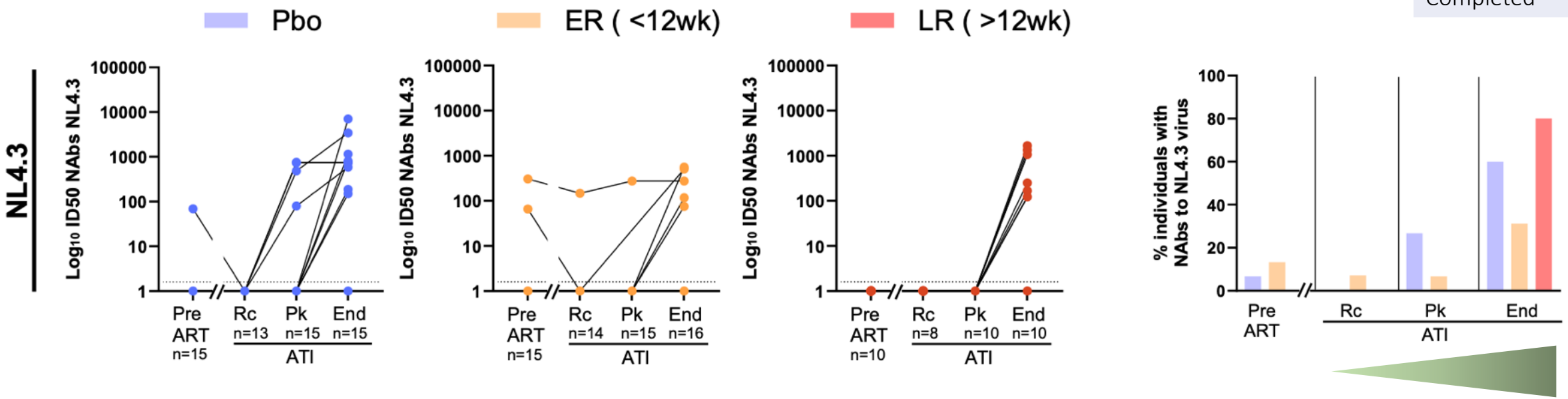
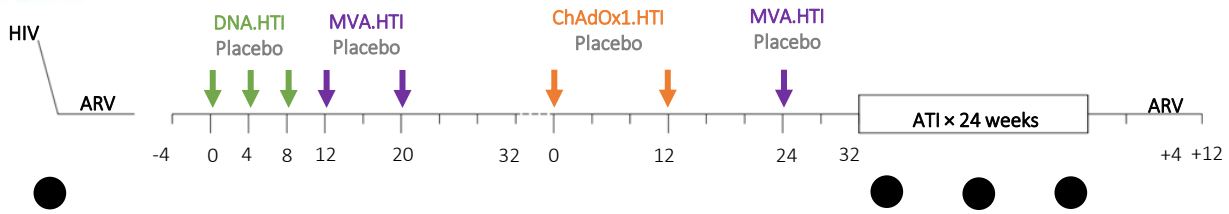


- Few neutralization detected in early-ART PWH
- Progressive neutralization during the ATI, but NOT at moment of viral recrudescence/peak viremia

Edwards Pradenas, Anna Pons-Grifols, Julià Blanco

KINATI - aNAbs



Days since HIV acquisition
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DDDMM – CCM
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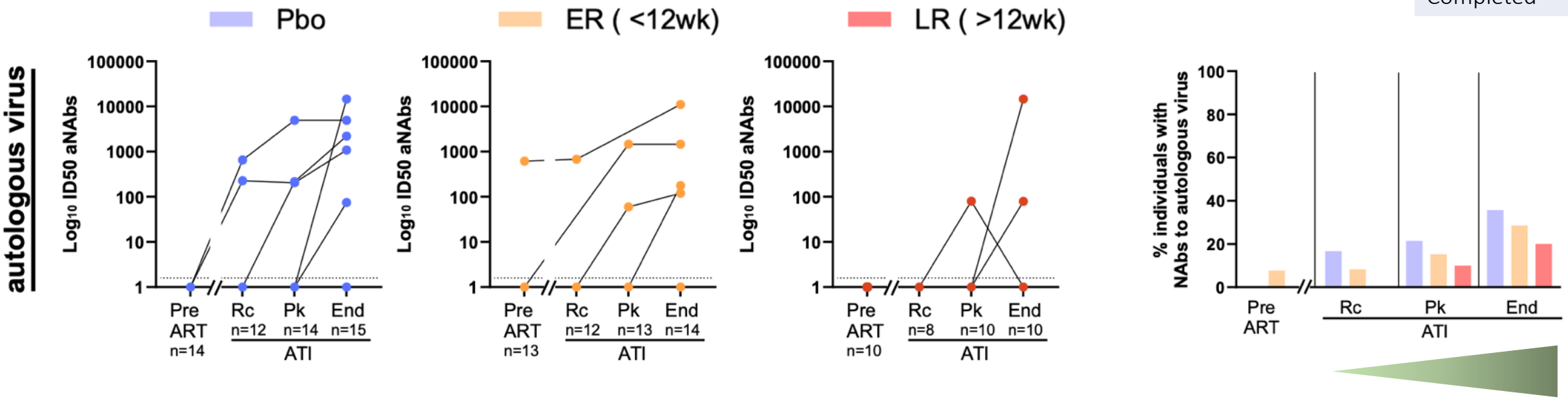


- Even less neutralization to autologous virus, NOT present at recrudescence (After 3-4 years on ART)
- 20-40% participants developed aNAbs during the ATI, regardless of Vax-Placebo.

Edwards Pradenas, Anna Pons-Grifols, Julià Blanco

KINATI - aNAbs

Pre-ART

Tier 2

NL4.3

14580	587
14580	249
11077	509
4941	754
2199	3442
1464	<60
1088	<60
178	<60
120	557
79	<60
75	1150
<60	118
<60	<60
<60	76
<60	<60
<60	188
<60	<60
<60	<60
<60	<60
<60	<60
<60	7074
<60	274
<60	<60
<60	803
<60	<60
<60	123
<60	150
<60	1068
<60	<60
<60	1665
<60	167
<60	121
<60	739
<60	<60
<60	<60
<60	<60
<60	1343
<60	1075

AELIX-002
NCT03204617

RCT, placebo controlled

DDDMM – CCM

N = 45, 2:1 randomization

Completed

- No neutralization to any of the Tier 2 viruses tested

Edwards Pradenas, Anna Pons-Grifols, Julià Blanco

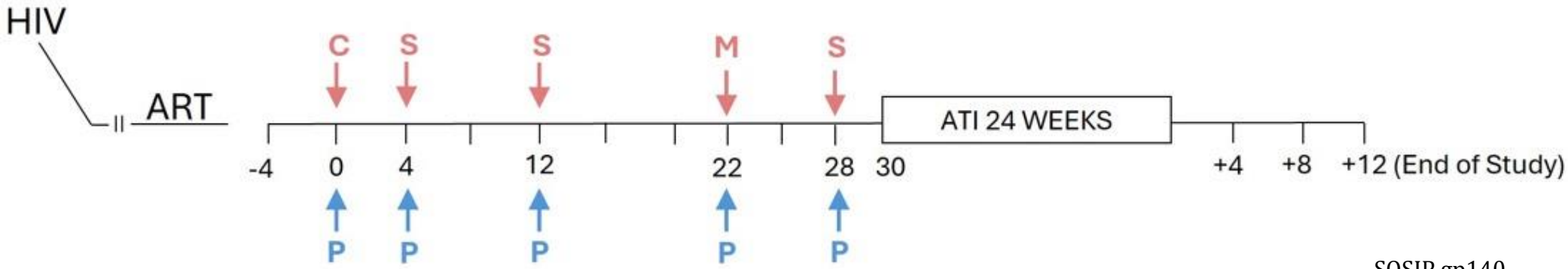
Lessons from T cell vaccine trials & ATI

- HTI vaccines safe & highly immunogenic in early –ART
- Both CD4 and CD8 T cells induced
- Polyfunctional T cells
- Good coverage of pre-ART (reservoir) viruses
- Ex-vivo viral inhibition to autologous virus
- No reduction of the viral reservoir
- Association between HTI vaccine responses and ATI outcomes

- Not clear role of aNAb responses in AELIX-002 outcomes or vaccinal effect → need of combination T & B vaccines?

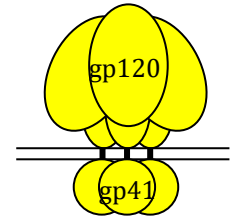
Could we increase humoral responses by combining T & B immunogens?

BCN03 NCT05208125
RCT, placebo controlled
CM + SOSIP.v7 gp140 adjuvanted MPLA
N = 30, 2:1 Chronic ART
Completed



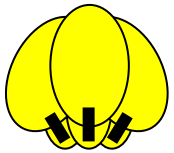
C = ChAdOx1.HTI
M = MVA.HTI
} T cell component

S = ConM SOSIP.v7 gp140
S = ConM SOSIP.v7 gp140
S = ConM SOSIP.v7 gp140
} B cell component

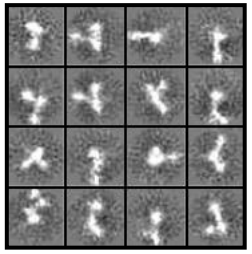


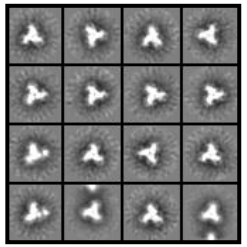
Native envelope spike

SOSIP gp140



Binley et al. J.Virol. 2000
Sanders et al. J.Virol. 2002





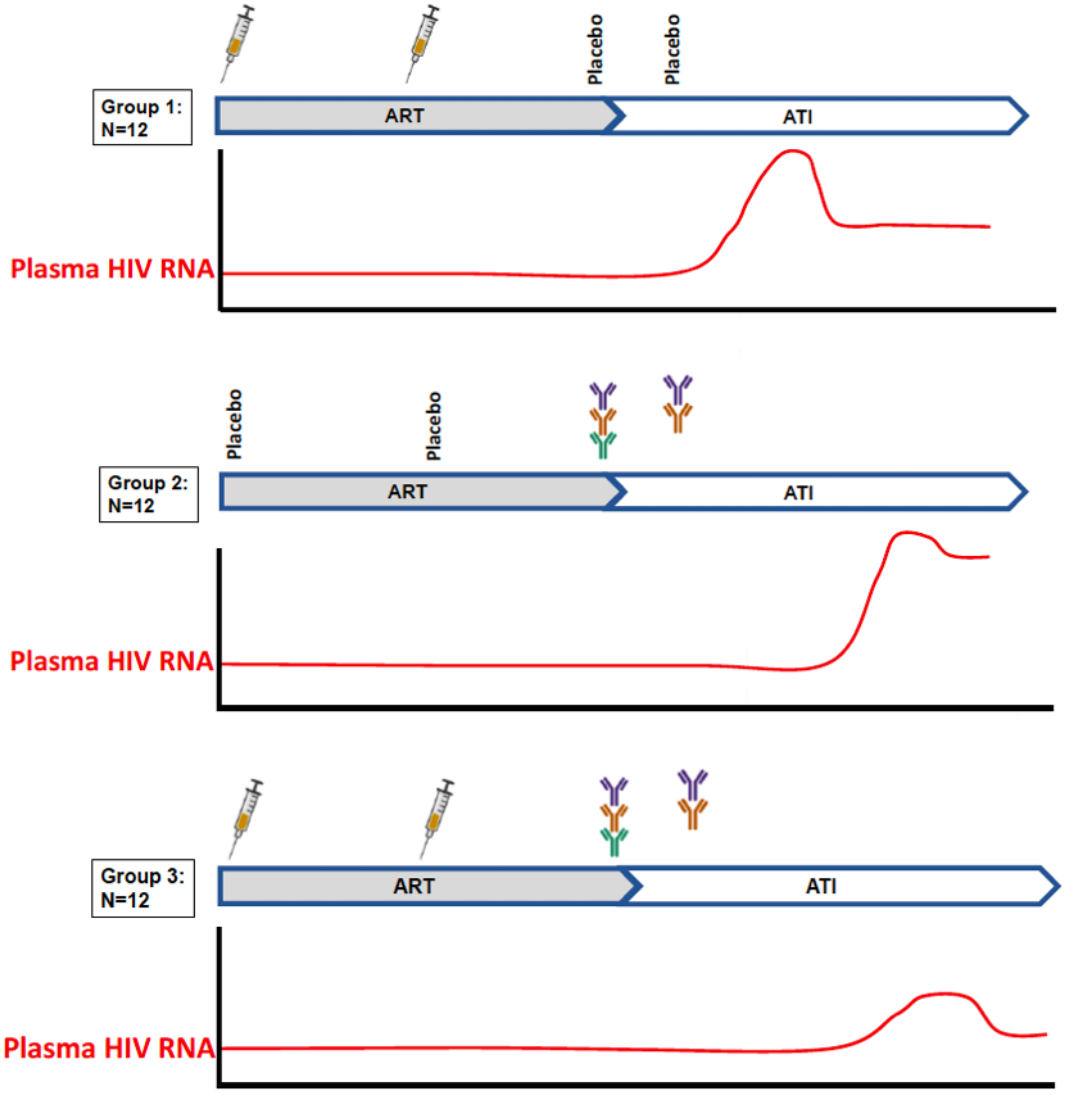
Could we increase humoral responses by combining T & ~~B immunogens~~ bNAbs?

Ad26/MVA Mosaic Vaccines (Env & Gag/Pol)
+ bNAbs x3 at ATI

- PGT121 (V3g – N332)
- PGDM1400 (V2g – N160)
- VRC07-523LS (CD4bs)

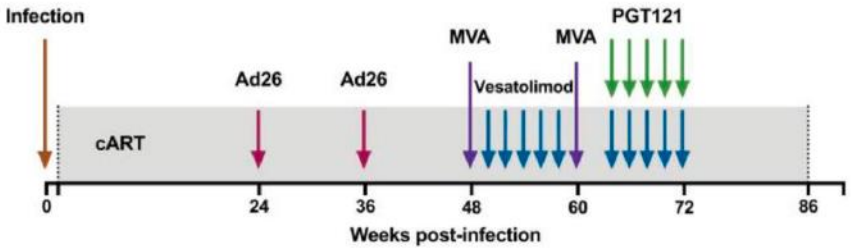
n=36 ART-suppressed (Chronic)
1:1:1

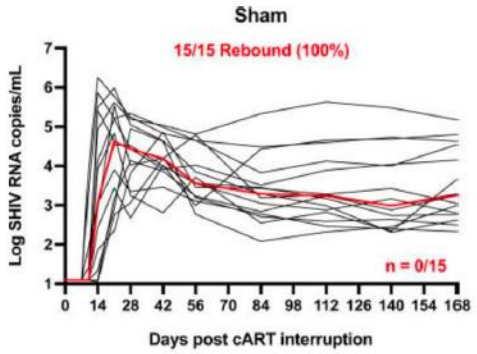
IPCAVD014/HTX1004
NCT04983030
Not-yet recruiting

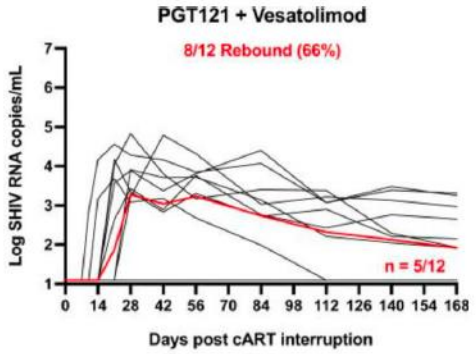


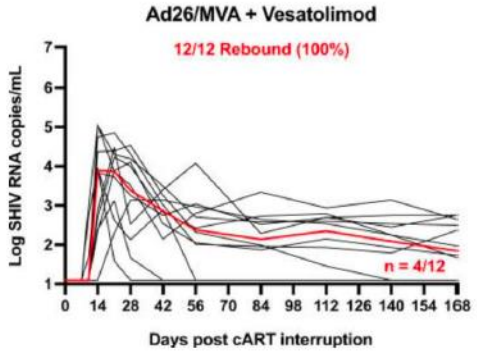
Julg B et al, Nat Med 2024

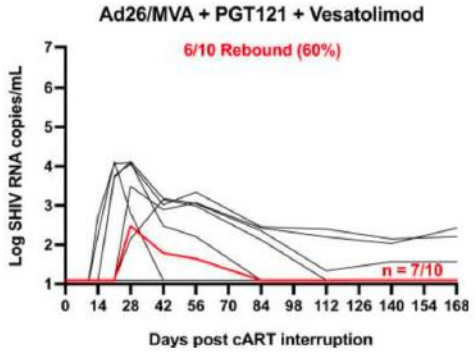
Triple combination in NHP

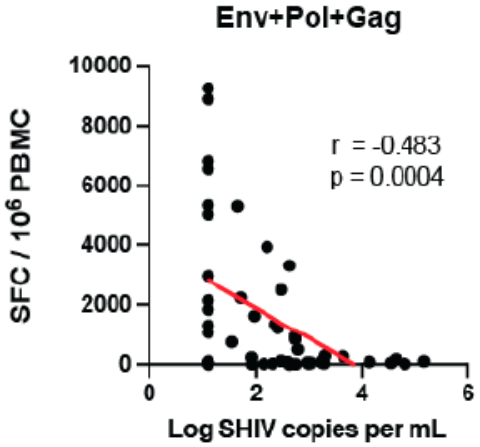












Walker-Sperling, Nat Communic 2022

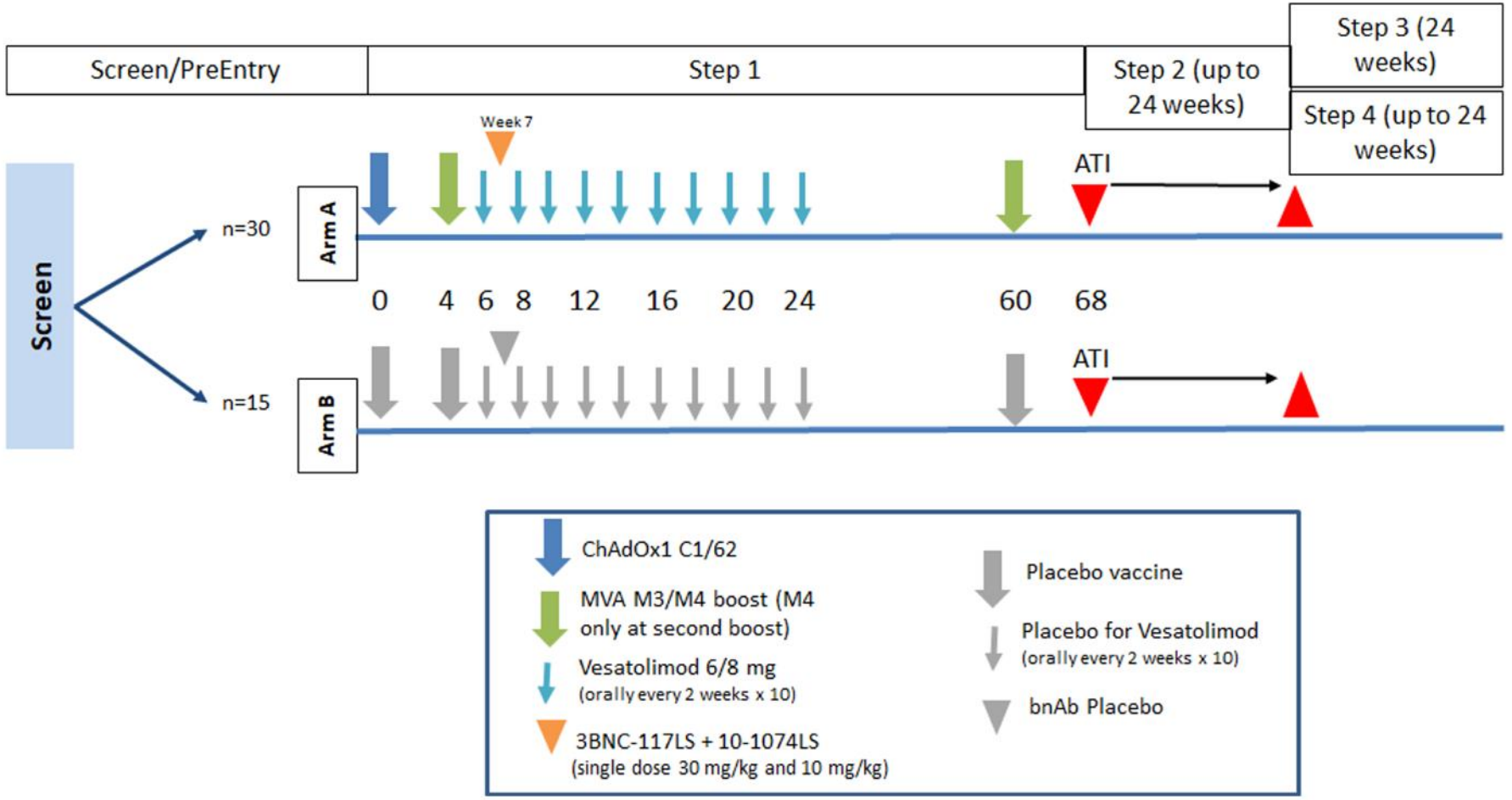
Translation into human trial?

ChAd/MVA expressing tHIVconsv
+ VES (6 → 8mg)
+ bNAbs during ART
- 3BNC117-LS (CD4bs)
- 10-1074LS (V3 loop base)

n=45 acute/early-treated (2:1)

ATI after clearance of bNAbs

ACTG A5374, NCT06071767
ongoing



Lessons from T cell vaccine trials & ATI

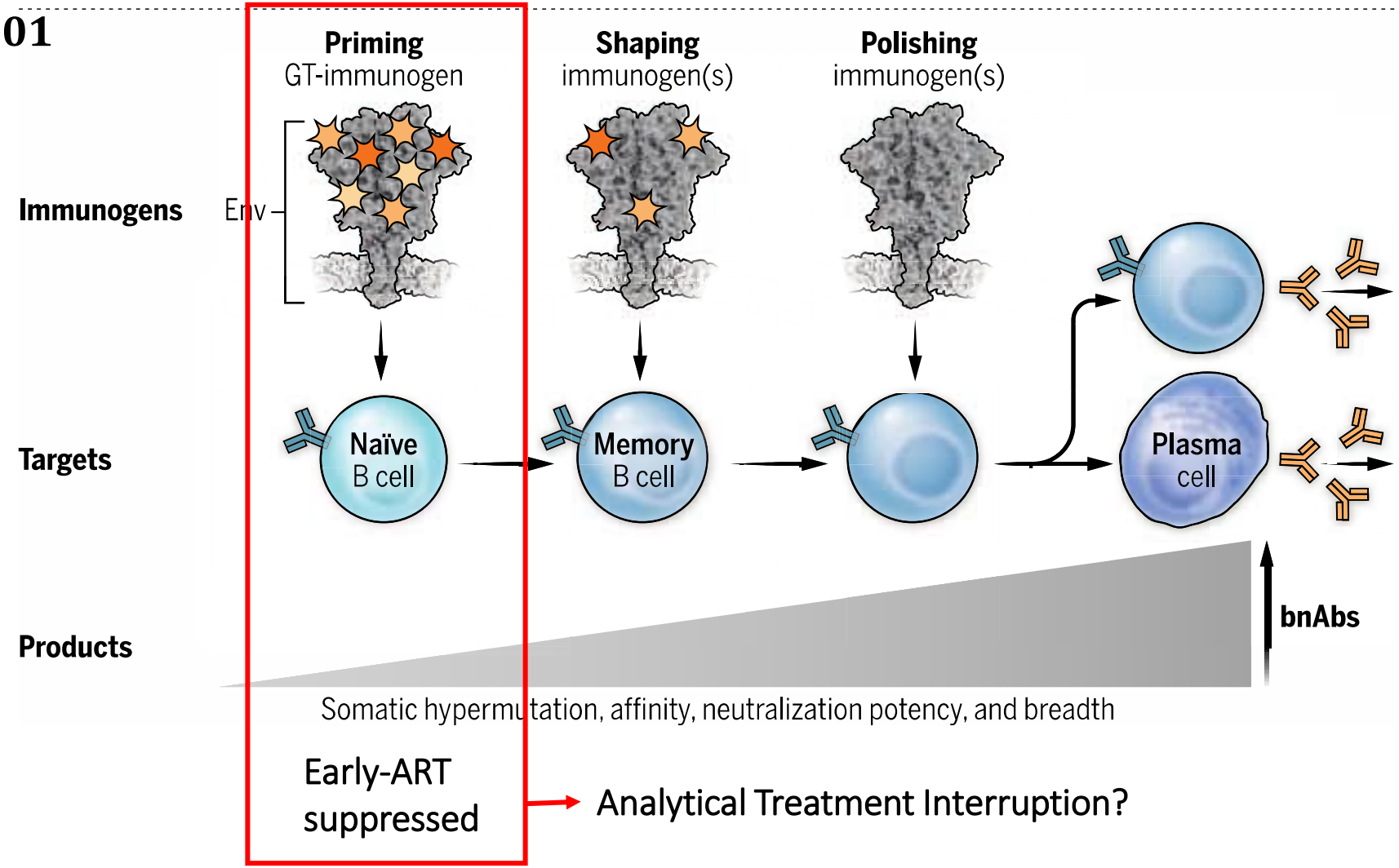
- HTI vaccines safe & highly immunogenic in early –ART
- Both CD4 and CD8 T cells induced
- Polyfunctional T cells
- Good coverage of pre-ART (reservoir) viruses
- Ex-vivo viral inhibition to autologous virus
- No reduction of the viral reservoir
- Association between HTI vaccine responses and ATI outcomes

- Not clear role of aNAb responses in AELIX-002 outcomes or vaccinal effect → need of combination T & B vaccines?

- Viral recrudescence during ATI increased neutralization to NL43 and to autologous pre-ART viruses

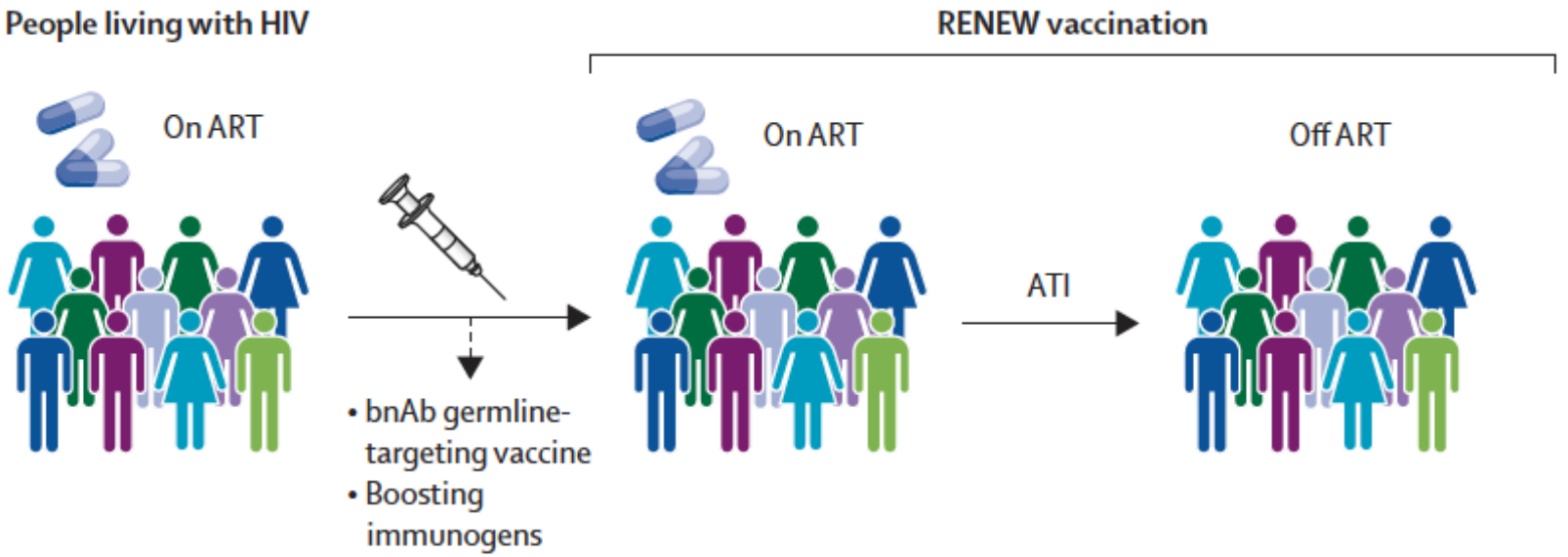
Sequential vaccination to promote bNAb developement

GT1.1 / IAVI C101



Sanders & Moore, Science 2024

RENEW vaccination



Characteristics
- Host genetics
- Ethnicity and gender
- Virus priming
  - Different subtypes
  - Priming length (onset ART)
  - Extent of HIV-specific antibody and T-cell response

Trkola & Moore, Lancet Inf Dis 2024

Conclusions

- Current bNAb vaccine development is informed by immunity in PWH
    - Germ-line targeting approaches & multiple sequential vaccination approaches can be tested in PWH with ATI to inform preventive vaccine development.
- Advance in testing bNAbs in combination cure strategies to limit viral recrudescence and for their potential vaccinal effect
- Several T cell vaccine concepts are informed by immunity in PWH with improved virological control
    - Insights from therapeutic vaccine trials can inform preventive vaccine development.

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