Vacunas

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2019
2020
2023

Orals

General

Sunday February 19th
Workshop 04 – CT desing & Analysis

9 – ADAPTIVE PLATFORM TRIALS
Michael D. Hughes

Wednesday February 22nd
Symposium 09 – Science Communication in the age of misinformation

46 – COUNTERING VACCINE AND HEALTH MIS & DISINFORMATION: AN EVIDENCE-BASED APPROACH
Scott C. Ratzan

HIV prevention

Tuesday February 21st
SPECIAL SESSION

MOSAICO
Susan Buchbinder

HIV VACCINE DEVELOPMENT POST MOSAICO
Lawrence Corey

HIV therap

Tuesday February 21st
Oral Abstract Session 5 – HIV Reservoirs & Cure strategies

136 The impact of 3BNC117, 10-1074 and Lefitolimod: TITAN
Ole S. Sogaard

143 Anti-IL10/PD1 immune mediated control of viral rebound in SIV infected macaques.
Susan Pereira Ribeiro

Wednesday February 22nd
Oral Abstract Session 10 – Immunopathogenesis & Vaccines

181 Anti-PD1 – rapid innate IFN response drive HIV reservoir decay
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Sunday February 19th

Workshop 04 – CT desing & Analysis

9 – ADAPTIVE PLATFORM TRIALS

Michael D. Hughes

Traditional RCTs: 'one population-one drug-one disease' strategy → improve efficiency?

Platform trial: multiple therapies for a single disease in a perpetual manner, with therapies entering or leaving the platform on the basis of a decision algorithm

-adaptive platform trial

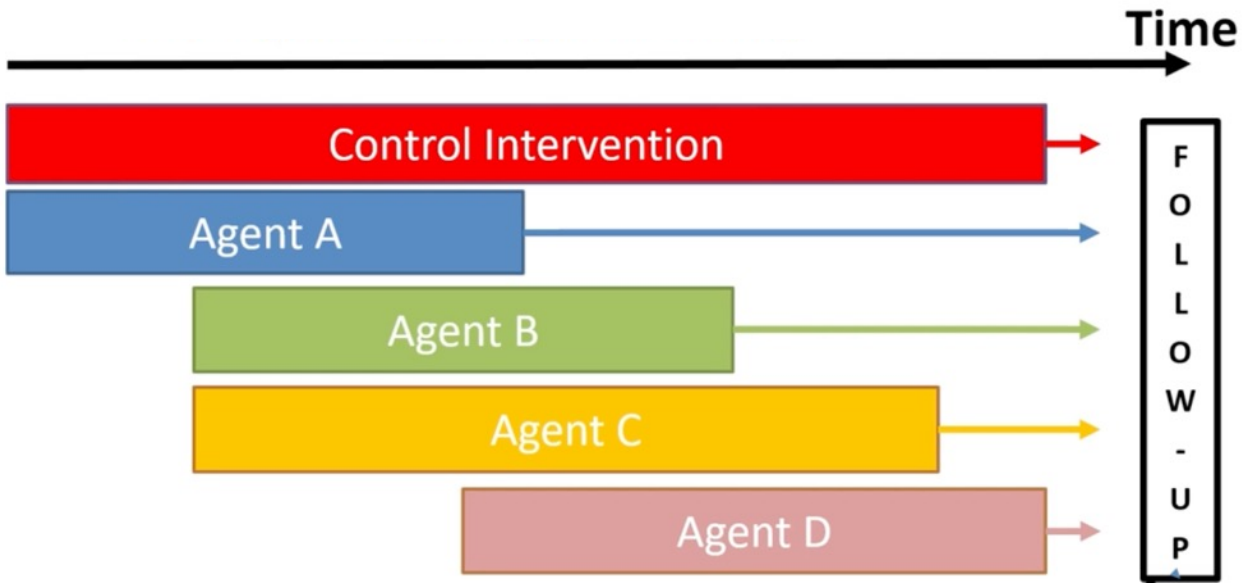
-extension of multi-arm multi-stage (MAMS) trials

Efficiency gains through:

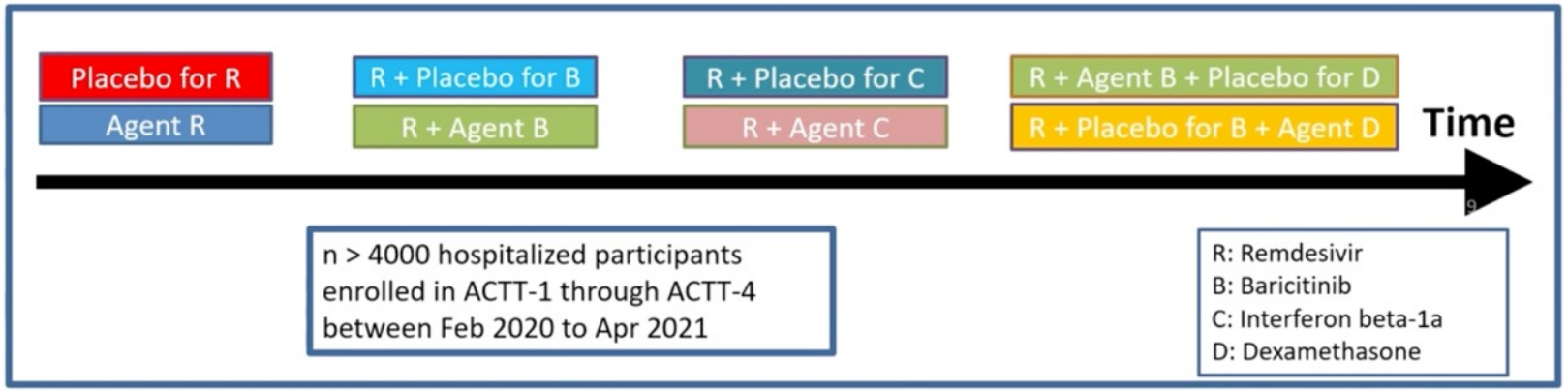
re-use of trial infrastructure

a highly standarized protocol for the multiple therapies

a possible reduction in overall sample size



Adaptive COVID-19 Treatment Trial (ACTT): Schematic of Enrollment Periods (Feb 2020 to Apr 2021)



- Series of phase 3 randomized, double-blind, placebo-controlled 2-arm trials
  - Built on existing infrastructure so very rapidly implemented in multiple countries
  - Highly efficient as re-using the same trial infrastructure
  - No sample size reduction (vs. separately conducted RCTs)

- Results for 11 treatments available on RECOVERY web site
- Further treatments in evaluation

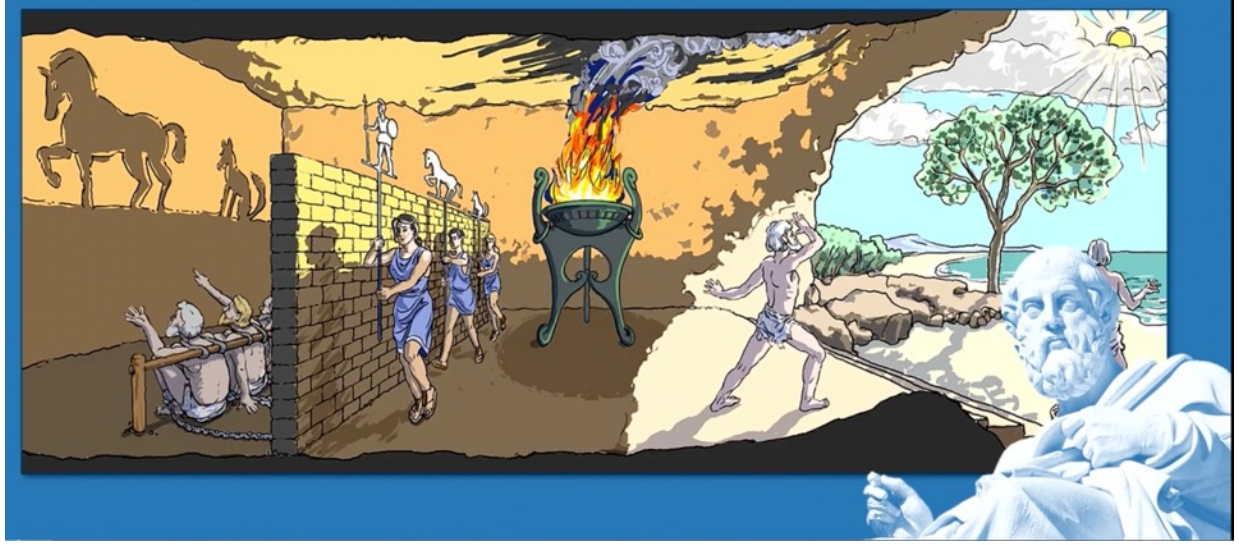
Wednesday February 22nd

Symposium 09 – Science Communication in the age of misinformation

46 – COUNTERING VACCINE AND HEALTH MIS & DISINFORMATION: AN EVIDENCE-BASED APPROACH

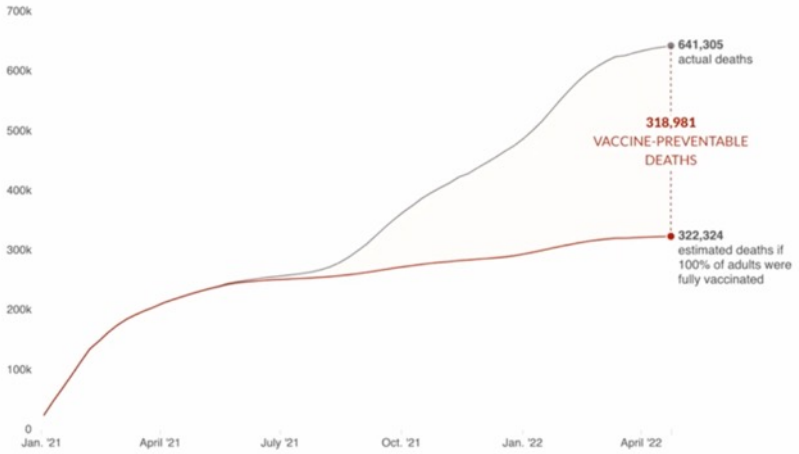
Scott C. Ratzan

Misinformation in Ancient Greece



Misinformation is a **public health threat**

Cumulative COVID-19 deaths among US adults, Jan 01 '21 to Apr 30 '22[1]



Since the widespread availability of the COVID-19 vaccine in the US, **almost half of COVID-19 deaths were preventable.**

Why not vaccinate?

Top 5 reasons given by unvaccinated US adults:

- **49%** are worried about side effects
- **42%** don't trust COVID-19 vaccines
- **35%** don't trust the government
- **32%** don't believe they need it
- **28%** plan to wait and see if it is safe

1. SouZhong M, Kshirsagar M, Johnston R, et al. Estimating Vaccine-Preventable COVID-19 Deaths Under Counterfactual Vaccination Scenarios in the United States. *MedRxiv*. Preprint published online May 21, 2022. doi:10.1101/2022.05.19.22275310 Also see Bollyky TJ, Kickbusch I, Petersen MB. *The Trust Gap: How to Fight Pandemics in a Divided Country*. FOREIGN AFFAIRS, January 30, 2023.
2. U.S. Census Bureau, Household Pulse Survey.. 2021. https://www.census.gov/library/stories/2021/12/who-are-the-adults-not-vaccinated-against-covid.html

Health is communicated ubiquitously, but communicated via *many* intermediaries

Health communication is a core public health function*

Health communication is the **science and art** of using communication to advance the health and well-being of people and populations.[1]

MS Program in Health Communication for Social Change

CUNY SPH GRADUATE SCHOOL OF PUBLIC HEALTH & HEALTH POLICY

1. https://www.societyforhealthcommunication.org/health-communication

*And so is addressing misinformation ; See Combating Misinformation as a Core Function of Public Health. January 18, 2023 NEJM Catalyst Innovations in Care Delivery

Innovative framing to address Vaccination: Vaccine Literacy

Vaccine literacy definition

'Vaccine literacy' occurs when the skills and abilities of people align with the content, processes and systems needed to access and get vaccinated.

It is knowing how and why vaccines work, the diseases they prevent, and their value to yourself and to society.

Vaccine Literacy, a Crucial Healthcare Innovation
S. Ratzan *Harvard Business Review* (February 28, 2011)

Vaccine Literacy—Helping Everyone Decide to Accept Vaccination, Ratzan. S. and R Parker. *Journal of Health Communication*, 25:10, 2020.

A Select Bibliography of Actions to Promote Vaccine Literacy Rauh L., Lathan H., Zorn M., Masiello M., Ratzan S., Parker R., *Journal of Health Communication*, 2021

Vaccine literacy is facilitated by eight principles

1. Individual knowledge informed by clear, trustworthy, up-to-date evidence
2. Ability to discern fact from fiction
3. Listening, encouraging questions, and dialogue
4. Providing understandable, trustworthy, up-to-date answers to questions
5. Understanding risks and benefits of vaccination for self and society
6. Successful education, access, and systems for vaccination
7. Prudent policies that incentivize vaccination and equity
8. Transparency, clarity, and confidence in vaccine quality, safety, and efficacy

Tuesday February 21st

SPECIAL SESSION

MOSAICO

Susan Buchbinder

Tuesday February 21st

SPECIAL SESSION

MOSAICO

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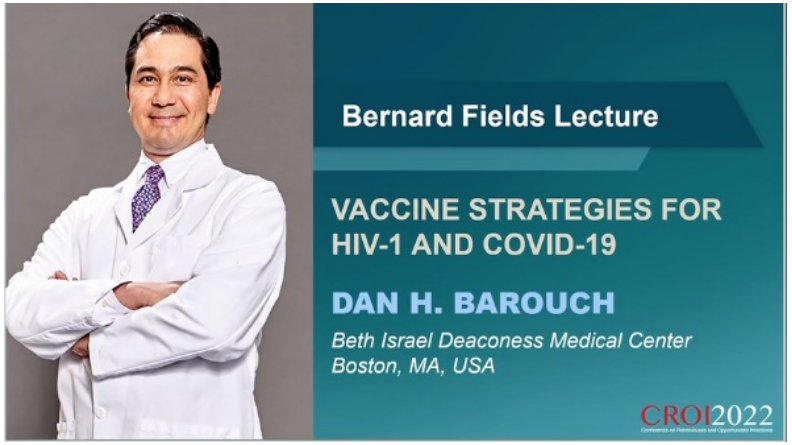
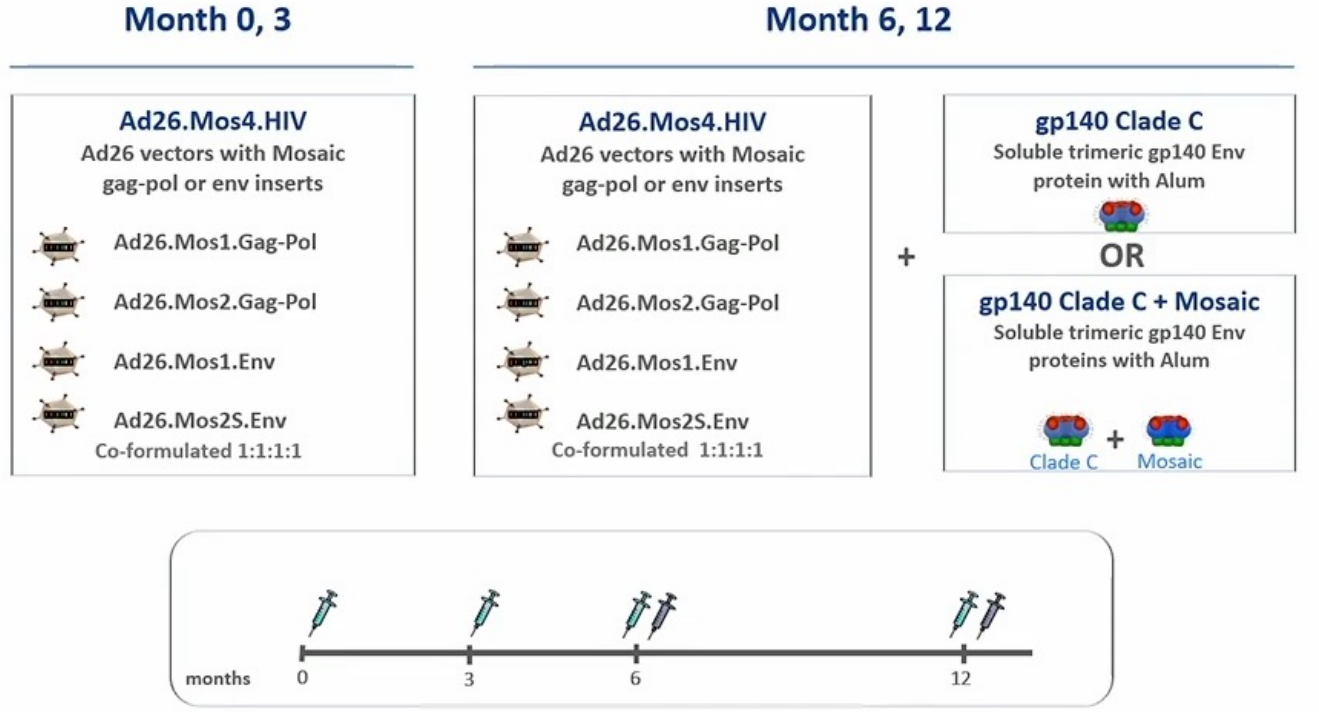




→ **Two Complementary Phase 2b/3 Efficacy Studies**

IMBOKODO

Phase: 2b

Enrollment: 2,637

Participants: Young Women (aged 18-35)

Location: 5 Southern African Countries

Timeline: Began Nov 2017, Vaccinations completed in July 2020

IMBOKODO

MOSAICO

Phase: 3

Target Enrollment: 3,800

Participants: MSM and TGI (aged 18-60)

Location: 8 Countries in the Americas and Europe

Timeline: Began end 2019, enrollment ongoing

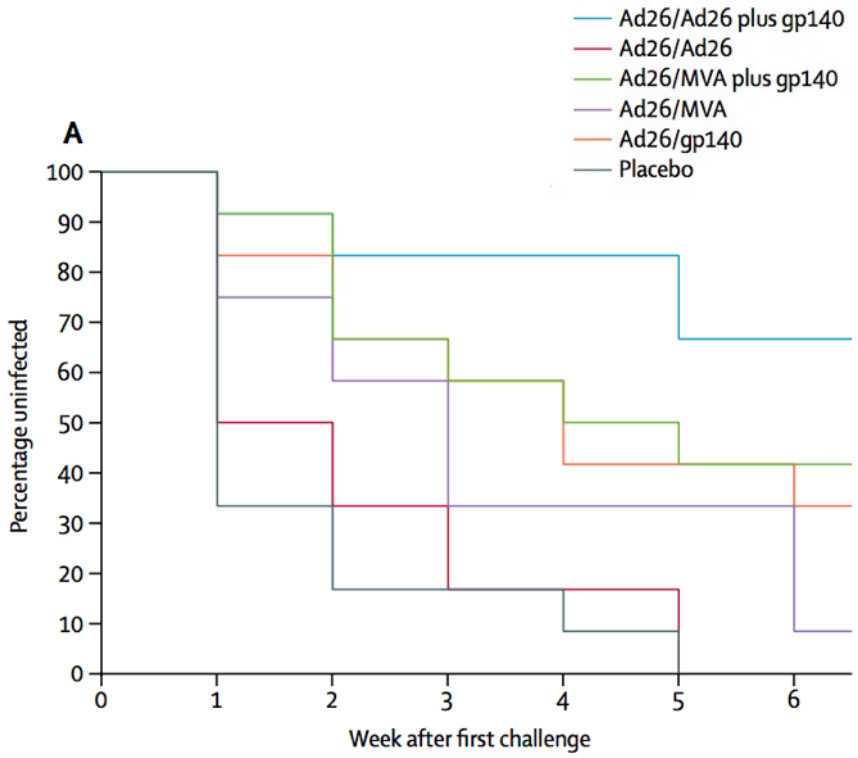
MOSAICO

MSM & TGW
PrEP implementation

Fisher W, et al. Nat Med 2007
Barouch Nat Med 2010
Barouch, Cell 2013

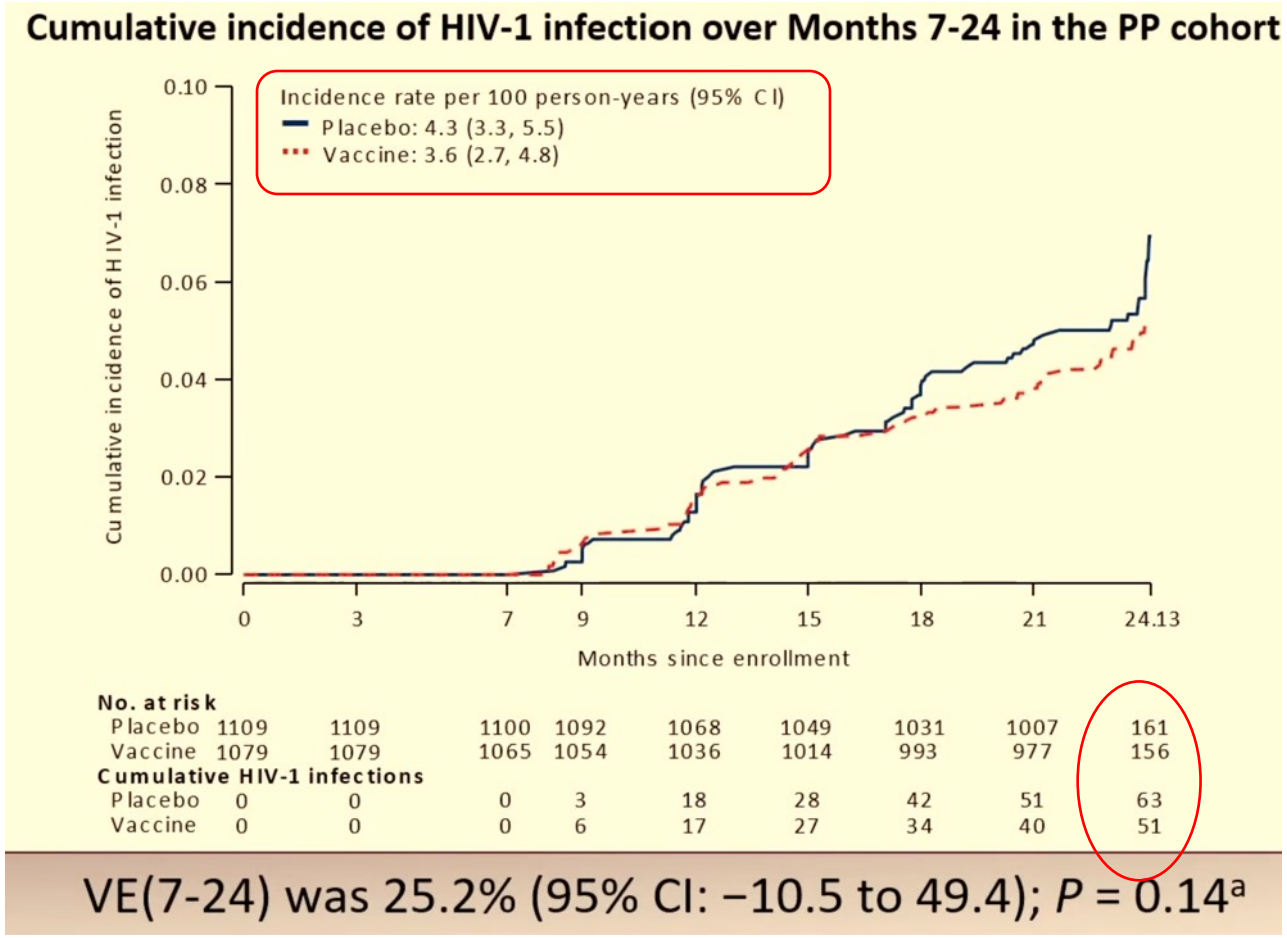
<u>Differences:</u> HIV-1 clade, gender, route, protein boost

NHP



Barouch, Lancet 2018

Human CT : IMBOKODO, CROI 2022



Human CT : MOSAICO, CROI 2023

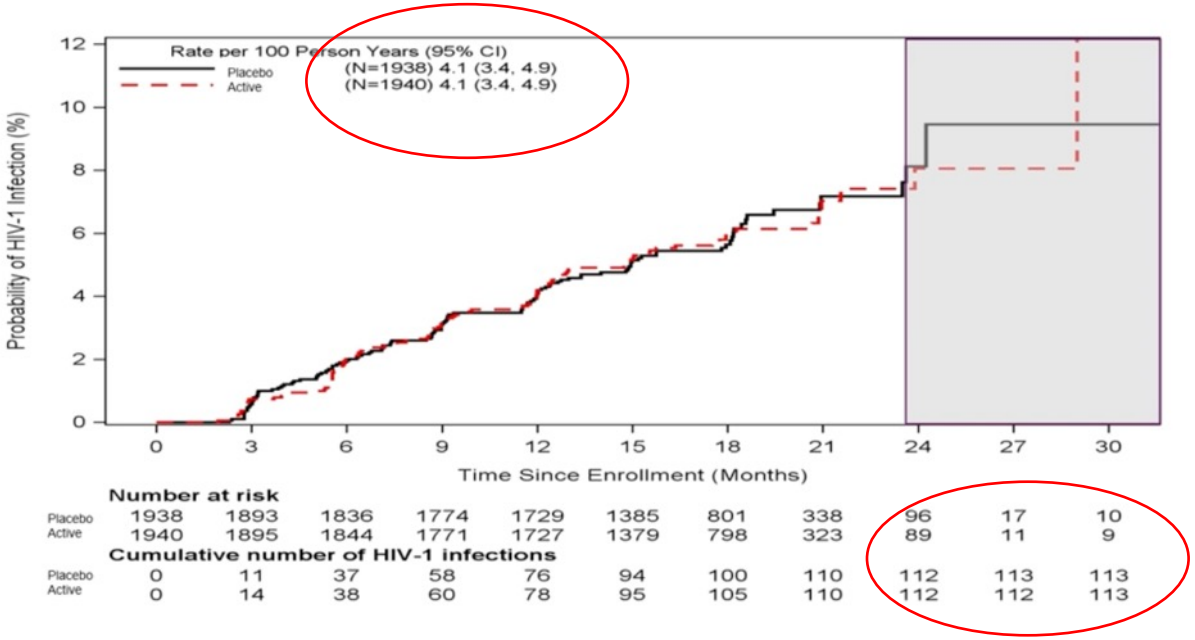
n=3,800 (1,900 per arm)
PrEP implementation program : Aprox 10% PrEP uptake
>93% retention despite COVID19 pandemic
No safety issues

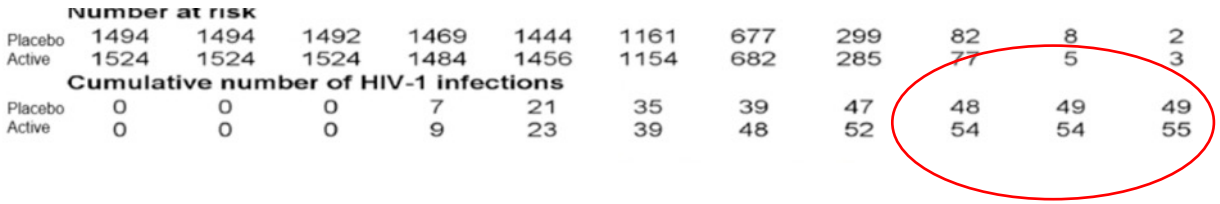
	Total Enrolled N=3887
Sex at birth	
Male	3870 (99.6%)
Gender at screening	
Male	3556 (91.5%)
Transgender Female (Male to Female)	194 (5.0%)
Transgender Male (Female to Male)	16 (0.4%)
Gender Queer	19 (0.5%)
Gender Variant/Non-conforming	36 (0.9%)
Female	48 (1.2%)
Other	15 (0.4%)
Age	
Median (min, max)	28.0 (18, 60)

Country	N Enrolled (%)
Argentina	402 (10.3%)
Brazil	852 (21.9%)
Italy	91 (2.3%)
Mexico	347 (8.9%)
Peru	1615 (41.5%)
Poland	116 (3.0%)
Puerto Rico	10 (0.3%)
Spain	262 (6.7%)
USA	192 (4.9%)

Human CT : MOSAICO, CROI 2023

Cumulative HIV Infections (mITT)





For VE% calculation the data was cut-off at month 23.7. Thereafter, the estimate is considered unstable due to too few subjects at risk

mITT criteria
- Randomized
- At least one vax
- HIV negative at first vax

Per protocol criteria:
- First 3 vax in window
- HIV neg test 4 weeks or later after 3rd vax
- No major PDs linked to incorrect product administration

	Placebo			
	# evaluated	# infected	# person-years	Incidence per 100 py
All ppts	1938	113	2757	4.1
Ages (yrs)				
18-20	213	15	295	5.1
21-34	1246	77	1758	4.4
35-44	325	15	471	3.2
45-60	154	6	233	2.6
Region				
Europe	235	5	355	1.4
Latin Am	1604	106	2252	4.7
US	99	2	150	1.3

	Vaccine			
	# evaluated	# infected	# person-years	Incidence per 100 py
All ppts	1940	113	2755	4.1
Ages (yrs)				
18-20	198	17	286	5.9
21-34	1271	74	1784	4.1
35-44	342	17	491	3.5
45-60	129	5	194	2.6
Region				
Europe	233	5	351	1.4
Latin Am	1614	108	2265	4.8
US	93	0	139	0

HIV vaccine development: ‘Post-MOSAICO’

HIV VACCINE TRIALS NETWORK

HIV Vaccines 1984-2014

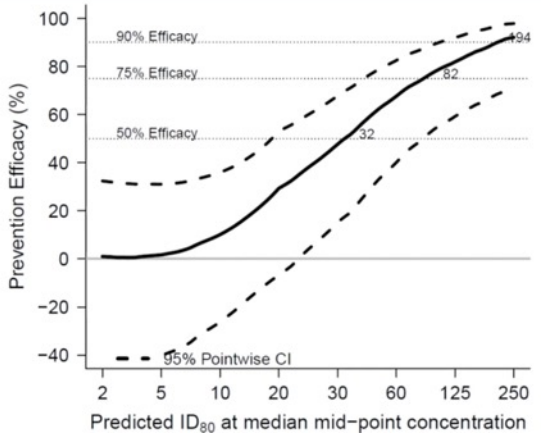
1984-2000
Optimism that recombinant monomeric envelope protein vaccines might work

2000-2010
T-cell based vaccines/recombinant proteins: STEP, Phambili HVTN 505; RV144, partial success: correlated to non neutralizing antibodies to V1V2 loop

2010-2015
HIV bNAbs isolated and shown to protect in NHP; Ad26 Mosaic vaccine similar protection in NHP

AMP ANTIBODY · MEDIATED · PREVENTION STUDY

Prevention Efficacy Smoothly Increased with PT_{80} in AMP



- The plot repeats the PE-by-IC_{80} results (Corey et al., 2021), scaling IC_{80} by the median mid-infusion visit concentration of VRC01 in AMP

Suggests

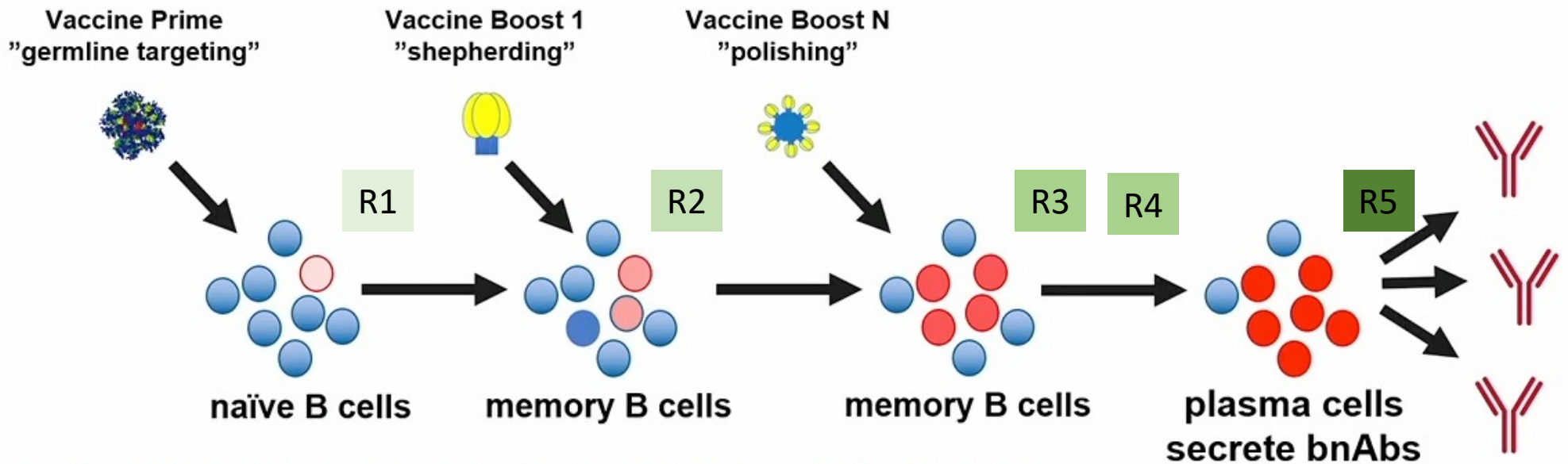
- **PT_{80} > 82** → ~75% PE ;
- **PT_{80} > 194** → ~90% PE

Neutralizing Vaccine Program

HIV VACCINE TRIALS NETWORK

Strategy to induce bnAbs:
Germline targeting approach

Germline targeting is an approach where the immune system is manipulated to elicit a very specific antibody response by finding the shortest **pathway from germline to affinity mature antibodies with strategically designed priming and boosting immunogens.***



*Elucidation of the unmutated common ancestor (UCA) of the bnAb lineage is paired with definition of the optimal Env immunogen to trigger appropriate B cell precursor

Somatic hypermutation

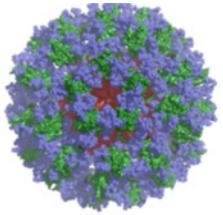
Neutralizing Vaccine Program

HIV VACCINE TRIALS NETWORK

VRC01-class bnAbs

- Engage the gp120 CD4bs
- Require VH1-2 and 5AA L-CDR3 to engage CD4bs
- Have diverse H-CDR3s and light chains

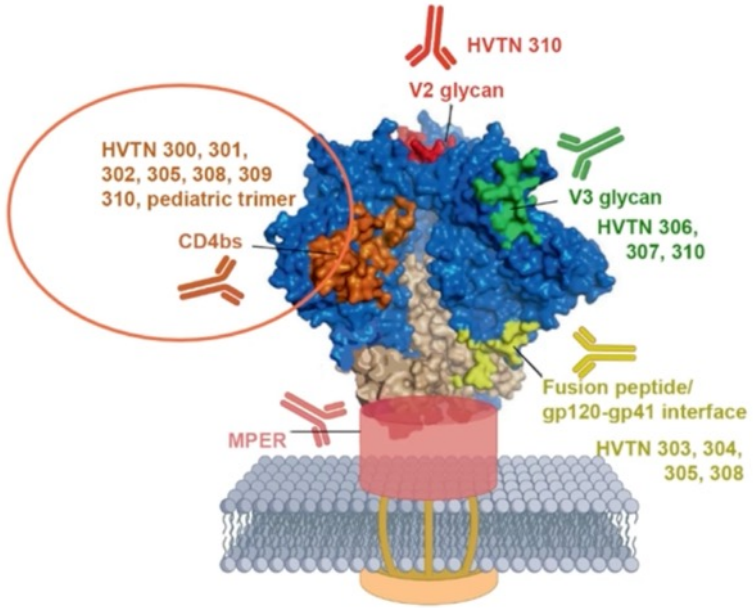
➢ Need priming immunogen with appreciable affinity and avidity for diverse VRC01-class human naïve precursors



Germline-Targeting Immunogen

- eOD-GT8 60mer
- Self-assembling nanoparticle presenting 60 copies of an engineered gp120 outer domain

✓ Has appreciable affinity and avidity for diverse VRC01-class human naïve precursors
✓ Primes VRC01-class responses in stringent mouse models
✓ Induces VRC01-class memory responses that can be boosted toward bnAb development in mouse models



CD4bs	Antigen	
300	CH505 TF 3M-052-AF/Alum	Protein
301	426c Core NP	Protein
302	BG505 trimers	mRNA
305	eOD-GT8	DNA
308	Deglycosylated NFL timer	Protein
309	CH505M5 trimer NP + CH505 TF	Protein
310	Deglycosylated 426 trimer	mRNA

FP/interface	Antigen	
303	FP NP + VRC 4571 trimer	Protein
304	BG505	DNA
305	eOD-GT8	DNA
308	Deglycosylated NFL trimer	Protein

V3 glycan	Antigen	
306	N332 GT5 + SMNP	mRNA
307	V3G CH848 trimer NP + M-052-AF + mRNA trimer	Protein + mRNA
310	426c + BG505	VLP

Post COVID-19 Vaccine Platforms

HIV VACCINE TRIALS NETWORK

- mRNA
- Peptide – Adjuvant Vaccines
- Protein Nanoparticles
  - Ferritin nanoparticles
  - Self assembling (eOD-GT8) nanoparticles
  - VLPs
- Viral Vector for clearance of infected cells
  - CMV

- HIV Vaccine infrastructure + ‘NASA’ of COVID-19 vaccine development
- Objective: making bNAbs to different targets : epitope-specific vaccines
- Target titer is serum neutralization of >1:200 in TZMBl assay
- mRNA platform should allow for a faster iteration of candidate vaccines

HIV therap

Tuesday February 21st

Oral Abstract Session 5 – HIV Reservoirs & Cure strategies

136 The impact of 3BNC117, 10-1074 and Lefitolimod: TITAN
Ole S. Sogaard

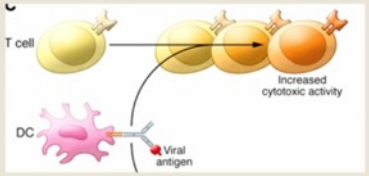
143 Anti-IL10/PD1 immune mediated control of viral rebound in SIV infected macaques.
Susan Pereira Ribeiro

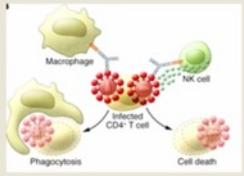
Wednesday February 22nd

Oral Abstract Session 10 – Immunopathogenesis & Vaccines

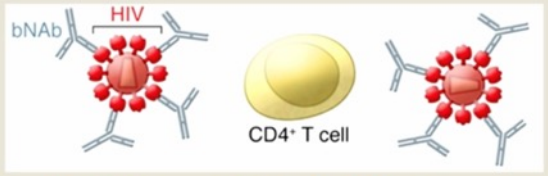
181 Anti-PD1 – rapid innate IFN response drive HIV reservoir decay
Ashish Arunkumar Sharma

- **TLR9 agonist** prime innate and adaptive immune cells prior to antigen exposure
  - Increase antigen pDC cross-presentation to CD8+ T cells
    - -> boost HIV-specific CTL-mediated immunity
  - Enhance antibody-dependent effector functions
- **bNAbs** mediate slow/controlled release of antigen (HIV) to allow for development of potent adaptive immune responses





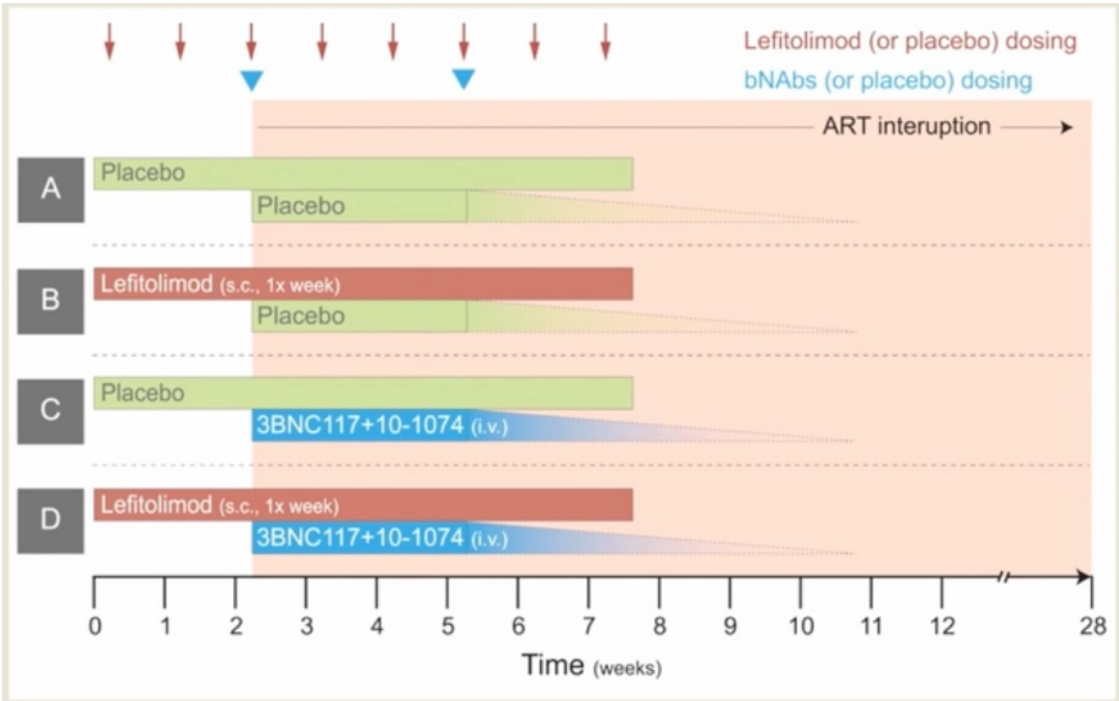
Lefitolimod (TLR9a)



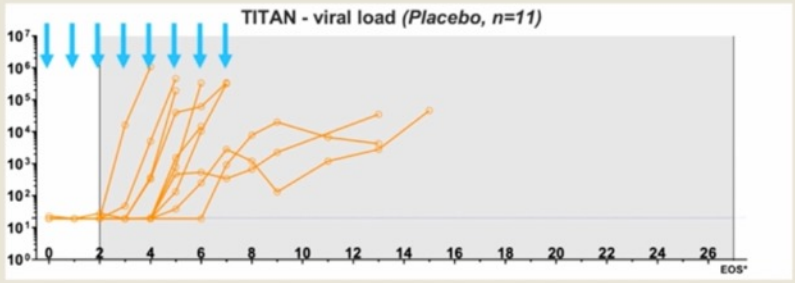
3BNC117 and 10-1074 (bNAbs)

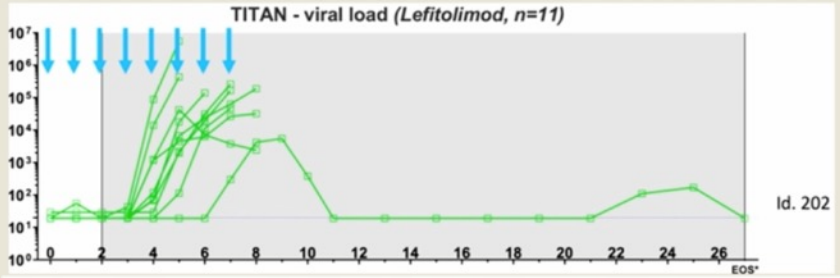
Vibholm et al. CID 2017, Vibholm et al. AIDS 2019, Halper-Stromberg and Nussenzweig JCI 2016; Nishimura et al Nature 2017

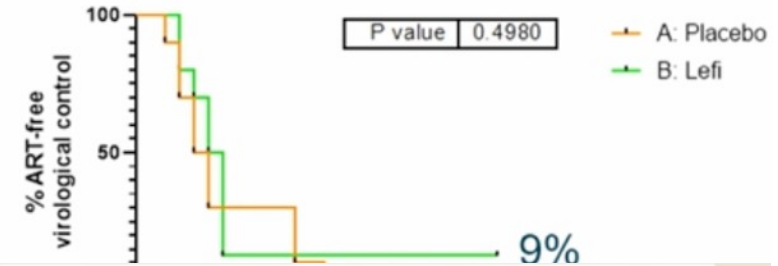
30th CROI 2023

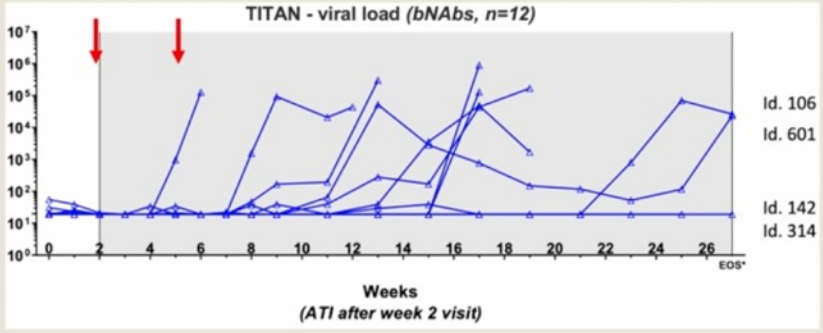


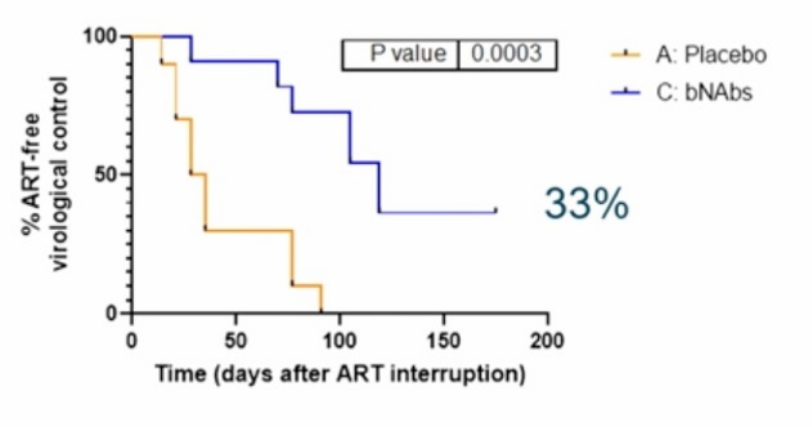
- Primary endpoint: Time to viral rebound (>1,000 c/mL for 4 weeks or x2 >100,000

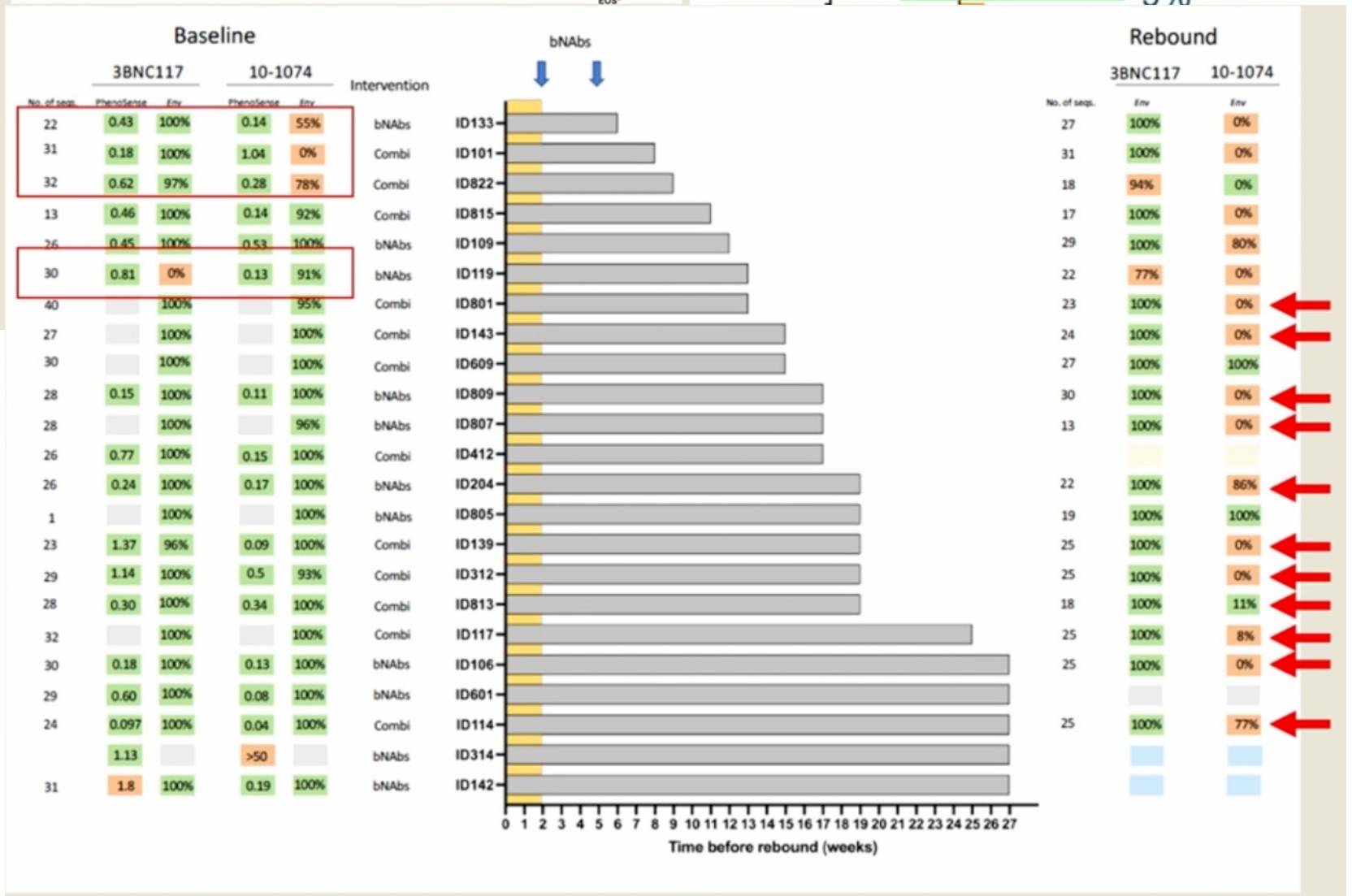

TITAN - viral load (Placebo, n=11)
EOS*


TITAN - viral load (Lefitolimod, n=11)
Id. 202
EOS*


% ART-free virological control
P value 0.4980
A: Placebo
B: Lefi
9%


TITAN - viral load (bNAbs, n=12)
Id. 106
Id. 601
Id. 142
Id. 314
EOS*
Weeks
(ATI after week 2 visit)


% ART-free virological control
P value 0.0003
A: Placebo
C: bNAbs
33%
Time (days after ART interruption)


Baseline
3BNC117
10-1074
Intervention
bNAbs
Rebound
Time before rebound (weeks)

HIV therap

Tuesday February 21st
Oral Abstract Session 5 – HIV Reservoirs & Cure strategies

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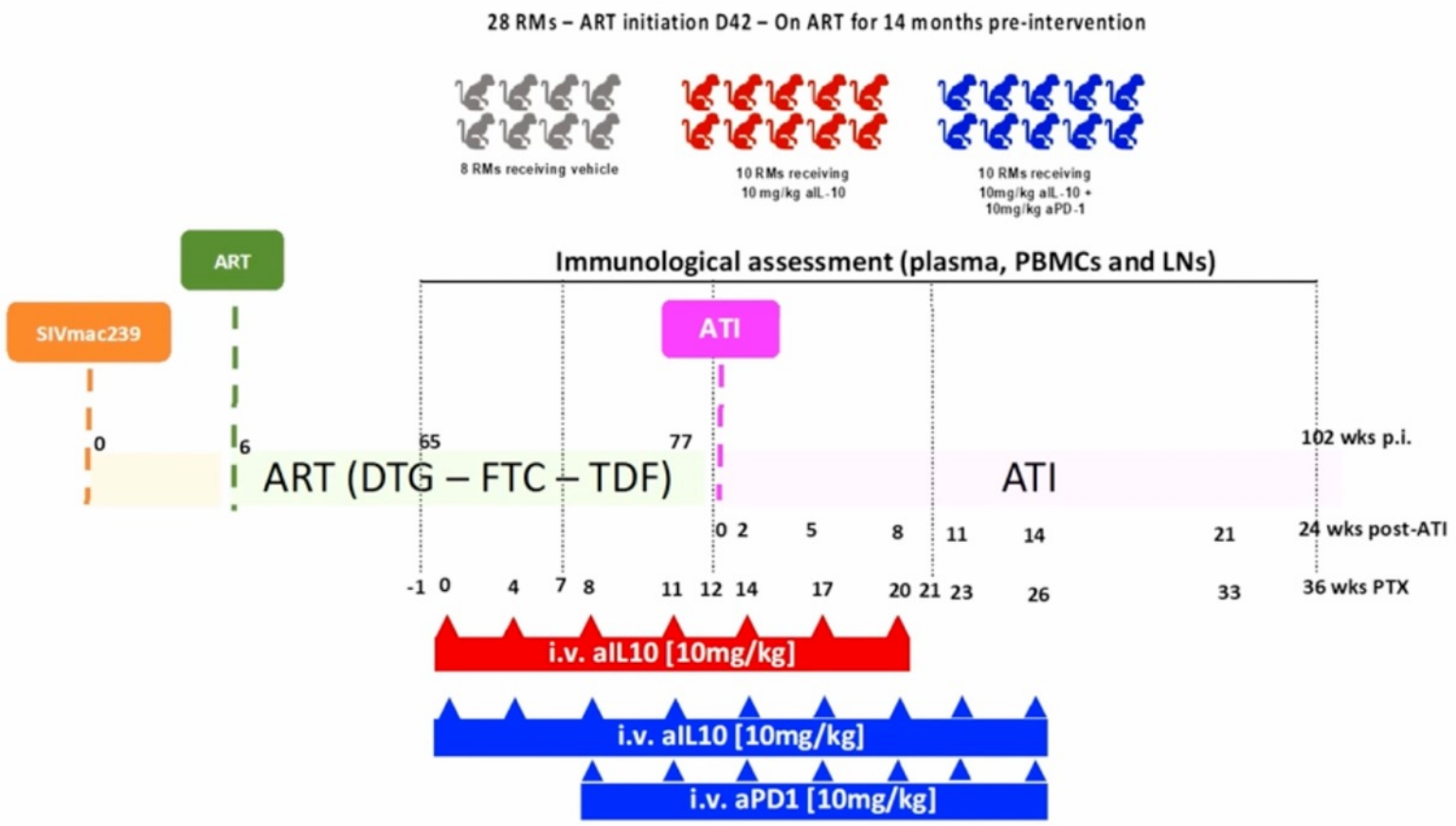
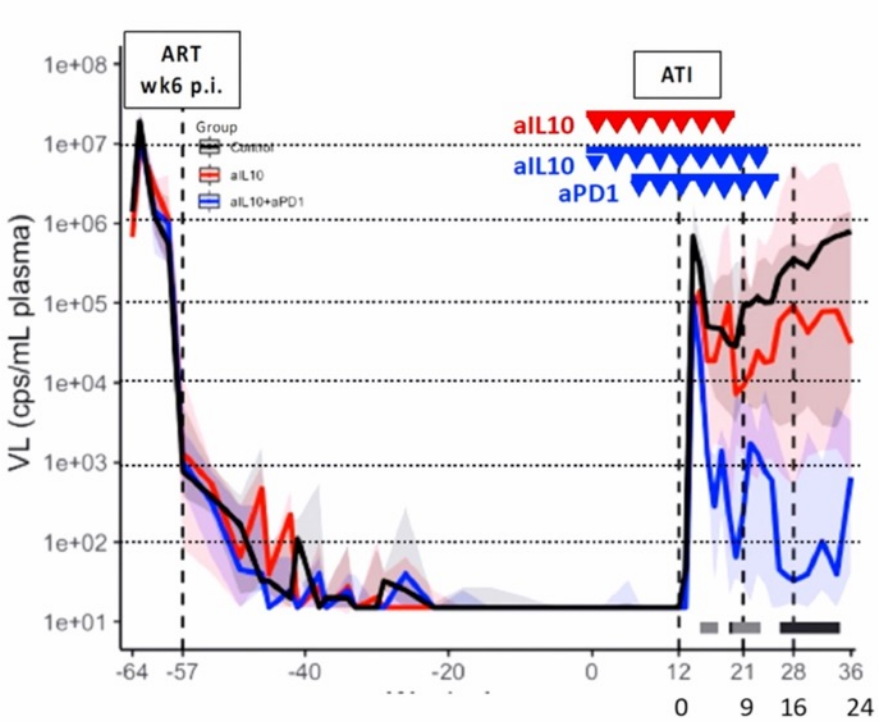
Ashish Arunkumar Sharma

a-IL10:
- Decrease survival of infected CD4
- Promote differentiation of quiescent TCM towards TEM
- Restore viral replication from latent cells

a-PD1:
- Syntergize to restore viral replication
- Promote effector T cell diferentiation with restored function



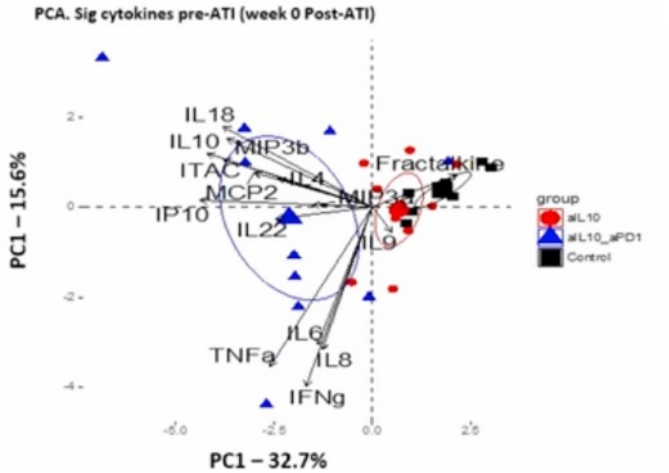


Durable viral load control post-ATI (less than a 1000 cps/mL in 90% of the animals up to 6 months) in the combo treated RMs was associated with a biphasic immune response:

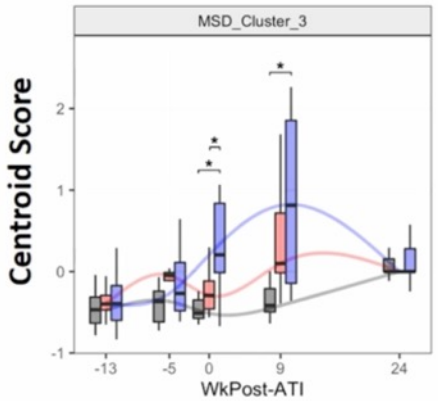
I) ***Pre-ATI*** poised immune response

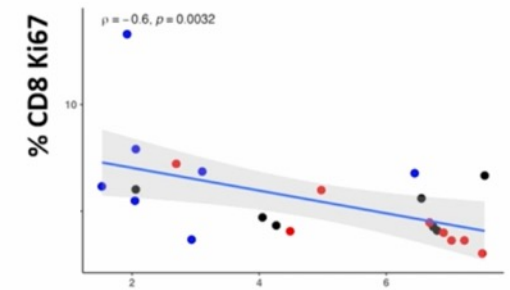
II) Post-ATI (6 months) strong expansion of effector SIV specific T cells that control VL and become long-lived SIV specific memory T cells once virus is cleared

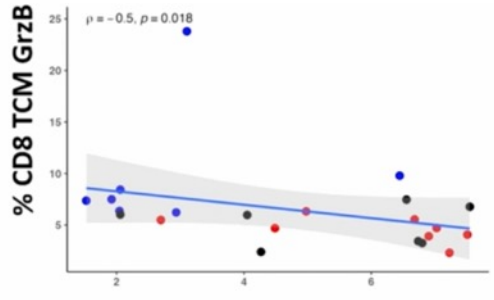
Elevated pro-inflammatory environment
IL1b, IL18, IP10, MIP3b and MCPs

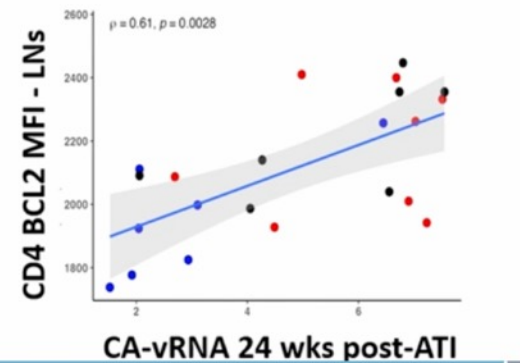


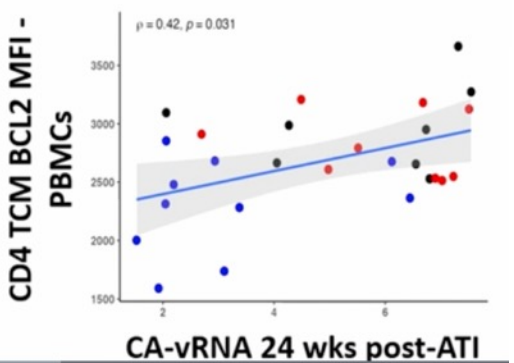
Cluster_3 Components
CTACK
I.TAC
IL10
IL.16
IL.17A
IL.18
IL.4
IP.10
MCP.1
MCP.2
MIP.3b











HIV therap

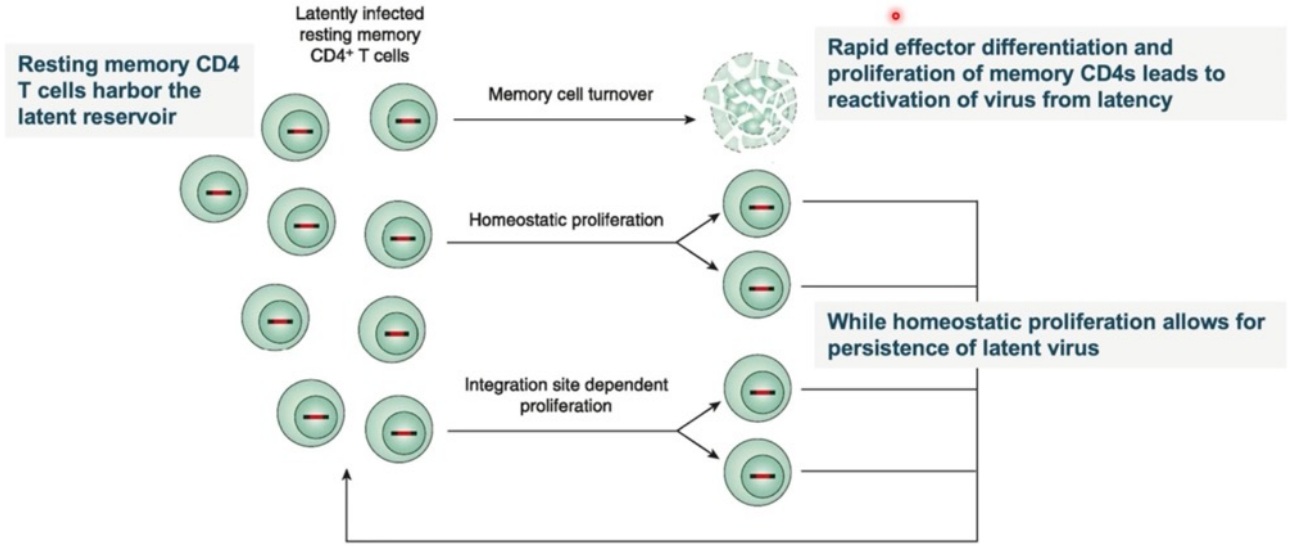
Tuesday February 21st
Oral Abstract Session 5 – HIV Reservoirs & Cure strategies

136 The impact of 3BNC117, 10-1074 and Lefitolimod: TITAN
Ole S. Sogaard

143 Anti-IL10/PD1 immune mediated control of viral rebound in SIV infected macaques.
Susan Pereira Ribeiro

Wednesday February 22nd
Oral Abstract Session 10 – Immunopathogenesis & Vaccines

181 Anti-PD1 – rapid innate IFN response drive HIV reservoir decay
Ashish Arunkumar Sharma

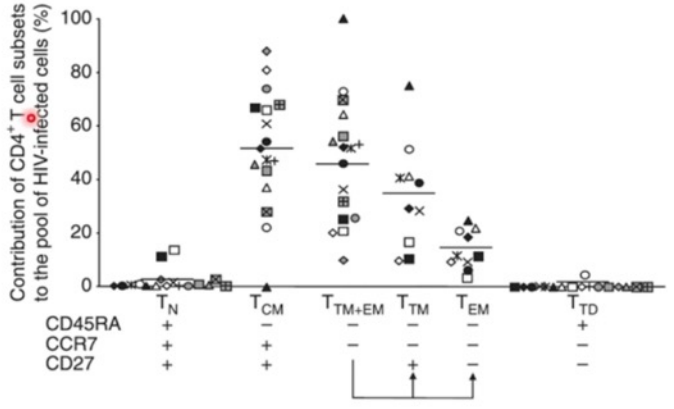


Dysfunctional PD-1+ CD4 T cells harbor the HIV reservoir

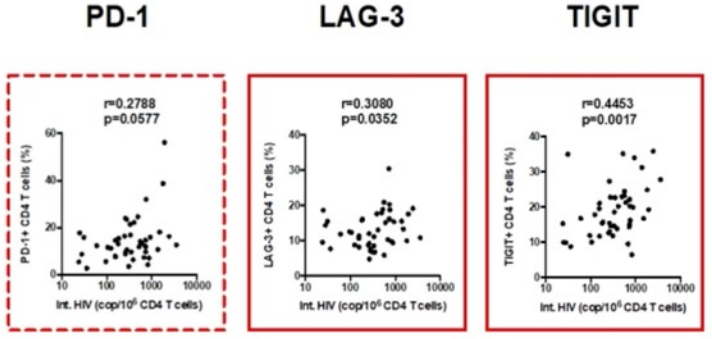
nature medicine

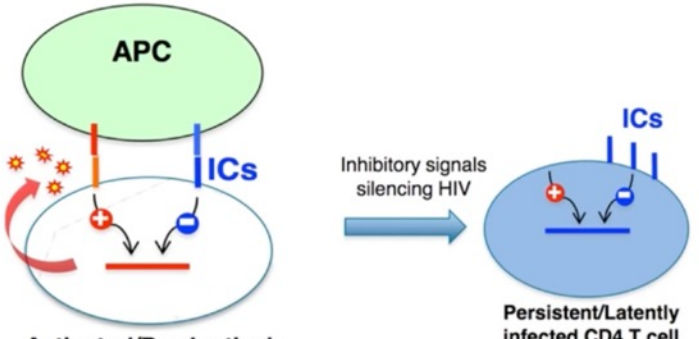
HIV reservoir size and persistence are driven by T cell survival and homeostatic proliferation

Nicolas Chomont[1–3], Mohamed El-Far[1–3], Petronela Ancuta[3], Lydie Trautmann[1–3], Francesco A Procopio[1–3], Bader Yassine-Diab[1–3], Geneviève Boucher[1], Mohamed-Rachid Boulassel[4], Georges Ghattas[5], Jason M Brenchley[6], Timothy W Schacker[7], Brenna J Hill[8], Daniel C Douek[8], Jean-Pierre Routy[4,9], Elias K Haddad[1–3,9] & Rafick-Pierre Sékaly[1–3,9–11]



HIV persists in CD4 T cells that are of the CM (quiescent) phenotype and express higher levels of markers associated with immune dysfunction (i.e., PD1, LAG3 and TIGIT)





30th CRC

CITN-12:
Anti-PD-1 Clinical Trial in PLWH and Advanced Cancer

30 PLWH

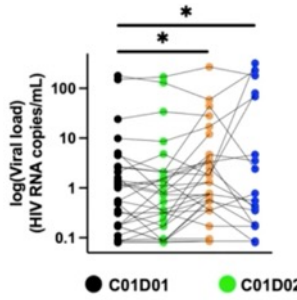
11 AIDS and Non-AIDS Cancers
1 CR, 4 PR

3 CD4 T cell count based cohorts
<200, 200-350, >350

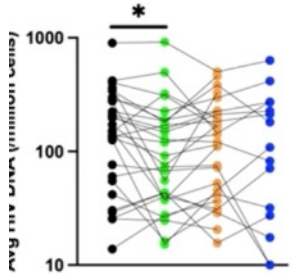
+ Pembrolizumab (anti-PD1)

C01 (21 days) C03-C013 → → → → End of Tx

PBMC and plasma collection
- D01 (pre-intervention)
- D02 (24 hours)
- D08 (1 week)
- End of Tx



- Significant latency reversal at 1-week post-intervention
- Latency reversal is sustained till the End of Treatment

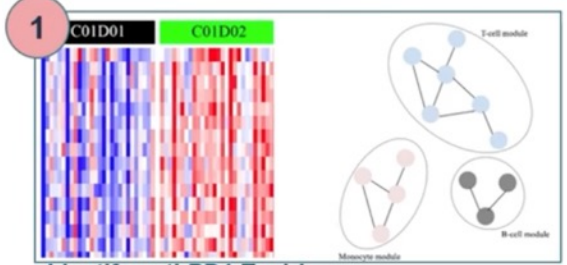


- Significant decreased in cell-associated HIV-DNA within 24 hours
- 10 of 15 participants have lower HIV-DNA at End of Tx

30th CROI 2023

Multiomic Analytics to identify anti-PD1 Tx driven mechanisms associated with HIV reservoir decay

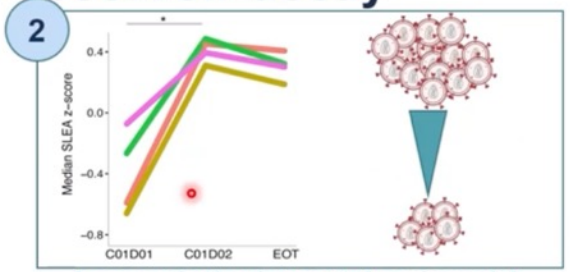
1



Identify anti-PD1 Tx driven
1. PBMC transcriptomic modules
2. Plasma cytokines

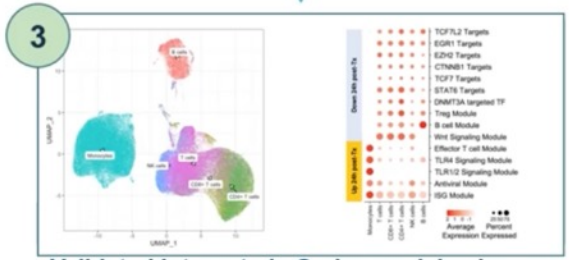
Generate Integrated –omics model

2



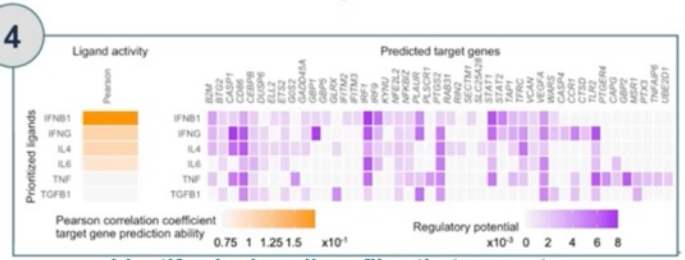
Assess whether integrated -omic model
1. Persists till the End of therapy
2. Associated with Lower Latency

3



Validated Integrated –Omics model using single-cell RNA-seq and flow cytometry

4



Identify single-cell profiles that promote reservoir decay after anti-PD-1 therapy

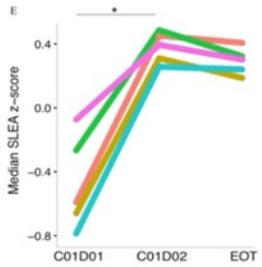
30th CROI 2023

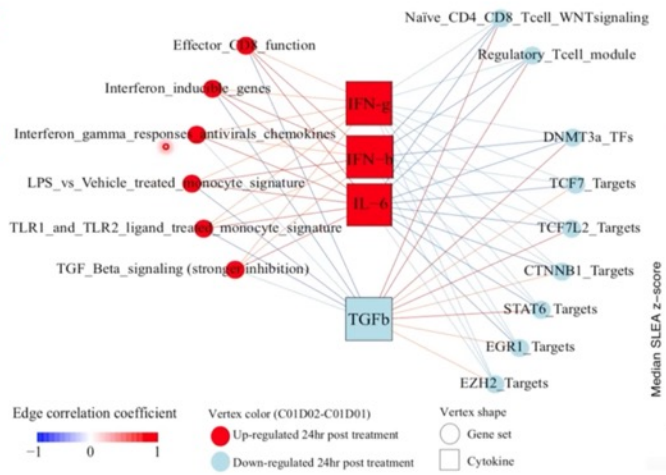
Ulrich, STM 2022

1 2 Multi-omic response signature induced 24h post-treatment and persists till the end of therapy

UPREGULATED MODULES

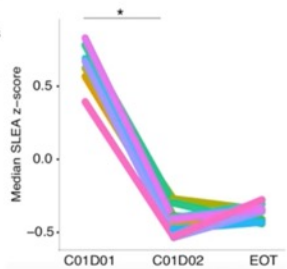
Effector CD8 function, IFN responses and monocyte signatures are correlated with plasma IFN-γ, IFN-β and IL-6 and low TGF-β



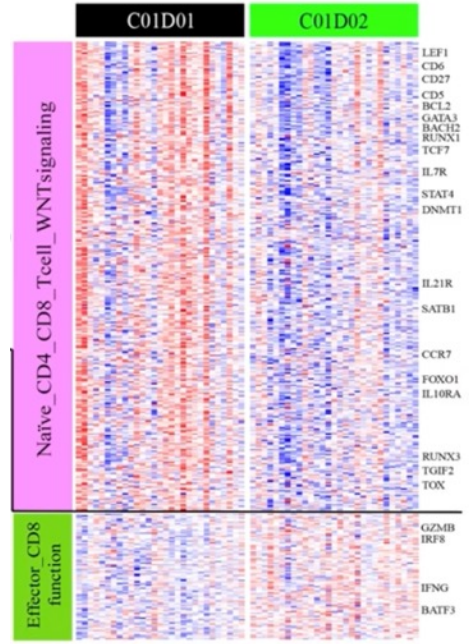


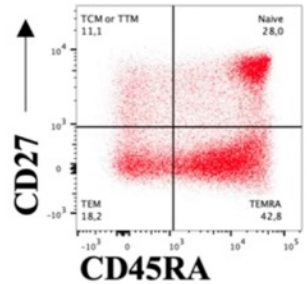
DOWNREGULATED MODULES

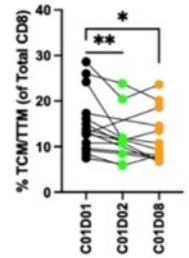
Naïve T-cell (and its TF targets), regulatory T-cell and B-cell modules are correlated with high plasma TGF-β

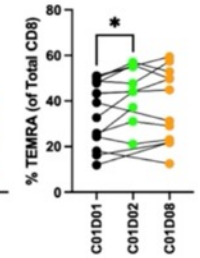


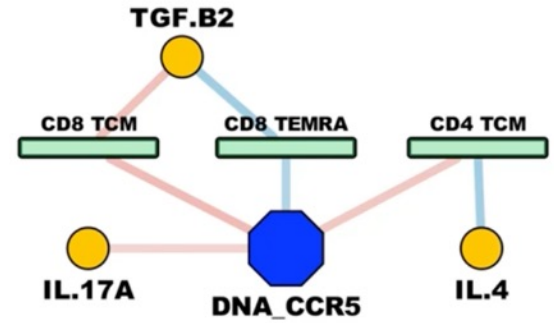
Analyses using MixOmics package in R
DEGs and pathway analyses using EdgeR, GSEA pipelines



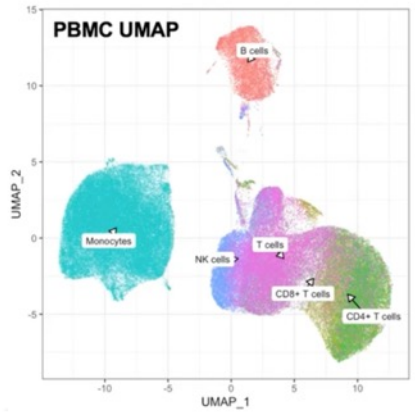


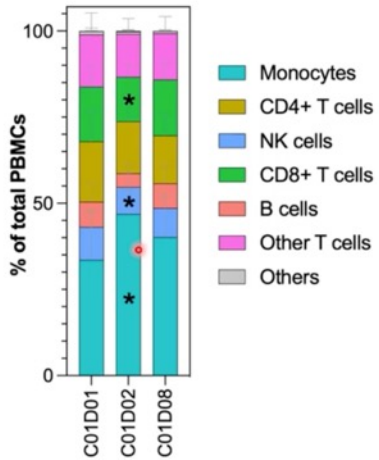




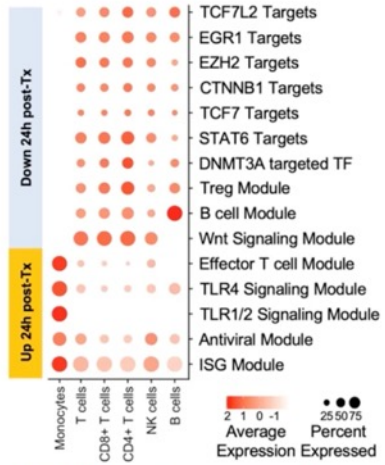


3 Innate (TLR) and ISG modules highly expressed in Monocytes





Frequency of monocytes increased 24h post-Tx

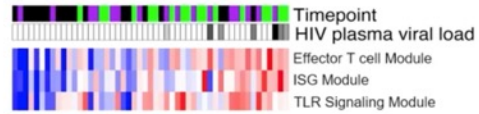


Bulk-RNA modules upregulated 24h post-Tx are highly expressed in Monocytes

Analyses: Cell Annotation using SingleR package in R
Analyses: Wilcoxon-ranked sum analyses (paired)
Analyses: Module scores per subset using Seurat package in R

2 4 Participants with lower latent reservoir have persistent expression of monocyte specific innate and ISG gene-sets

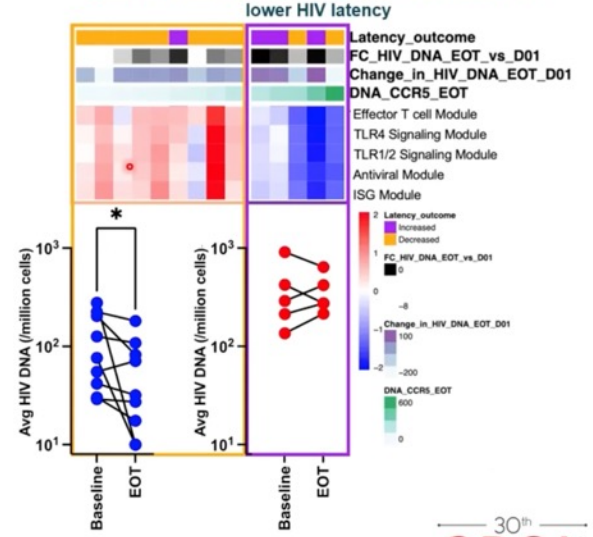
Levels of plasma HIV associated with ISG/TLR module expression



KEY MECHANISTIC TAKEAWAYS

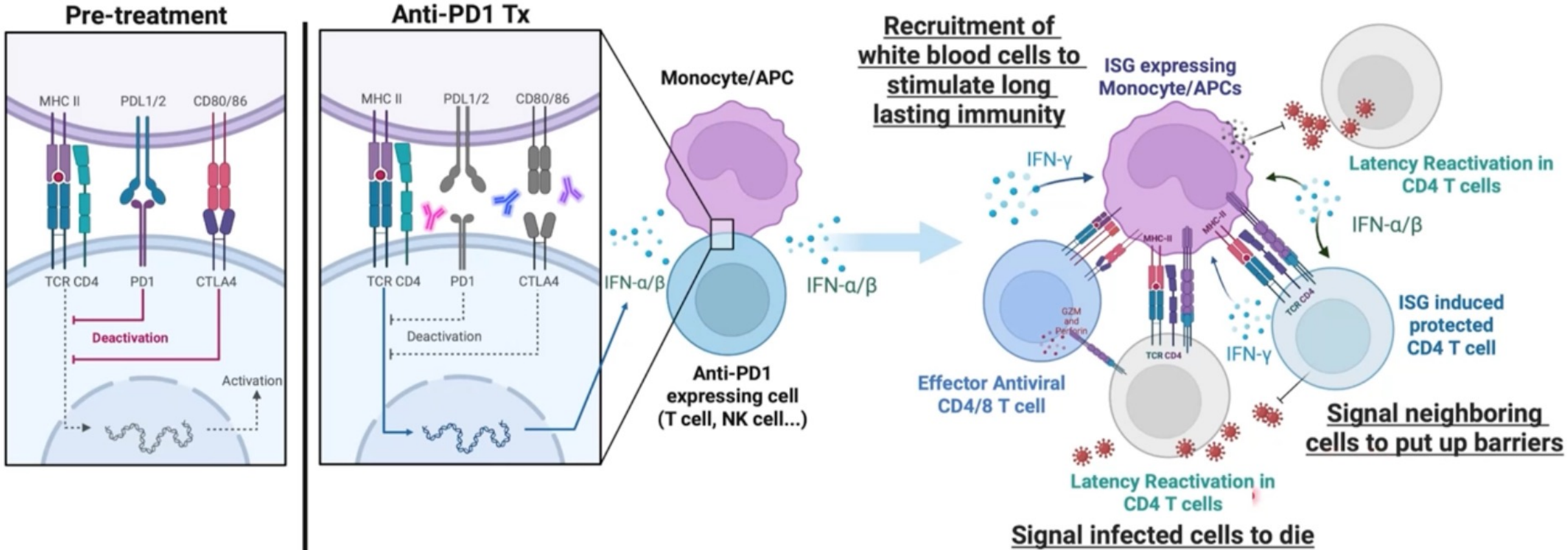
- **Anti-PD1 therapy rapidly causes**
  - **Peripheral monocyte frequencies**
  - **Plasma IFN-β, IFN-γ and IL-6**
- **While reduced plasma TGF-β which associated with higher effector CD8 and CD4 T cell responses**
- **Higher plasma IFN-β drives expression of ISGs in a unique cluster of monocytes that has reduced expression of classical monocyte signatures (TLRs)**
- **Higher expression of this ISG signature is associated with**
  - **Reactivation from latency during treatment and**
  - **Significant decay in the reservoir**

End of Tx ISG/TLR module expression associated with lower HIV latency



Analyses: Wilcoxon-Ranked Sum (Paired)

Anti-PD-1 therapy induced rapid innate interferon responses drive HIV reservoir decay



Posters

Monday February 20th

D1 bNAbs

308 Assessing immunogenicity barriers of the HIV-1 Env trimer
Nikolas Friedrich

I2 Resistance to bNAbs

580 – 581 - 582

Tuesday February 21st

D3 Immune modulation & Vaccines

316 DNA launched bNkillers
SusKanya Ghosh

324 CD40.HIVRI.Env Vaccine – ANRSVRI06 trial
Jean-Daniel Lelievre (Yves Levy)

328 Germline-targeting Env trimer elicits bNAbs precursors in infant (not juvenile) monkeys
Yasmine Iassah

Tuesday February 21st

E6 Interventions to target the viral reservoir & delay viral rebound

428 Reduction in HIV reservoir markers with Gag/Pol/Il-12 DNA
Kara W. Chew

431 BEAT2: Peg-IFN-a2B +bNAbs
Pablo Tebas

433 AELIX-003: RCT w/ HTI vax + aTLR7
Beatriz Mothe

435 'Kitchen': DNA +aTRL9 + bNAbs
Michael Peluso

436 Immunocore: HIV GAGxCD3 soluble TCR bispecific
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Linos Vandekerckhove

A Placebo-Controlled Randomized Trial of the HTI Immunogen Vaccine and Vesatolimod

Beatriz Mothe,[1*] Adrià Curran,[2] Juan Carlos López Bernardo de Quirós,[3] Julen Cadiñanos,[4] Ignacio de los Santos,[5] Juan Ambrosioni,[6] Arkaitz Imaz,[7] Santiago Moreno,[8] Pere Domingo,[9] Yanhui Cai,[10] Romas Geleziunas,[10] Devi SenGupta,[10] Ian McGowan,[11] Christian Brander,[1,11,12] Jose Ramon Arribas,[4] for the AELIX-003 Research Group

[1]Infectious Diseases Department, IrsiCaixa AIDS Research Institute, HUGTiP, CIBERINFEC, Barcelona, Spain; [2]Hospital Universitari Vall d'Hebron, Vall d'Hebron Institut de Recerca, Barcelona; [3]Hospital General Universitario Gregorio Marañón, Madrid, Spain; [4]Hospital Universitario La Paz, CIBERINFEC, Madrid; [5]Hospital Universitario de La Princesa, CIBERINFEC, Madrid; [6]Hospital Clínic de Barcelona; [7]Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Barcelona; [8]Hospital Ramón y Cajal, Madrid; [9]Hospital de Sant Pau, Barcelona; [10]Gilead Sciences, Inc, Foster City, CA; [11]AELIX Therapeutics SL, Barcelona; [12]ICREA, Barcelona

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Foster City, CA 94404
800-445-3235

Methods

Figure 1. AELIX-003 Study Design

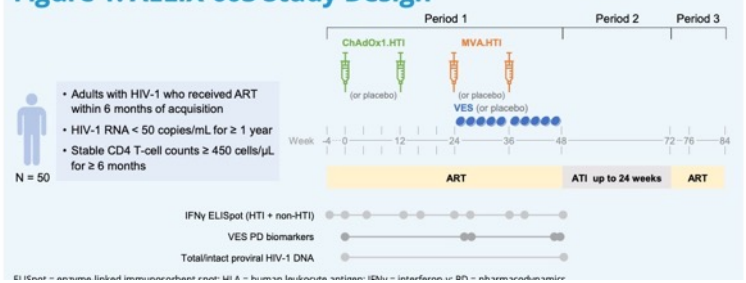


Figure 2. HTI Immunogenicity Profile in Placebo and CCMM + VES Recipients

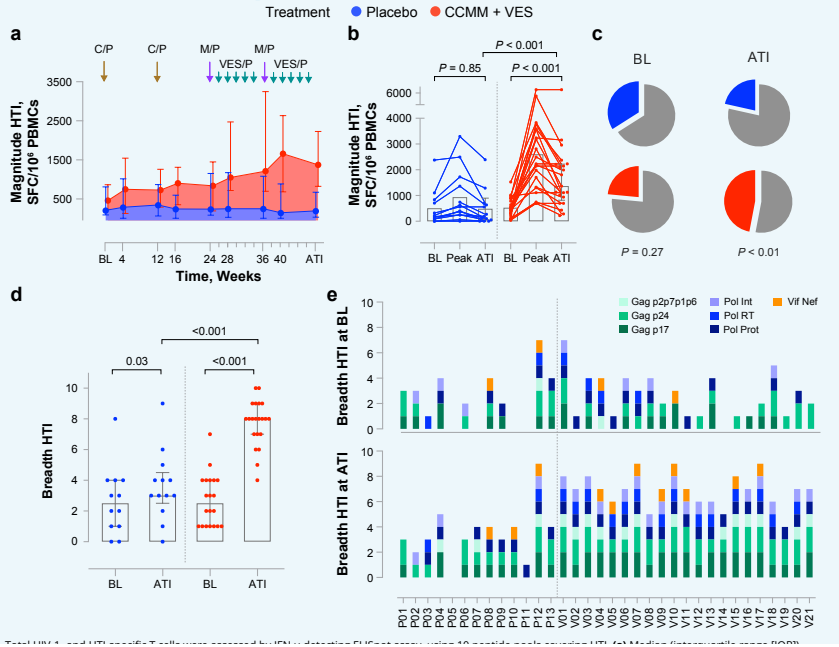
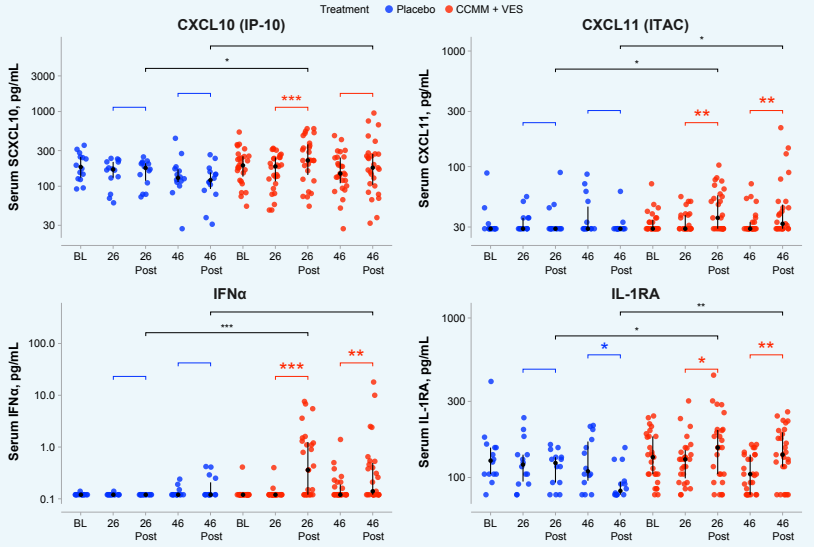


Figure 3. PD of VES in Placebo and CCMM + VES Recipients



Serum levels were measured by single-molecule array assay for IFNα, and multiplex cytokine assay for ITAC, IP-10, and IL-1RA at BL, before and 24 hours after 2nd VES/placebo dose (Week 26), and before and 24 hours after 10th (last) VES/placebo dose (Week 46). *Colored-coded dots* represent data collected from individual participants. Median and IQR are shown with *black dots* and *lines*. Wilcoxon test was used to compare between groups or 2 different timepoints. *$P \le 0.05$, **$P \le 0.01$, ***$P \le 0.001$. CXCL = C-X-C motif chemokine ligand.

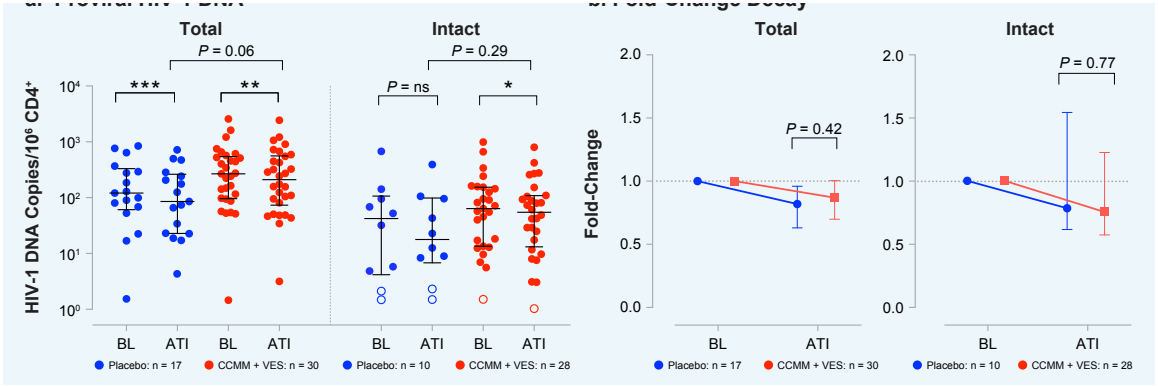
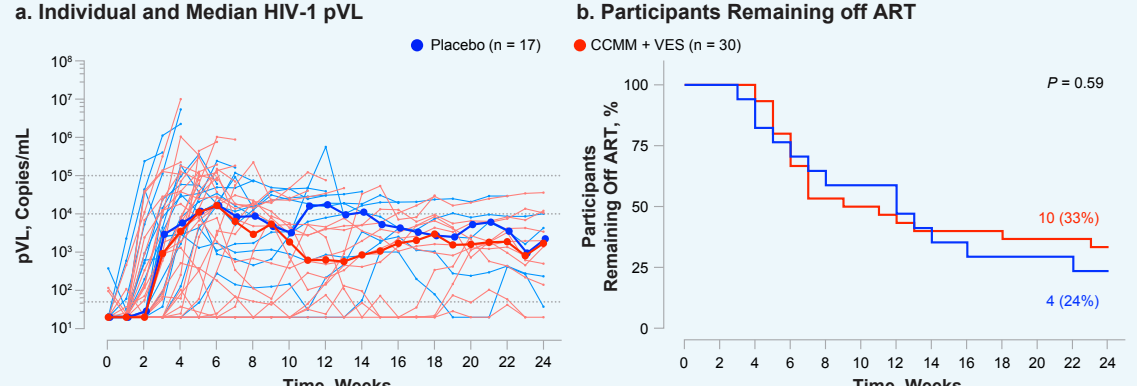


Figure 5. HIV-1 pVL and Percentage of Participants Remaining ART-Free During 24-Week ATI



HIV Gag x CD3 soluble TCR bispecific: safety and activity in a first in human trial

436 LB

Linos Vandekerckhove[1], Julie Fox[2], Borja Mora-Peris[3], Jordi Navarro[4], Sabine Allard[5], Alison Uriel[6], Santiago Moreno[7], Marta Boffito[8], Frank Post[9], Vicente Estrada[10], Beatriz Mothe[11], Yuan Yuan[12], Adel Benlahrech[13], Lucy Dorrell[13], Sarah Fidler[3]
[1]HIV Cure Research Center, Ghent University & Ghent University Hospital, Belgium; [2]King's College London, UK; [3]Imperial College London, UK; [4]Hospital Universitari Vall d'Hebron, Barcelona, Spain; [5]Vrije Universiteit Brussel, Universitair Ziekenhuis Brussel, Brussels, Belgium; [6]North Manchester General Hospital, Manchester, UK; [7]Hospital Ramon y Cajal, Madrid, Spain; [8]Chelsea and Westminster Hospital, London, UK; [9]King's College Hospital, London, UK; [10]Hospital Clínico San Carlos, Madrid, Spain; [11]Irsicaixa Institute for AIDS Research, Badalona, Spain; [12]Immunocore , Rockville MD, USA; [13]Immunocore Ltd, Abingdon, UK
Research collaborators: Praveen K Singh[13], Haseeb Rahman[13], Zoë Wallace[13], Agatha Trevell[13], Kathryn Lamming[13], Andrew D Whale[13]

IMC-M113V is a soluble TCR bispecific protein targeting HIV Gag

Figure 1a. ImmTAV structure

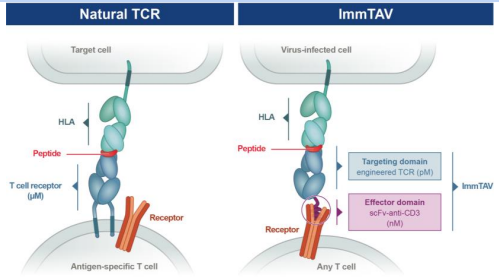


Figure 1b. Mechanism of action of IMC-M113V (Gag x CD3)

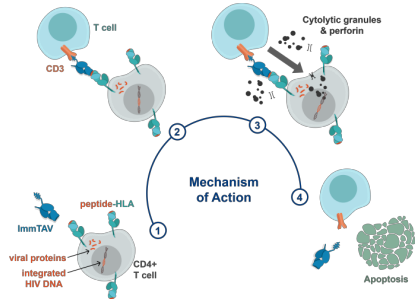
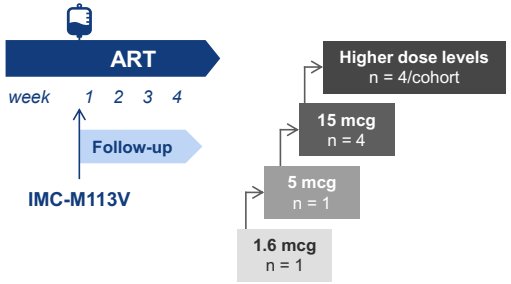


Figure 3. Single ascending dose study schema



Key eligibility criteria

- HLA-A*02:01+ PLWH
- Age 18-65
- On ART 1-7 years
- Viral load < 50 c/ml
- CD4 count > 500 cells/μl
- CD4 nadir > 200 cells/μl

Participants were allocated sequentially to ascending dose cohorts: starting dose was based on the minimum anticipated biological effect level; dose increments were ≤ 3-fold. Minimum number of subjects per cohort is indicated. Study design allowed for enrolment of higher dose cohorts (up to 7 in total).

IMC-M113V was given as a single IV infusion of IMC-M113V on Day 1. Subjects were followed weekly to Day 29.

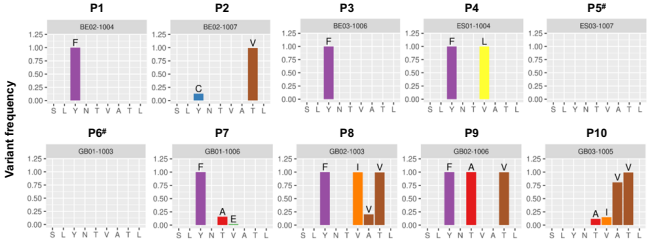
Results

Results 1. IMC-M113V was well tolerated and not associated with cytokine release syndrome at doses ≤15 mcg

92 pre-screened for HLA
↓
35 HLA-A*02:01+
↓
16 completed screening for Part 1
↓
3 SAD cohorts completed (n = 6)
↓
Cohort 3 (15 mcg) expanded from 4 to 10 participants
↓
12/12 completed follow-up

- Subjects enrolled at sites in UK, Belgium and Spain
- Doses were well tolerated; no dose-limiting toxicities
- No cytokine release syndrome of any grade
- No neurotoxicity
- No SAEs
- No Grade ≥ 3 hematology, chemistry or liver function test abnormalities
- HIV viral load remained < 50 c/ml through dosing and follow-up
- CD4 cell counts remained within normal range

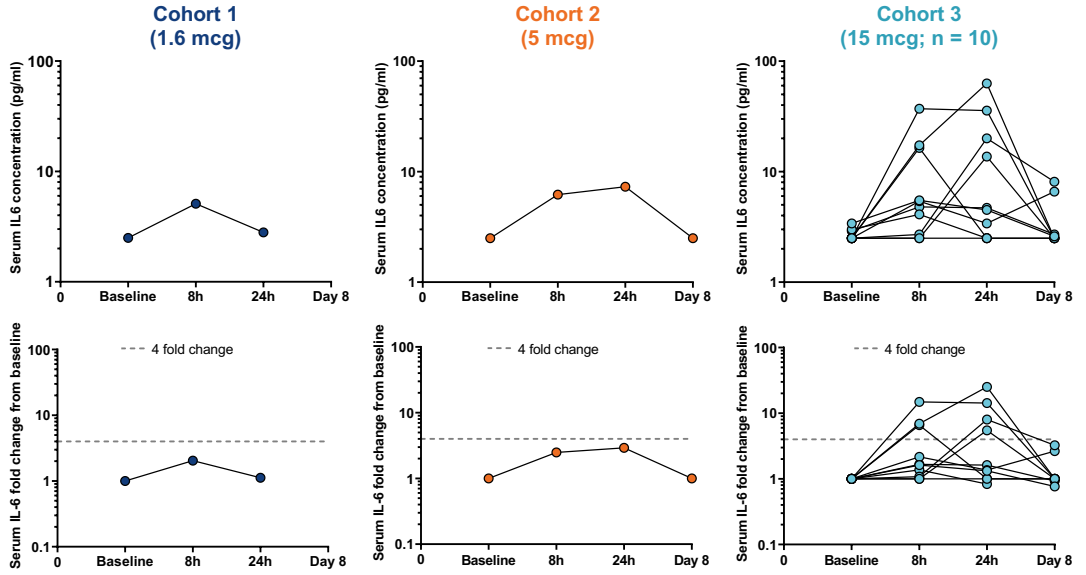
Results 2. Gag_{77-85} sequences obtained from cell-associated RNA pre-dose indicate the presence of druggable, transcriptionally active proviruses



Nextera XT Libraries sequenced on Illumina MiSeq Platform, created from targeted amplification of CA-RNA Gag from purified CD4+ cells isolated pre-dose from the ten participants (P1-10) in cohort 3 (15 mcg). # Gag_{77-85} sequence matched cognate (SLYNTVATL) in participants P5 and P6.

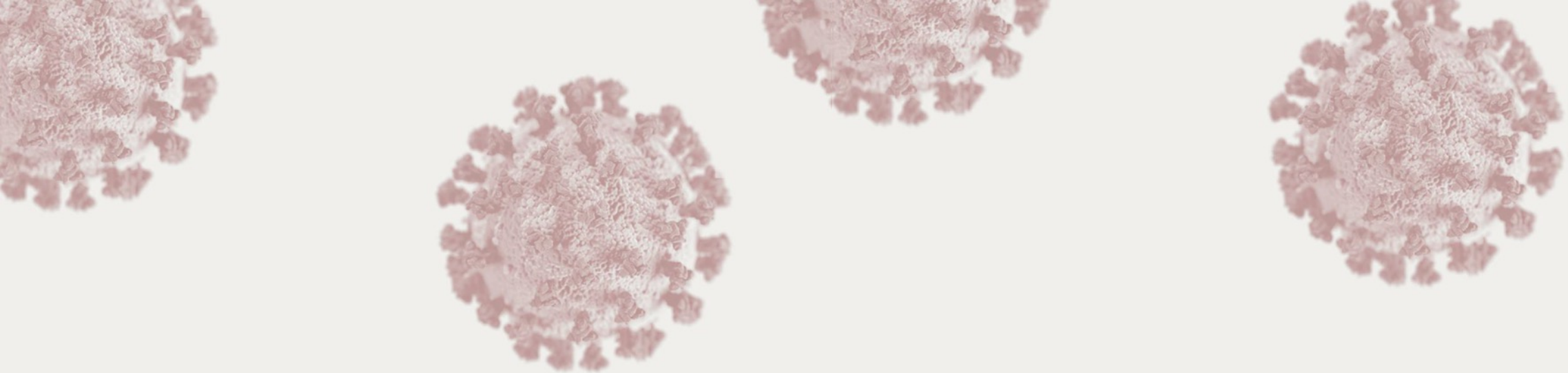
- Anticipated variability in Gag_{77-85} observed in study participants
- Baseline viral sequencing will inform clinical and antiviral signals

Results 3. Tolerable and biologically active dose identified in SAD study



- 15 mcg dose fulfilled criteria to stop escalation in SAD and open MAD study

References



¡MUCHAS GRACIAS!

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