Advances in Therapeutic HIV Vaccine Development

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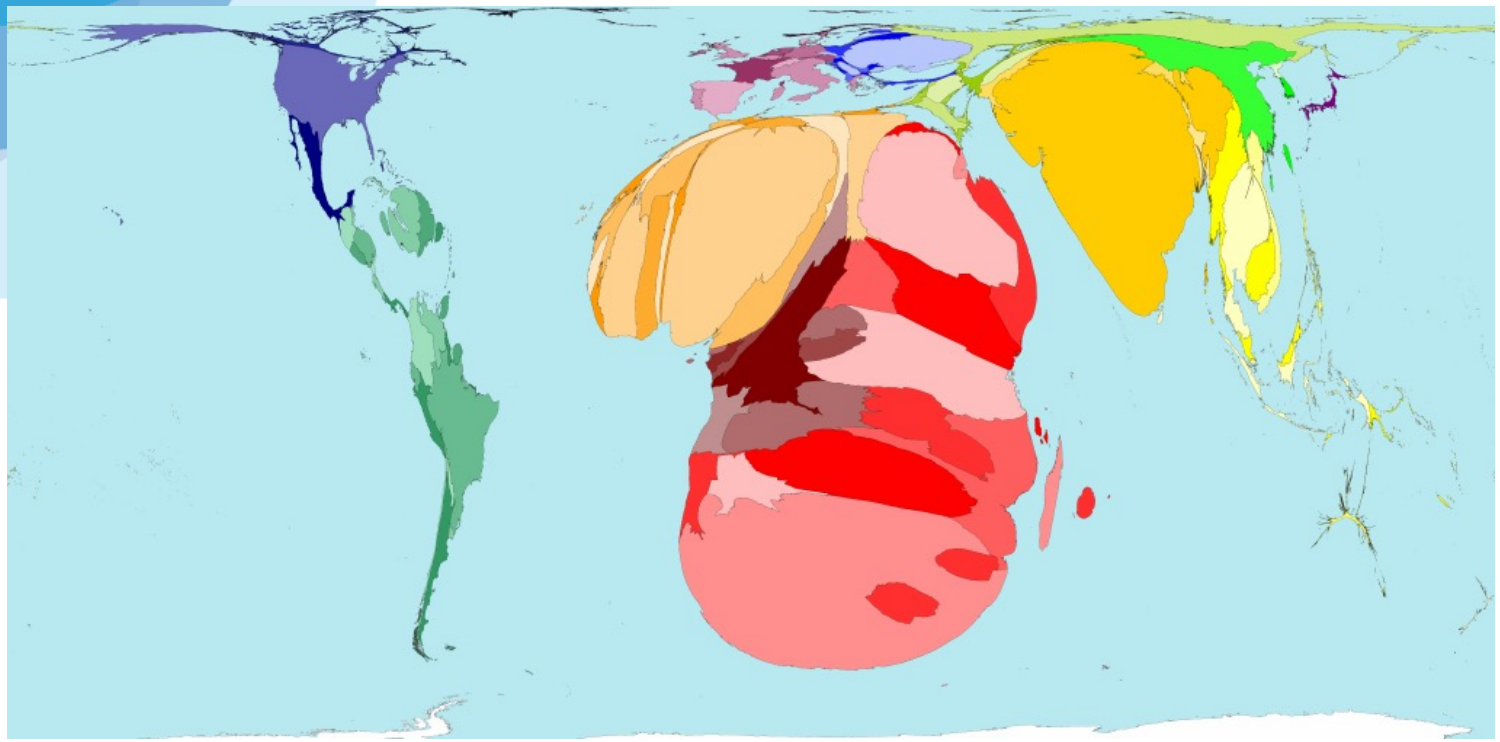
Sitges

IrsiCaixa
Institut de Recerca de la Sida

Advances in Therapeutic HIV Vaccine Development

- The problem with HIV (chronicity)
- T cell vaccines for HIV cure
- Recent advances in HIV therapeutic vaccination

The HIV pandemic is still ongoing



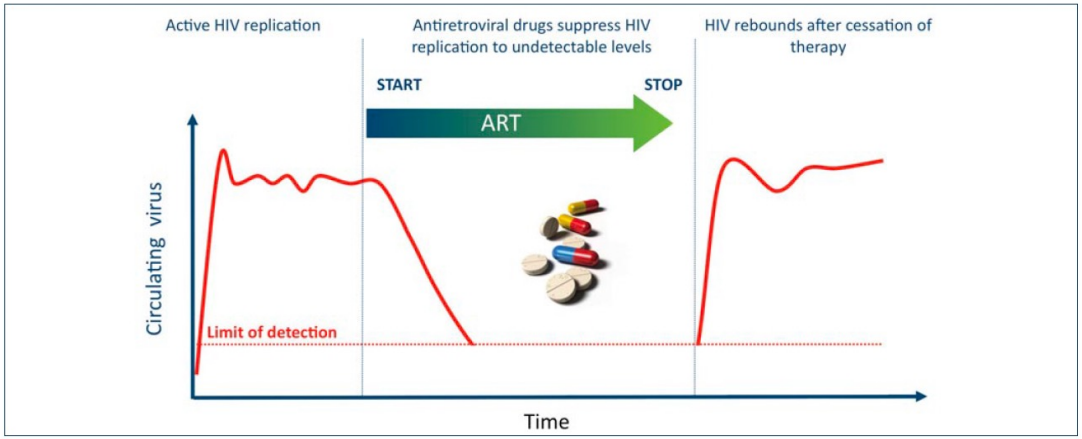
36.7 Million HIV + (PLWH)

19 million living in Africa
1.1 million deaths every year
Since HIV was first identified, 78 millions estimated infections (35 million deaths)
1 in 4 people who are HIV positive do not know their HIV status

World Health Organization UNAIDS

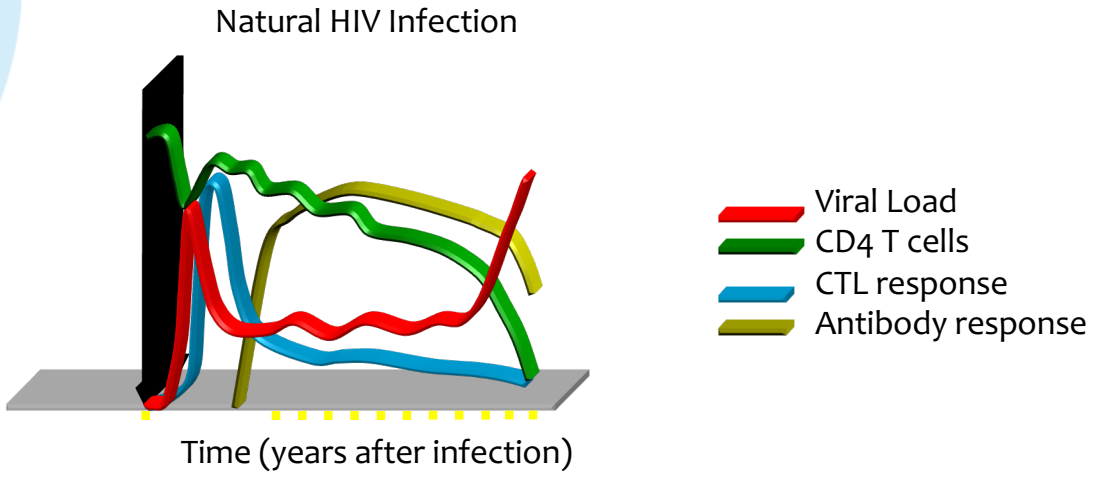
The many hurdles to HIV Cure and Eradication

- HIV establishes a life-long, latent reservoir shortly after acute infection
- The decay kinetics of the reservoir under Antiretroviral Treatment (ART) are too slow to eliminate the virus from the body.
- Latently infected cells are largely invisible to the immune system
- Treatment interruptions lead to rapid rebound of viremia
- Unclear what immune responses a therapeutic vaccination should target as functional (!) immune correlates of virus control remain poorly defined



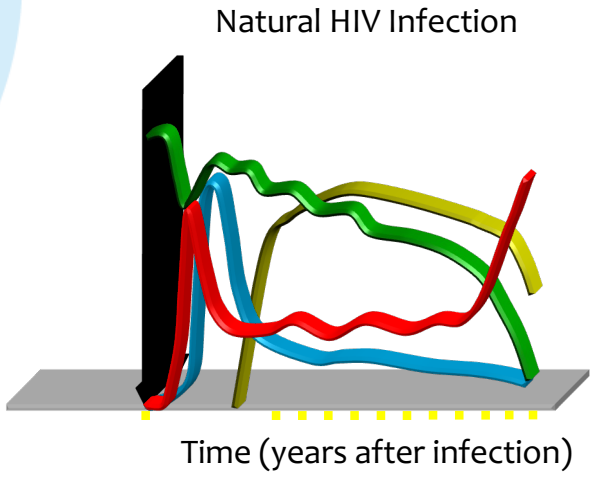
Kulpa. J. Virus Erad. 2015

The Rational for Therapeutic HIV Vaccination



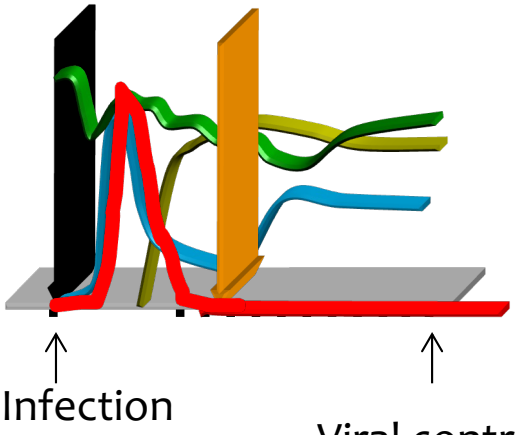
- Essentially everybody who becomes infected with HIV makes a strong immune response to the virus
- The vast majority of PLWH show progressive HIV disease if left untreated
- Evidently then, the immune response that we measure upon natural infection does not (fully) protect from infection and HIV disease progression
- HLA-association studies, CD8 T cell depletion in SIV infected monkeys, viral evolution analyses, etc all support a role of CD8+ cytotoxic T lymphocytes in virus control

The Rational for Therapeutic HIV Vaccination



Viral Load
CD4 T cells
CTL response
Antibody response

Therapeutic Vaccine



Potential components of a <u>therapeutic</u> vaccine:

T cell response to viral proteins

- CD8 CTL "killer T cell" to kill infected cells
- CD4 T-helper cells to maintain functional CTL
- Combination approaches with nAb
- Viral reservoir activators

➢ Modulation of a pre-existing, ineffective immunity

Catalan HIVACAT Vaccine Program (2008-2022)

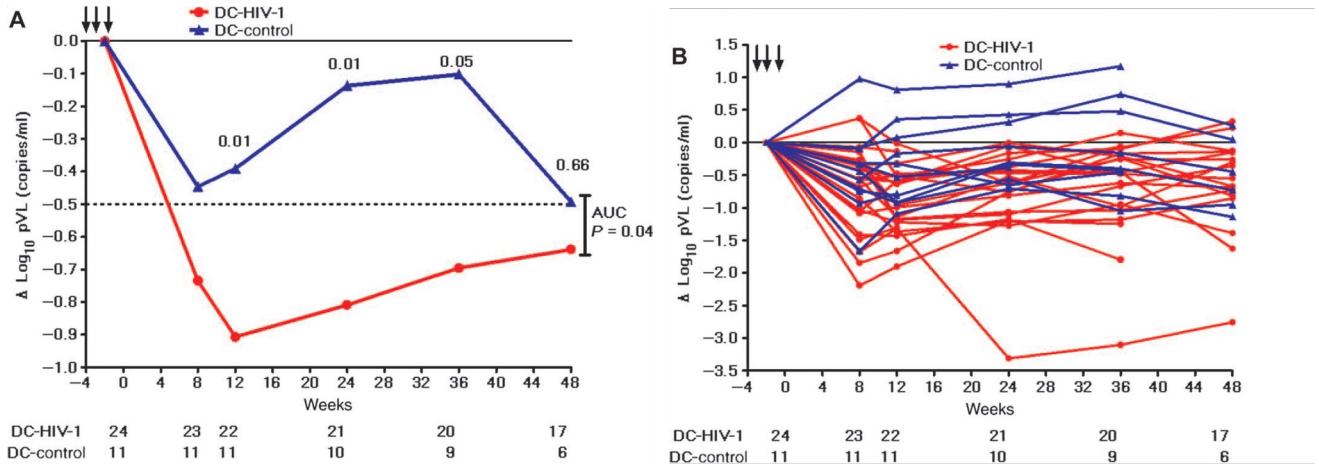
- Therapeutic Strategies:
  - IL2, AUTOVAC, TIBET, 2X4 (Clotet, Ruiz, Arno,..)
    - autologous virus released by treatment interruption, cytokines
  - (Kick and) kill strategies: 2008 onwards
    - DCV-02: autologous virus on DC (Gil 2011, Garcia 2013)
    - RISVAC-03: MVA/DSF (Mothe 2015, Rosas-Umbert 2017)
    - HIVARNA: mRNA delivered HTI (Leal, 2021)
    - BCN01/BCN02: ChAd-MVA +Rmd (Mothe 2020, Rosas Umbert 2020)
    - AELIX-002: DNA-ChAd-MVA -HTI (Bailon 2022)
    - AELIX-003: ongoing (ChAd-MVA +TLR7)
    - BCN03: ongoing (ChAd-MVA +SOSIP)
    - HIVACAR: ongoing (conserved epitopes RNA)

Therapeutic HIV Vaccine Program Barcelona

DCV-02 (autologous virus-loaded dendritic cell vaccine)

2008

- Isolation of autologous virus during 1st treatment interruption, in vitro expansion, heat-inactivation, pulsed on autologous, in vitro matured dendritic cells



Garcia et al STM, 2013

- 55% active vs 9% placebo with >1log lower viral set point 12 and 24w after ART stop

- Aside from "complex" development process , still elevated viral loads during analytic treatment interruption (ATI), making this unsafe for the patients and their sexual partners

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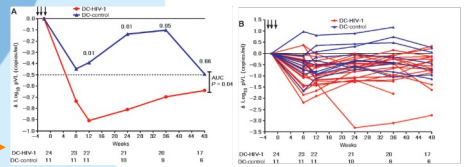
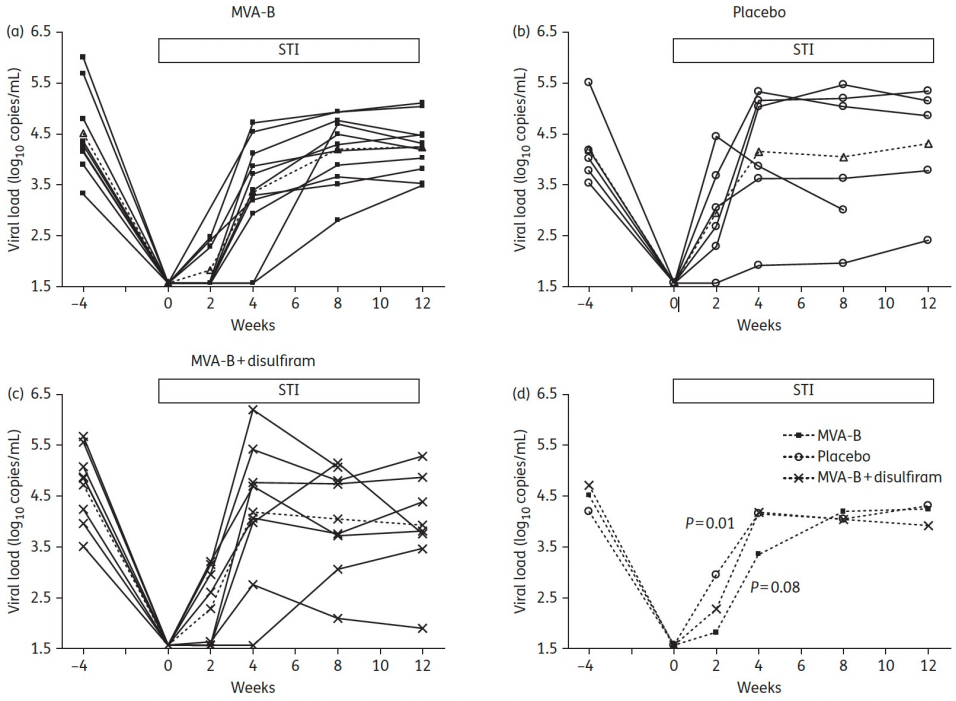
DCV-02



RISVAC 03 (kick-and kill, MVA vaccine and disulfiram LRA)

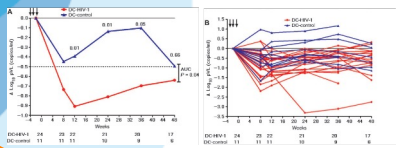
- MVA-B (but not MVA-B + DSF) vaccination showed modestly delayed viral rebound (2 weeks)
- Reduced peak viremia related to level of virus adaption to host genetics
- Proviral HIV-1 DNA (i.e. measure of reservoir size) at study entry associated with delayed HIV-1 RNA rebound and lower peak viremia

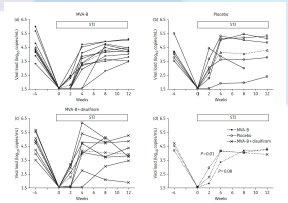


Mothe et al JAC, 2015

Therapeutic HIV Vaccine Program Barcelona

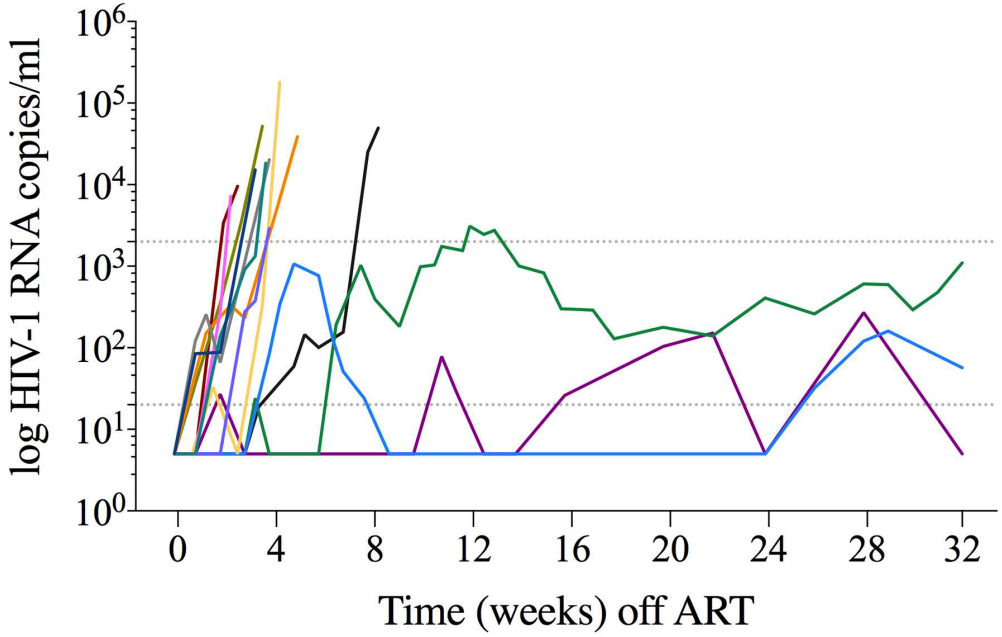
DCV-02





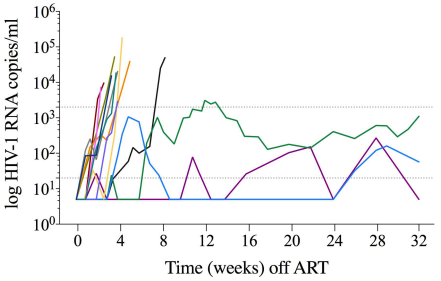
RISVAC 03

BCN-01/02 (Kick and kill strategy using ChAd and MVA vaccines expressing HIVCons plus Romidepsin)



Mothe et al Front Imm, 2020

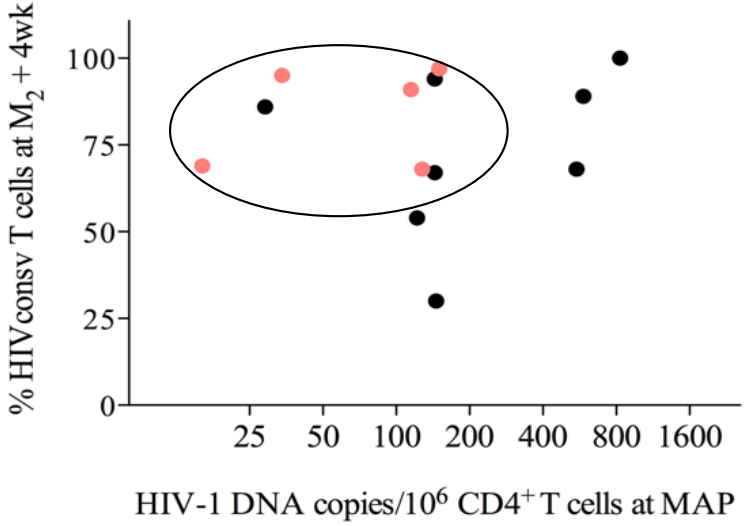
Insights gained from BCN02



1) No placebo control, what is the rate of Post-Treatment-Control (PTC: 8-13%)

2) Romidepsin safe yes, but effective ?
   - minor peaks in viremia
   - transient increase in apoptotic T cells
   - reduced polyfunctional cells
   - in vitro antiviral (VIA) activity preserved

3) Reservoir possibly important, no reduction up to ATI (like RIVER, AELIX002, etc)



Mothe et al Front Imm, 2020
Rosas-Umbert Front Imm 2020

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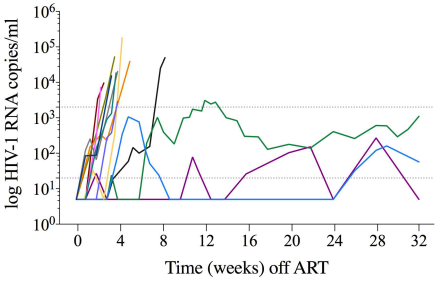

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4) Bacteroidales/Clostridiales ratio predicts HIV-1 reservoir size and virus control

Borgognone *et al. Microbiome* (2022) 10:59
https://doi.org/10.1186/s40168-022-01247-6

Microbiome

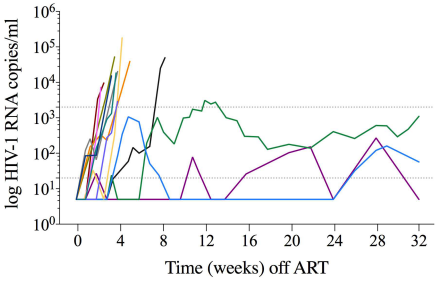
RESEARCH Open Access

Gut microbiome signatures linked to HIV-1 reservoir size and viremia control

Alessandra Borgognone[1*], Marc Noguera-Julian[1,2,3], Bruna Oriol[1,4], Laura Noël-Romas[5,6], Marta Ruiz-Riol[1,2], Yolanda Guillén[7], Mariona Parera[1], Maria Casadellà[1], Clara Duran[1,4], Maria C. Puertas[1,2], Francesc Català-Moll[1], Marlon De Leon[5], Samantha Knodel[5,6], Kenzie Birse[5,6], Christian Manzardo[8], José M. Miró[2,8], Bonaventura Clotet[1,2,3,4,9,10], Javier Martinez-Picado[1,2,3,11], José Moltó[2,9,10], Beatriz Mothe[1,2,3,9,10], Adam Burgener[5,6,12], Christian Brander[1,2,3,11], Roger Paredes[1,2,3,4,5,9,10*] and the BCN02 Study Group

Mothe et al Front Imm, 2020
Rosas-Umbert Front Imm 2020
Borgogno MBIO, 2022 in press

Insights gained from BCN02



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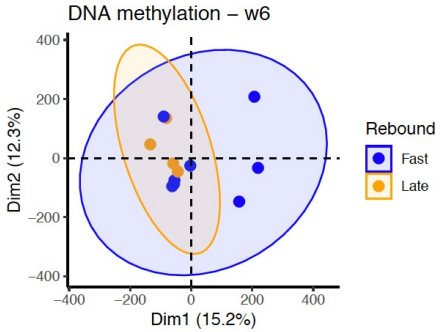
4) Bacteroidales/Clostridiales ratio predicts HIV-1 reservoir size and virus control

5) Pre-ATI (and pre-vaccination) methylation imprints associated with ATI control

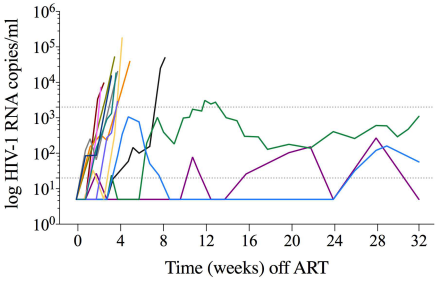
Epigenetic landscape in the kick-and-kill therapeutic vaccine BCN02 clinical trial is associated with antiretroviral treatment interruption (ATI) outcome

Bruna Oriol-Tordera, Anna Esteve-Codina, María Berdasco, Miriam Rosàs-Umbert, Elena Gonçalves, Clara Duran-Castells, Francesc Català-Moll, Anuska Llano, Samandhy Cedeño, María C. Puertas, Martin Tolstrup, Ole S. Søgaard, Bonaventura Clotet, Javier Martinez-Picado, Tomás Hanke, Behazine Combadiere, Roger Paredes, Dennis Hartigan-O'Connor, Manel Esteller, Michael Meulbroek, María Luz Calle, Alex Sanchez-Pla, José Moltó, Beatriz Mothe, Christian Brander, and Marta Ruiz-Riol



Mothe et al Front Imm, 2020
Rosas-Umbert Front Imm 2020
Borgogno MBIO, 2022
Oriol-Tordera EBioM, 2022
Oriol-Tordera Plos Path 2021

Insights gained from BCN02



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5) Pre-ATI (and pre-vaccination) methylation imprints associated with ATI control

6) T-cell specificity, effector function and T cell receptor (TCR) repertoire may be linked to outome (epitope-specific 10Xsc and OMNISCOPE OS-T analyses)

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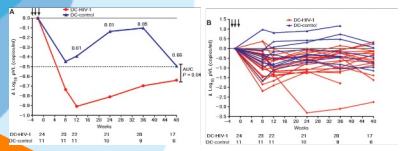
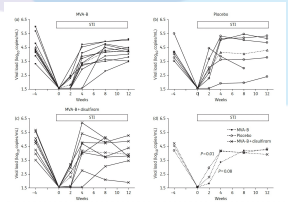
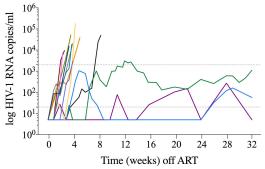
DCV-02



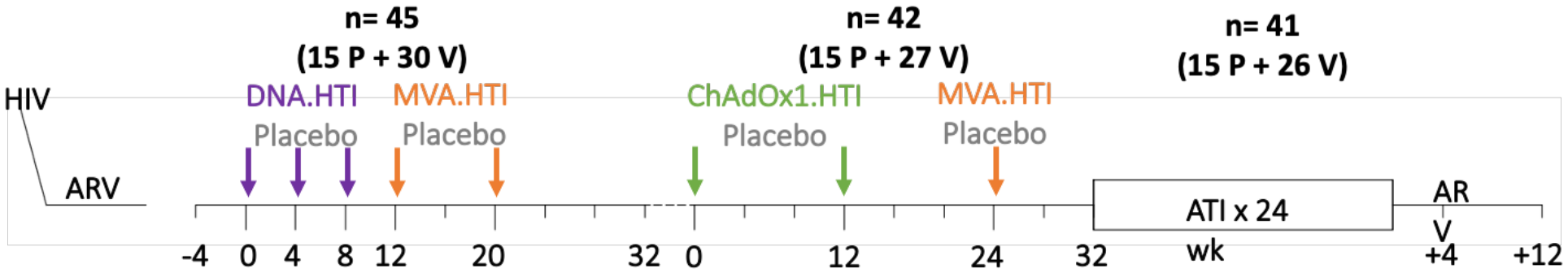


RISVAC 03



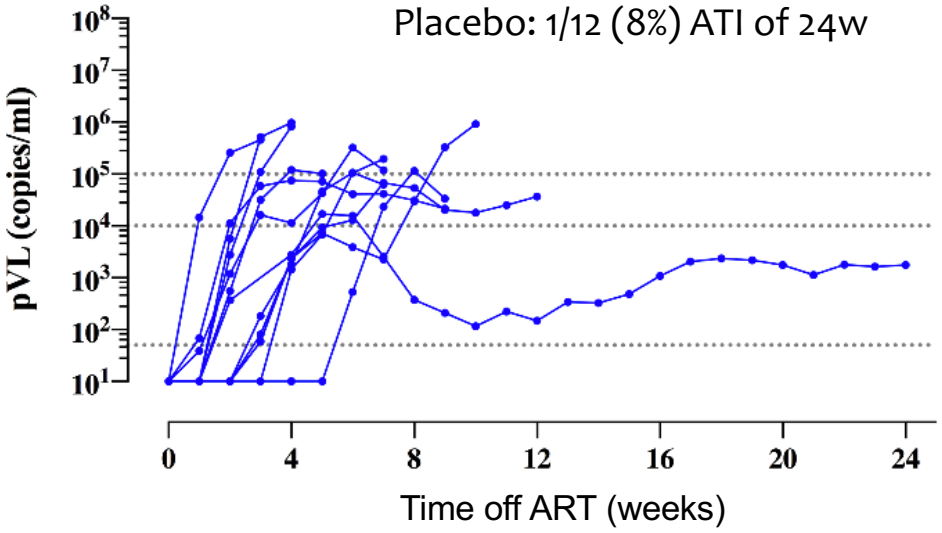
BCN-01/02

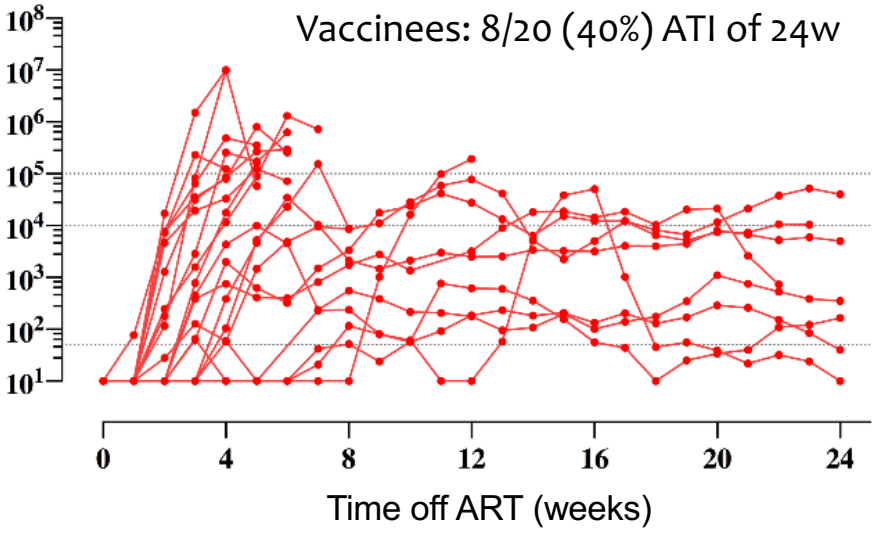
AELIX-002



Mothe CROI 2021
Bailon, submitted

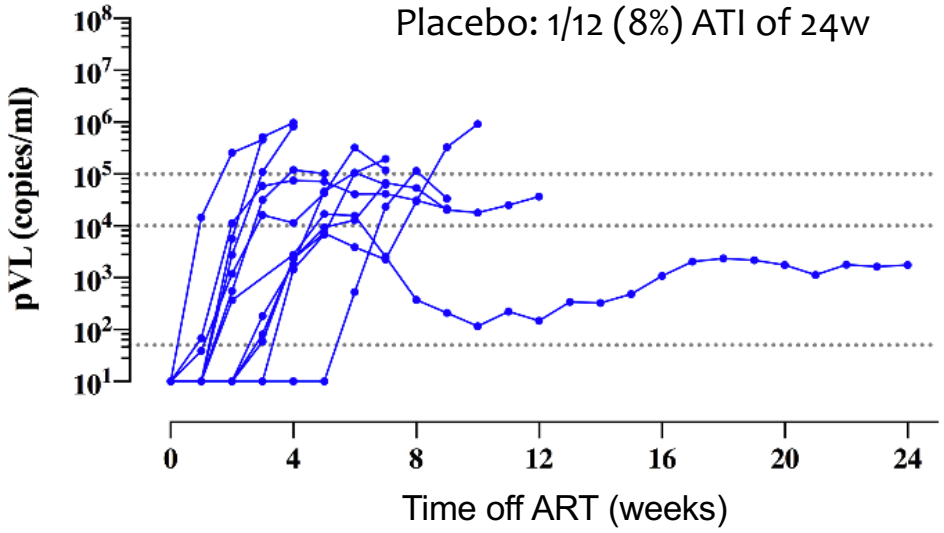
AELIX-002: HTI vaccination mediates improved Viral Control in ATI

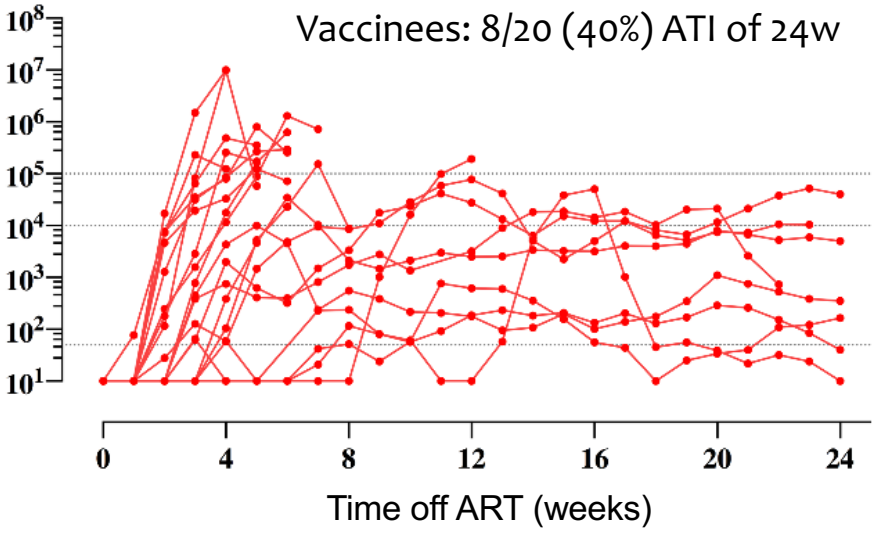




Mothe CROI 2021
Bailon, submitted

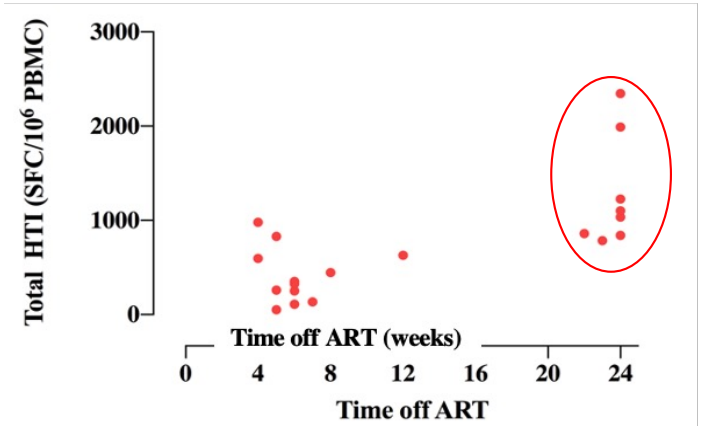
AELIX-002: Time off ART is correlated with the strength of the vaccine induced HTI immunity





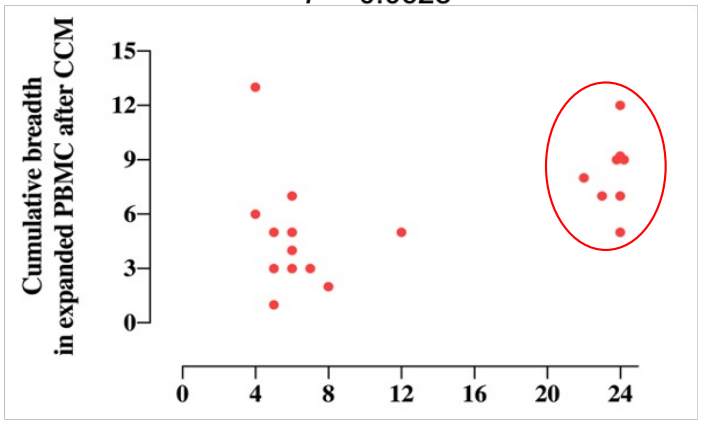
HTI Magnitude at ATI

N=20 Vaccine
Rho = 0.6469
P = 0.0021



HTI Cumulative Breadth at ATI

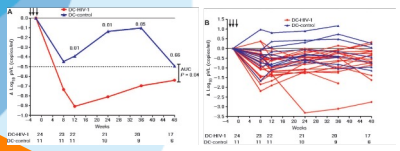
N=20 Vaccine
Rho = 0.4235
P = 0.0628

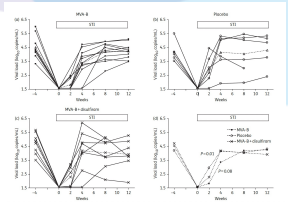


Mothe CROI 2021
Bailon, submitted

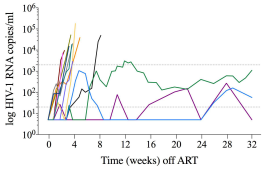
Therapeutic HIV Vaccine Program Barcelona

DCV-02

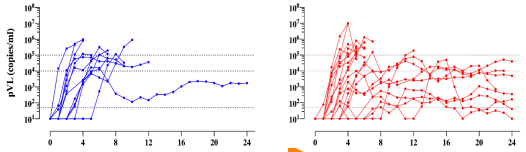




RISVAC 03

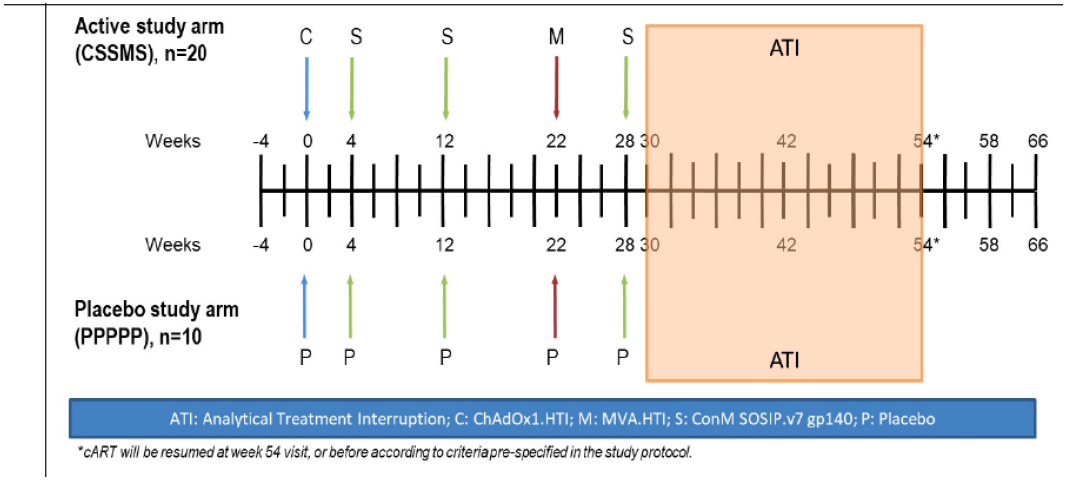


BCN-01/02



AELIX-002

AELIX-003 (HTI + TLR7)



HIVACAR mRNA

BCN-03
(combined T and
B cell vaccination)

Conclusions - Next steps

- Years of clinical trials of therapeutic HIV vaccination have yielded until recently mostly frustrating results
  - Target population (early, chronic, reservoir size)
  - Immunogen design (T cell specificity, viral evolution, adapted reservoir)
  - Manufacturing and up-scale hurdles
- Clinical trials of therapeutic HIV vaccination start showing clinically relevant efficacy signals (AELIX-002)
  - Biomarkers of virus control
  - Target population definition
  - Modulation of pre-existing conditions (epigenetics, microbiota)
- Effective HIV cure strategies will likely require combination strategies to harness humoral and cellular immunity and to effectively tackle the latent viral reservoir
  - Latency reactivators
  - Combined T and B cell vaccination strategies (BCN03)
  - May inform prophylactic vaccine setting

Acknowledgments

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Marta Ruiz-Riol
Alex Olvera
Bruna Oriol
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Anuska Llano
Tuixent Escribà
Pep Coll