EPIICAL Consortium U01 Grant Application

"Targeting HIV Reservoirs in Children with HIVIS DNA and MVA-CMDR Vaccines"

In response to NIAID RFA-AI-16-086

Jintanat Ananworanich

PIM 2017
27th - 30th April 2017, San Servolo, Venice

Innovation

- First prime-boost HIVIS DNA/MVA-CMDR therapeutic vaccines in children
- The first testing of late boost strategy in children
- Novel strategy giving a licensed vaccine to adjuvant HIVIS DNA
- Inclusion of children from 3 continents with diverse HIV clades
- Support EPIICAL's long-term goal to develop efficacy vaccine studies in children

Collaborative Study

EPIICAL
Cohorts
Advisory boards
Biostatistics
Meetings
In-depth analyses

MHRP
Vaccines
US FDA IND submission
Regulatory
Data management
Coordinating center

Laboratories
Reservoir: Deborah Persaud
Immunology: Paolo Palma
RNA seq: Savita Pahwa
Single copy RNA:
Robert Gorelick

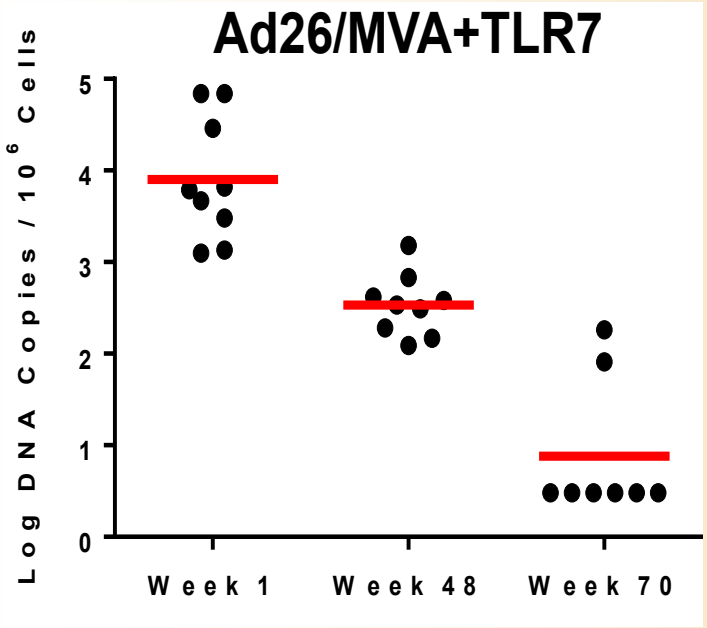
Principal investigators
Paolo Palma
Jintanat Ananworanich

Clinical sites
S. Africa: Mark Cotton
Thailand: Thanyawee Puthanakit
Italy: Paolo Palma

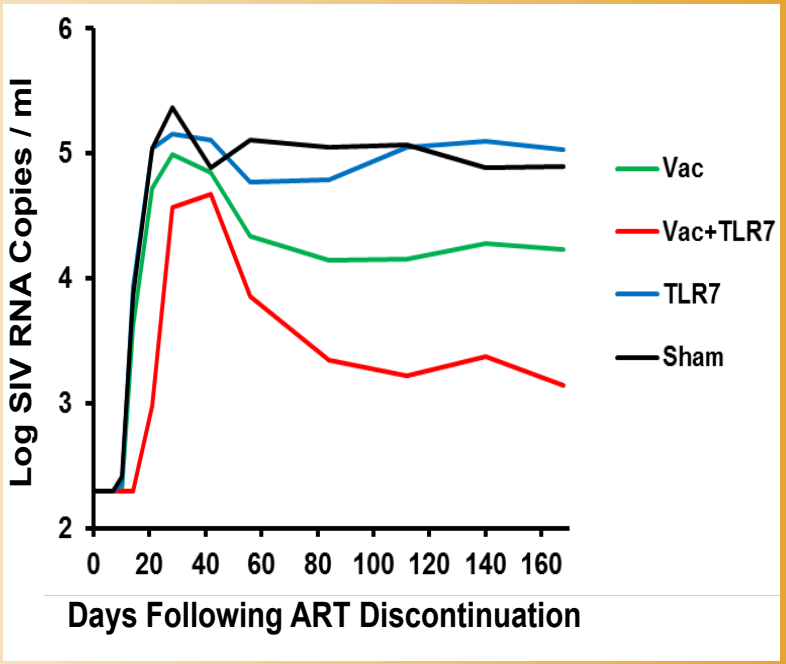
Scientific Premise

- HIVIS DNA/MVA-CMDR vaccines induce cross-clade immune responses important for clearing infected cells and have ample safety data
- Early treated children have healthy immunity and small HIV reservoirs
  - Better immune responses to HIV vaccines
- Giving TLR4 agonist as an adjuvant could increase efficacy of vaccine
  - Licensed Cerverix® vaccine against HPV
- Late boost concept with MVA-CMDR
  - The only 10 HIV-infected children worldwide that had HIVIS DNA (PEDVAC study)

TLR7 agonist adjuvant to Ad26/MVA vaccination in monkeys



Reduced SIV reservoir on ART



Reduced VL set point off ART (3/9 monkeys in remission)

Borducchi EN, Nature 2016

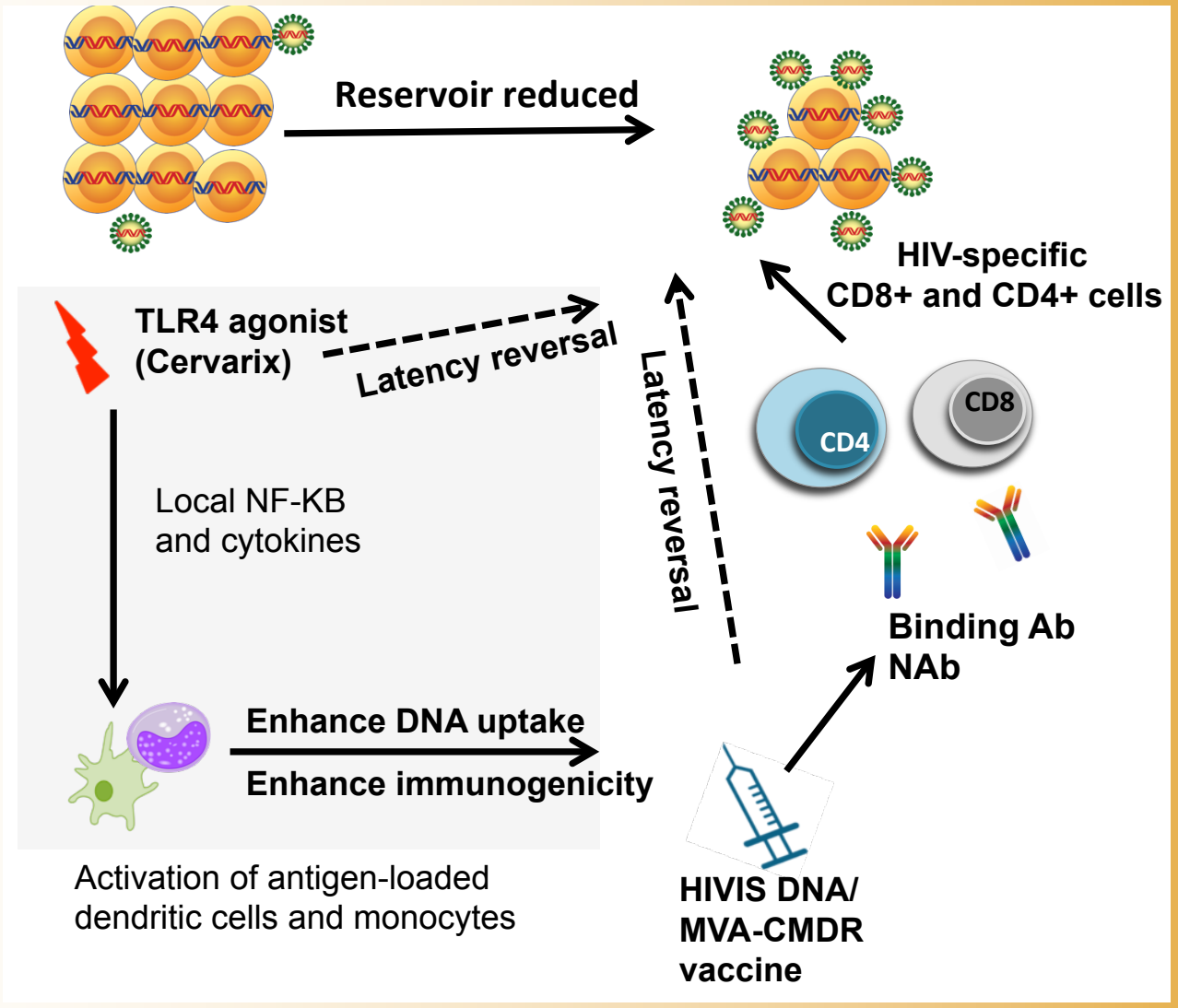
Specific Aims

- Aim 1: To quantitate and characterize the **HIV reservoirs** before and after HIVIS DNA ± TLR4 agonist and MVA-CMDR vaccination

- Aim 2: To characterize **HIV-specific cellular and humoral immune responses** before and after vaccination and assess their relationship to the HIV reservoir endpoints

- Aim 3: To quantitate and characterize the immunogenicity and HIV reservoir endpoints in youth **previously vaccinated with HIVIS DNA** and receiving MVA-CMDR late boost

Conceptual Framework

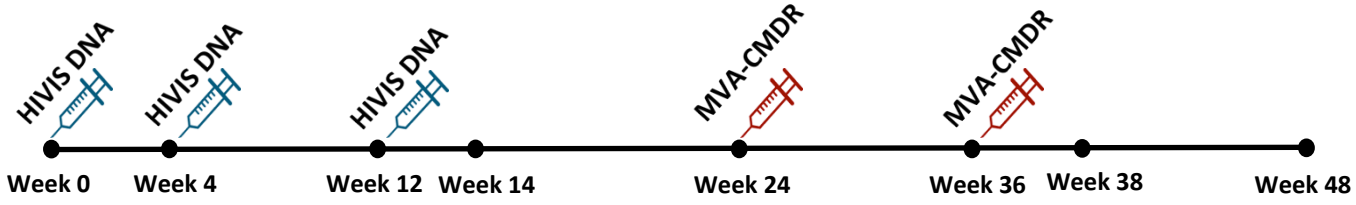


Study Population

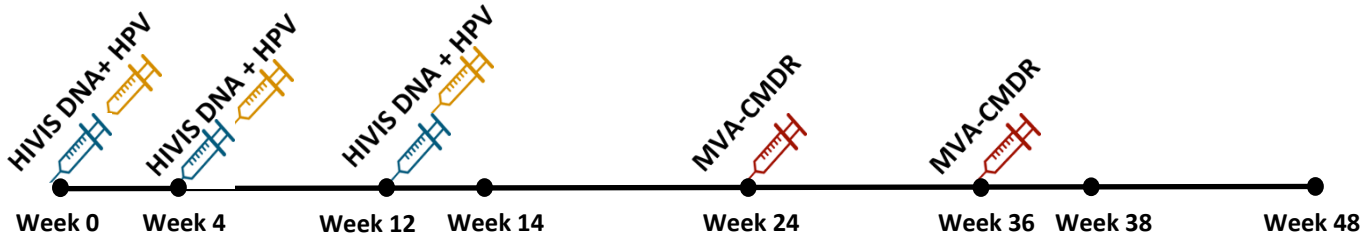
- Group A (n=25, arms 1-3) – HIVIS DNA/MVA-CMDR +/- TLR4 agonist
  - Perinatally HIV-infected children from S. Africa, Thailand, Rome
  - Know their HIV status
  - ≥ 9 years old
  - Initiated ART < 6 months of age
  - VL < 50 copies/ml
  - Never had Cervarix
- Group B (n=10, arm 4) – MVA-CMDR boost
  - Received HIVIS DNA in PEDVAC study at the Rome site
  - 14-24 years old

Study Design

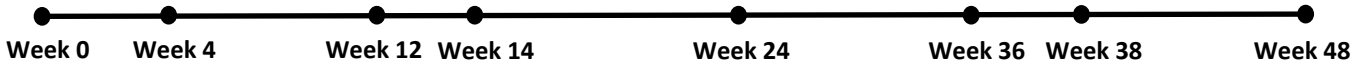
Arm 1 (n=10): HIVIS DNA/MVA-CMDR



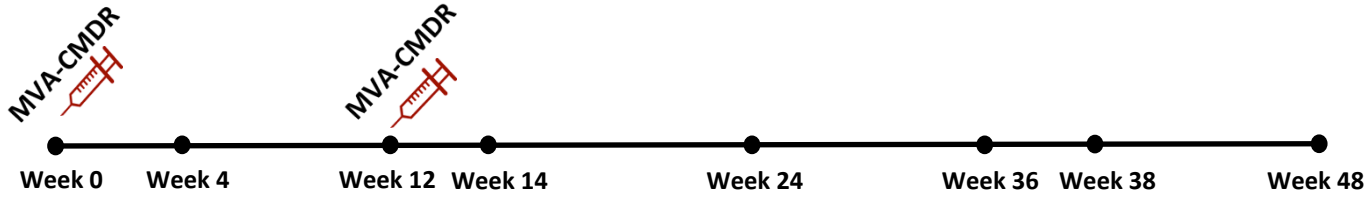
Arm 2 (n=10): HIVIS DNA/MVA-CMDR and TLR4 agonist adjuvant (HPV)



Arm 3 (n=5): control (no intervention)



Arm 4 (n=10): MVA-CMDR late boost



Endpoints

Immunologic endpoints: 2 weeks after the final vaccine dose
Reservoir endpoints: 12 weeks after the final vaccine dose

Reservoirs

Primary Endpoint

Replication competent virus (QVOA)

Secondary Endpoints

Inducible RNA (TILDA)
us- and ms-RNA
Single copy HIV RNA
Total HIV DNA

Immune responses

Primary Endpoints

CD8+/CD4+ T cells function (ICS)
Immunophenotypes of T, B, NK
ADCC activity
HIV antibody/neutralization activity

Secondary Endpoints

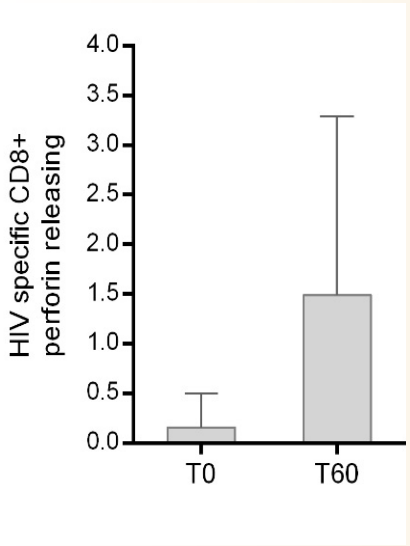
Global gene expression (RNA seq)
Gene expression on HIV-specific T cells (Fluidigm Biomark)

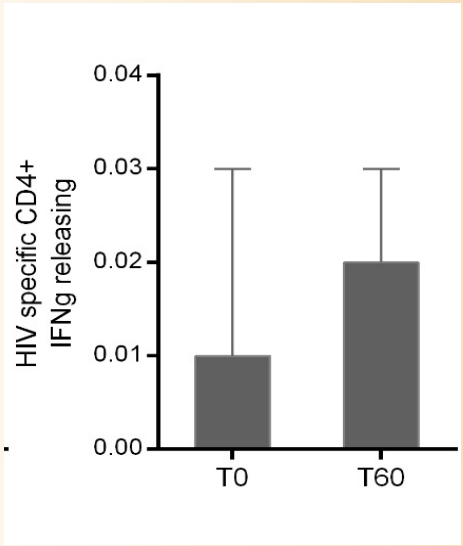
Timeline

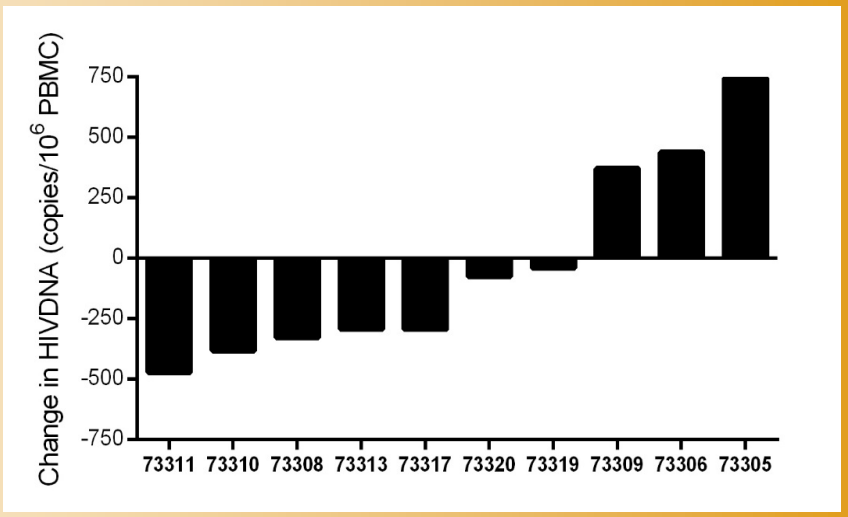
- Submission date: March 2017
- Study section: ZAI1 JBS-A (S1)
- Council date: Oct 2017


PENTA - ID
www.penta-id.org

Response to HIVIS DNA in Children (PEDVAC)







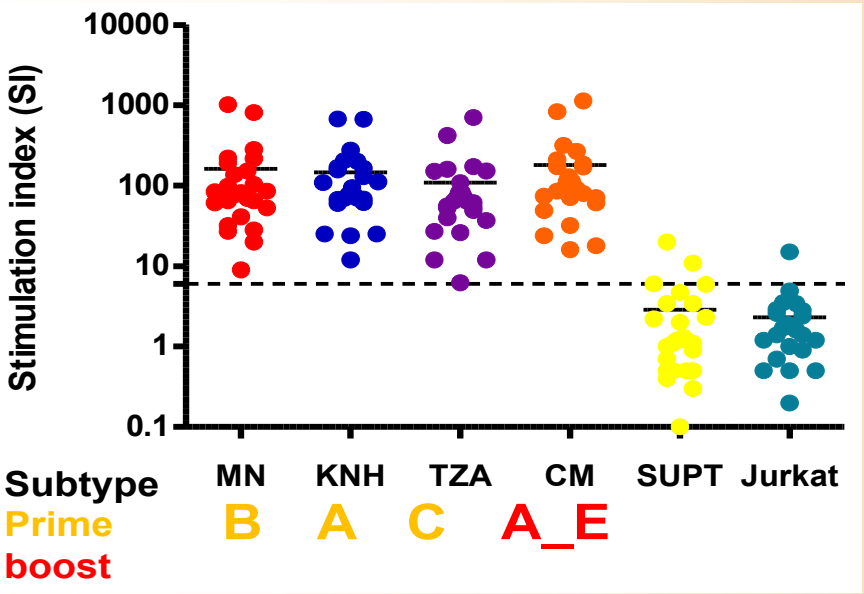
↑HIV-specific CD8

↑HIV-specific CD4

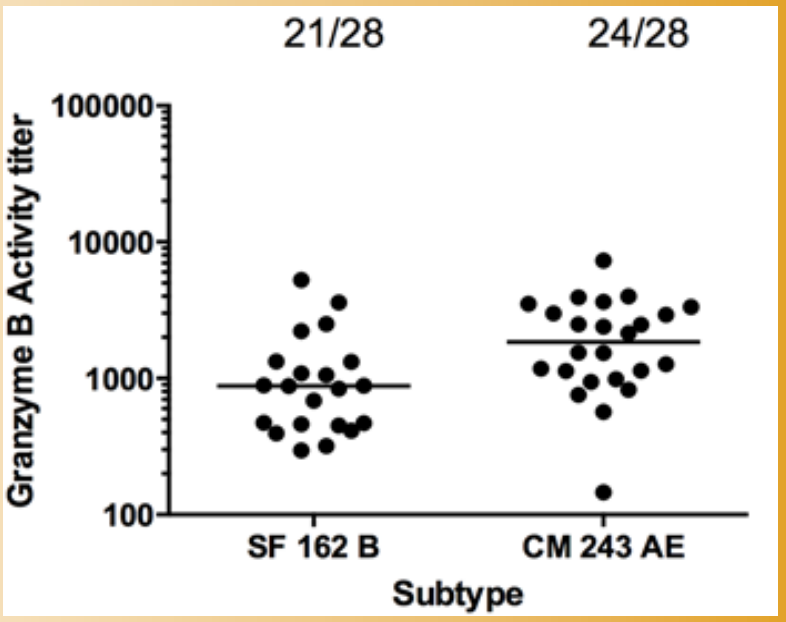
↓ HIV reservoir size in some children

Palma, Rossi et al, Plos One 2013; Vaccine 2011

Cross clade responses for HIVIS DNA/MVA-CMDR regimen



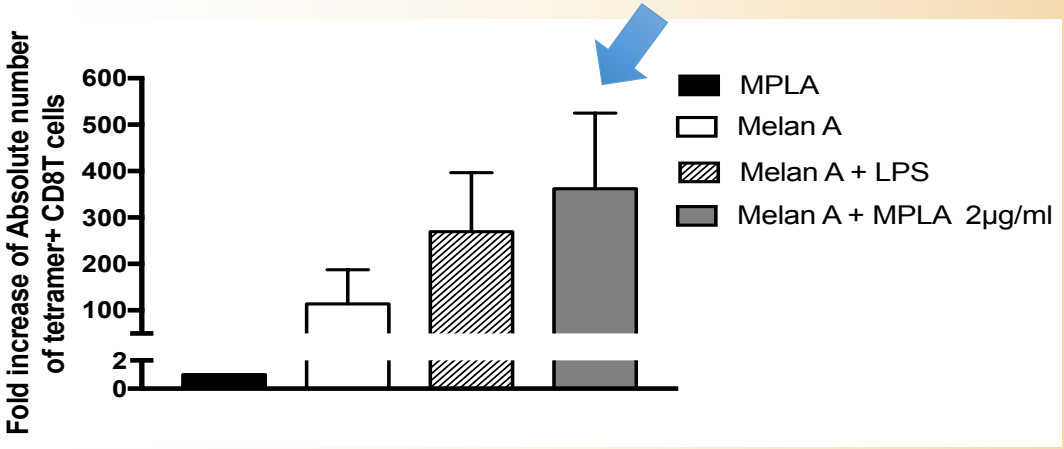
High proliferative responses



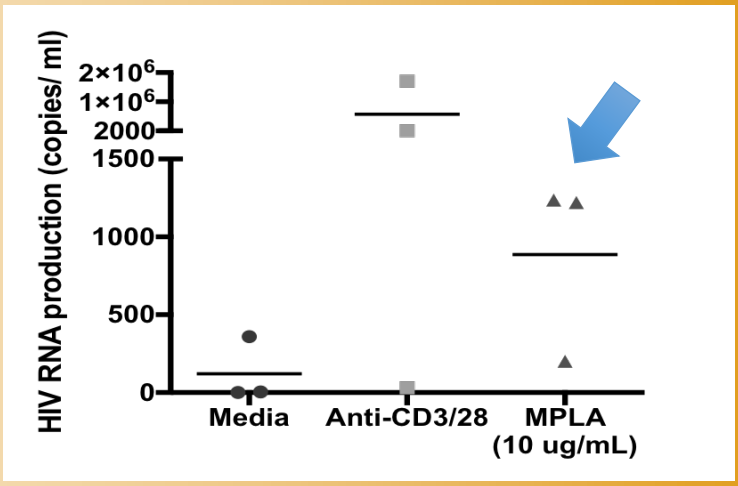
High ADCC responses

Provided by Prof. Britta Warren (Karolinska Institute/University of Rome)

Preliminary data showing effects of TLR4 agonist (MPLA)



MPLA boosts CD8+ T cell priming



MPLA reactivates latent HIV reservoir

Data generated by Dr. Lydie Trautmann (MHRP)