VACCINES AND VACCINATION DURING AND POST COVID PANDEMICS "VAC&VAC 2022"

On line, December 7-9, 2022

Therapeutic vaccines for periatally HIV-1 Infected patients, update from update from the HVRRICAN study

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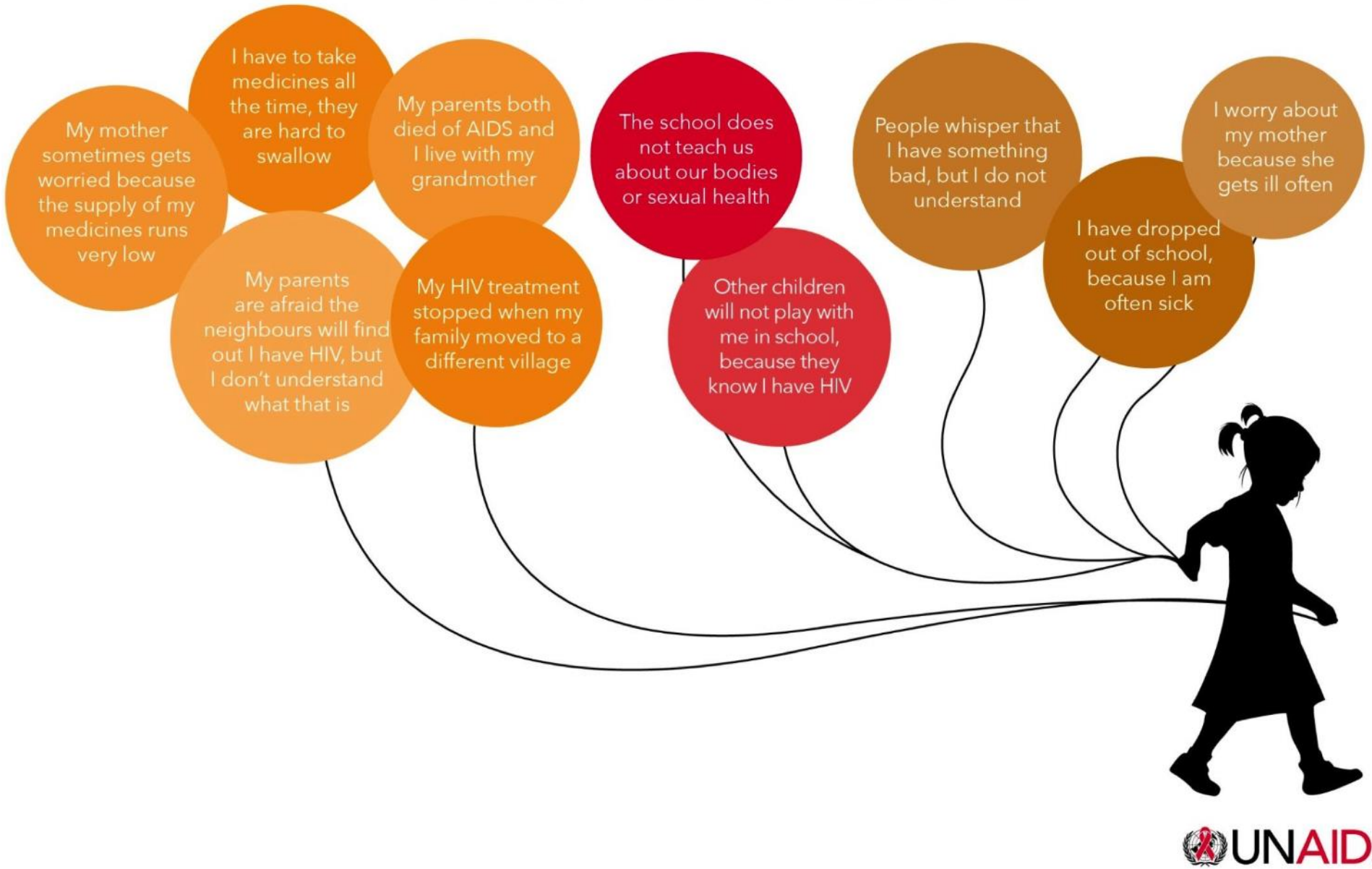
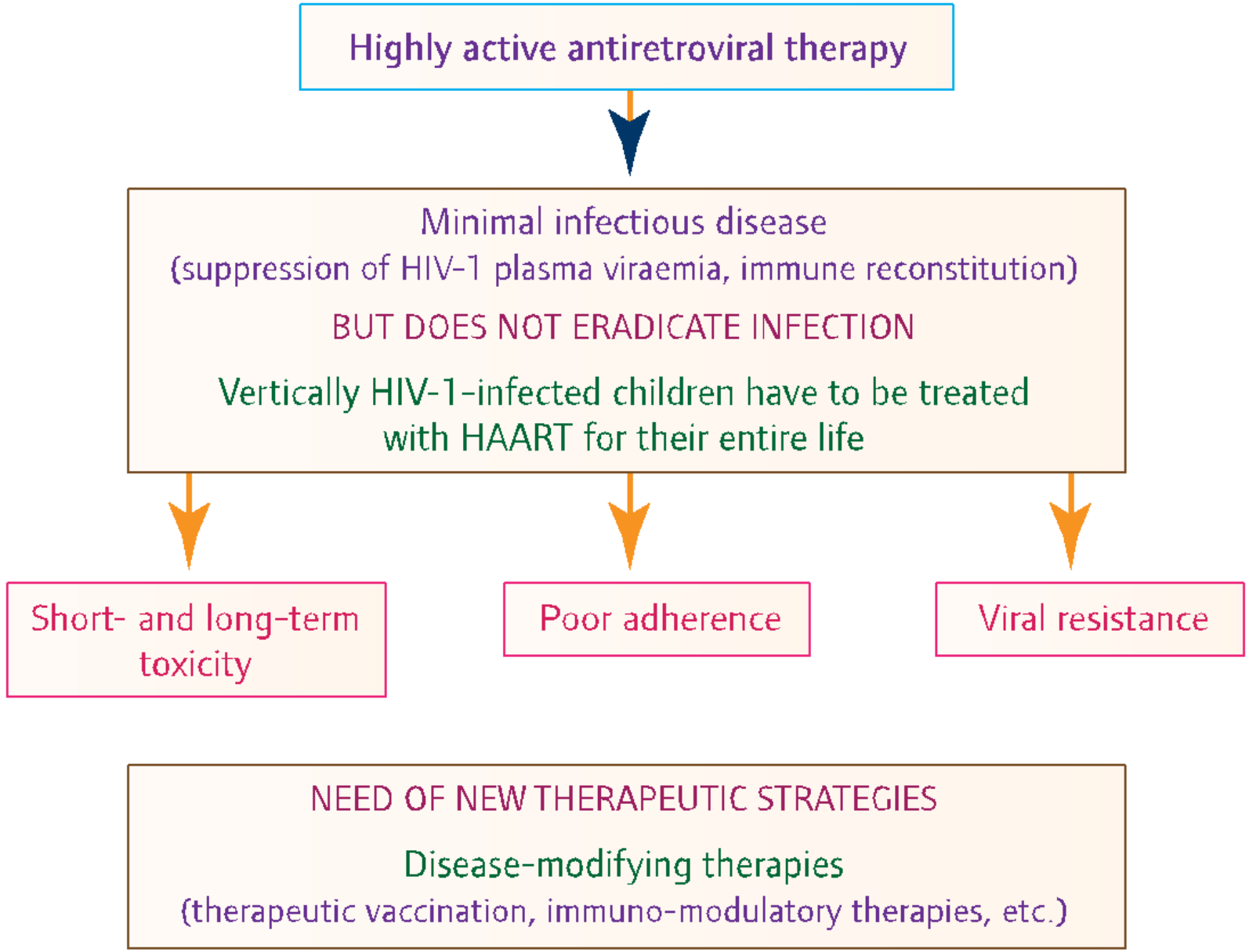
I AM A CHILD LIVING WITH HIV.
I FACE THESE ISSUES



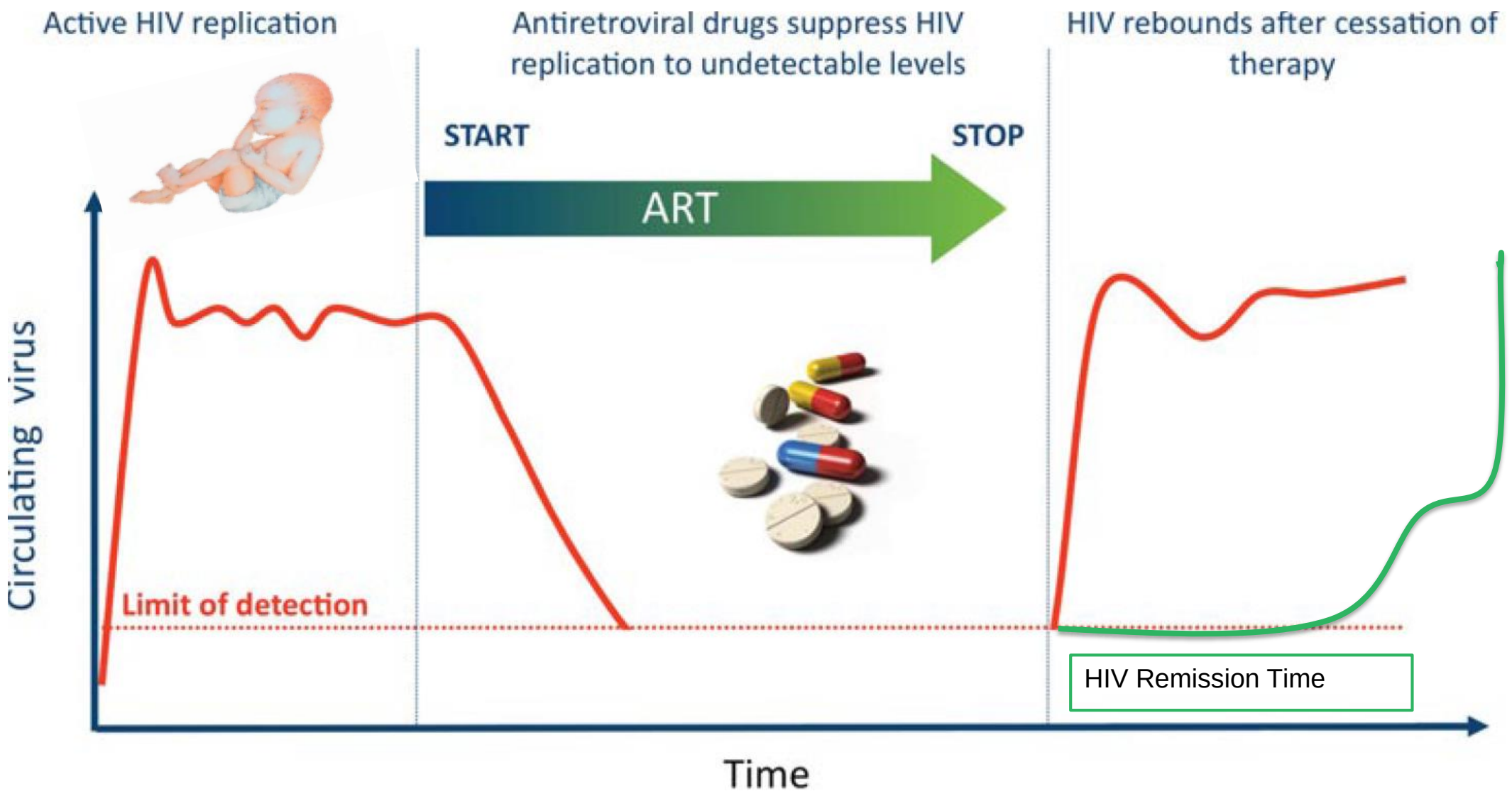
THE TREATMENT GAP IN CHILDREN

Source: UNAIDS estimates 2014

UNAIDS



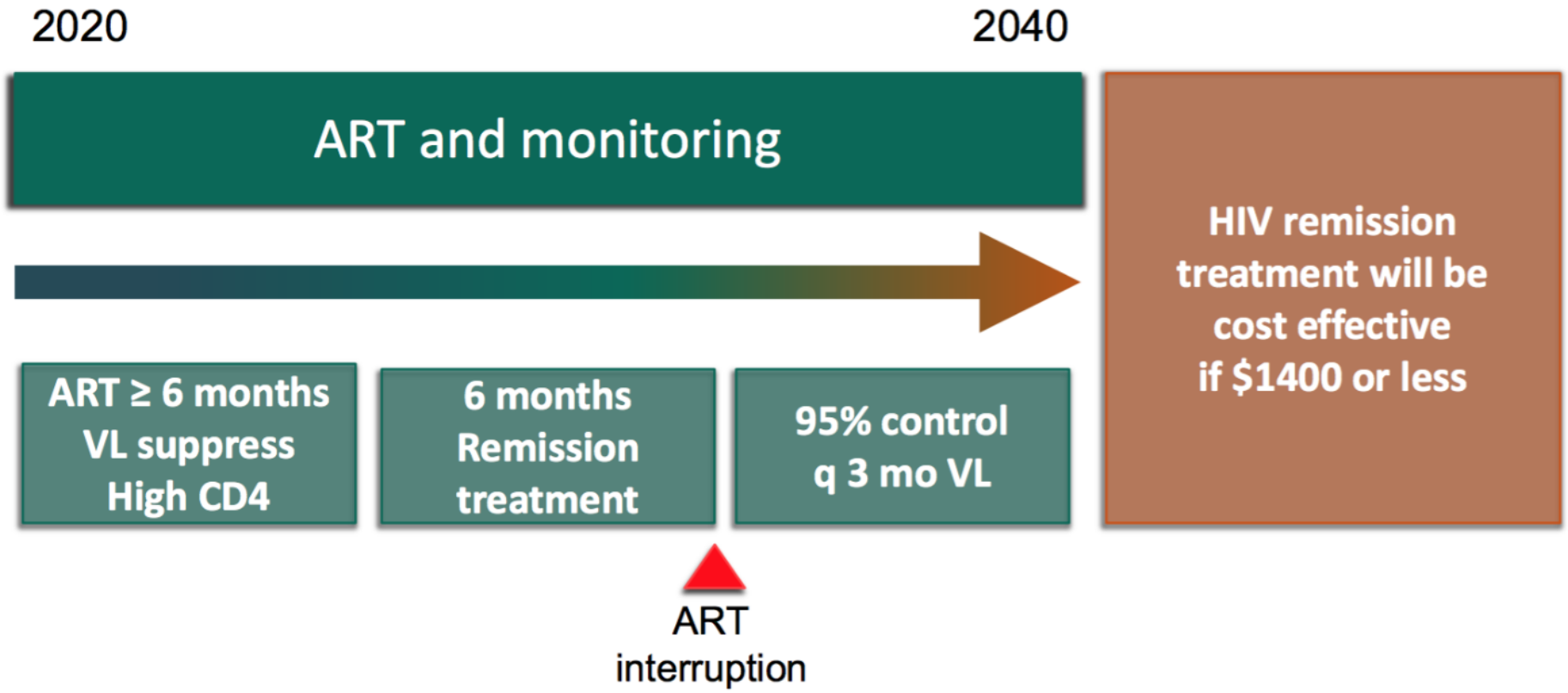
Palma P. et al, Journal of Virus Eradication 2015; **1**: 134–139



adapted

Deanna A Kulpa[1] and Nicolas Chomont*[2] *Journal of Virus Eradication* 2015; 1: 59–66

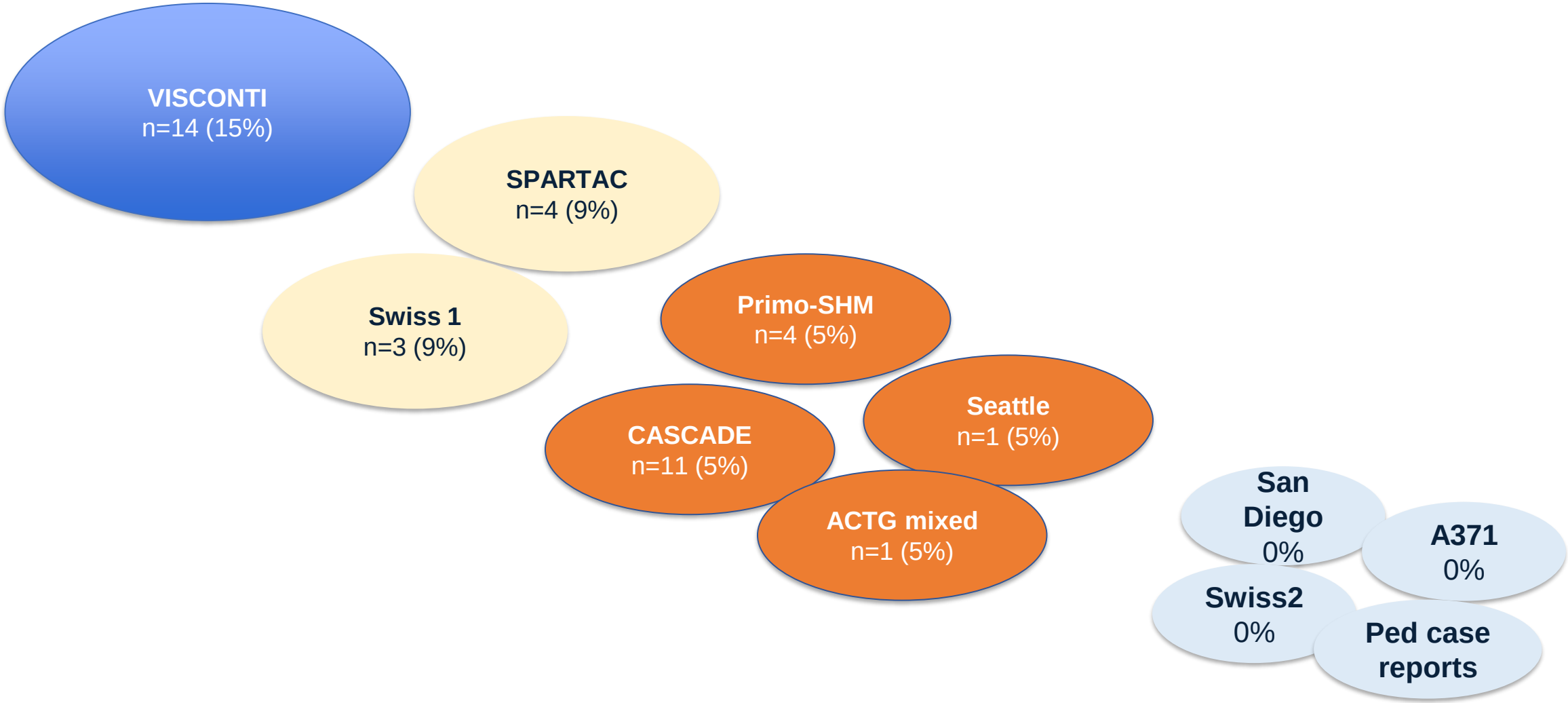
Cost-effectiveness of HIV Remission Treatment



- HIV remission interventions would have to be inexpensive and highly effective to be cost-effective for the general HIV population

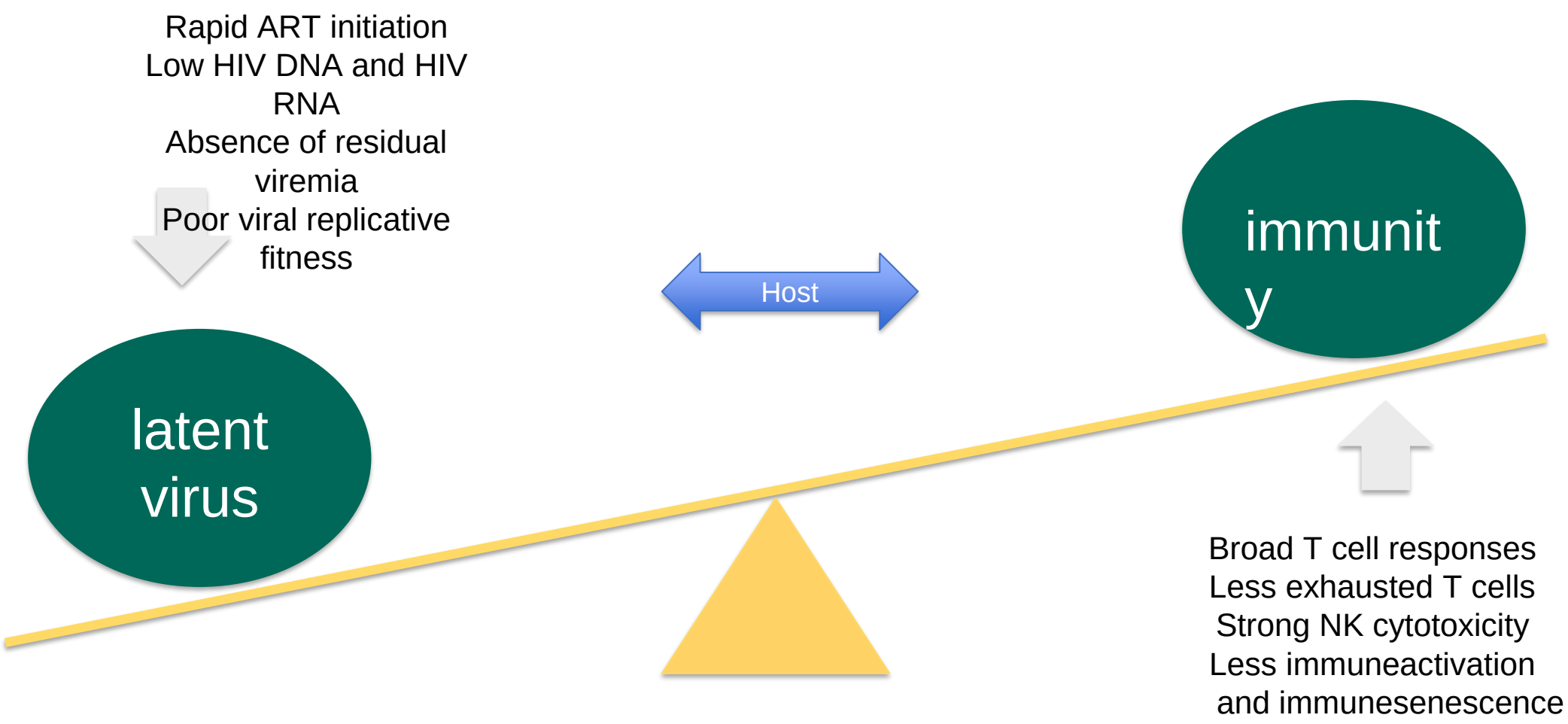
Phillips, Lewin, Deeks, Hallett, J Infect Dis 2016

HIV remission is uncommon even in early treated people



VISCONTI (Hocqueloux L, 2010; Saez-Cirion A, 2013): SPARTAC (Fidler S, 2013, Stohr 2013); Swiss 1 (Gianella S, 2011)
Primo SHM (Grijsen ML, 2012); Cascade (Lodi S, 2012) Seattle (Maenza J, 2015); ACTG mixed (Li J, CROI 2015)
San Diego (Gianella S, 2015); Swiss 2 (von Wyl V, 2011); A371 (Volberding P, 2009); Ped (Ananworanich J, 2015);

HIV Remission:
Complex Interplay between Reservoir and Immunity

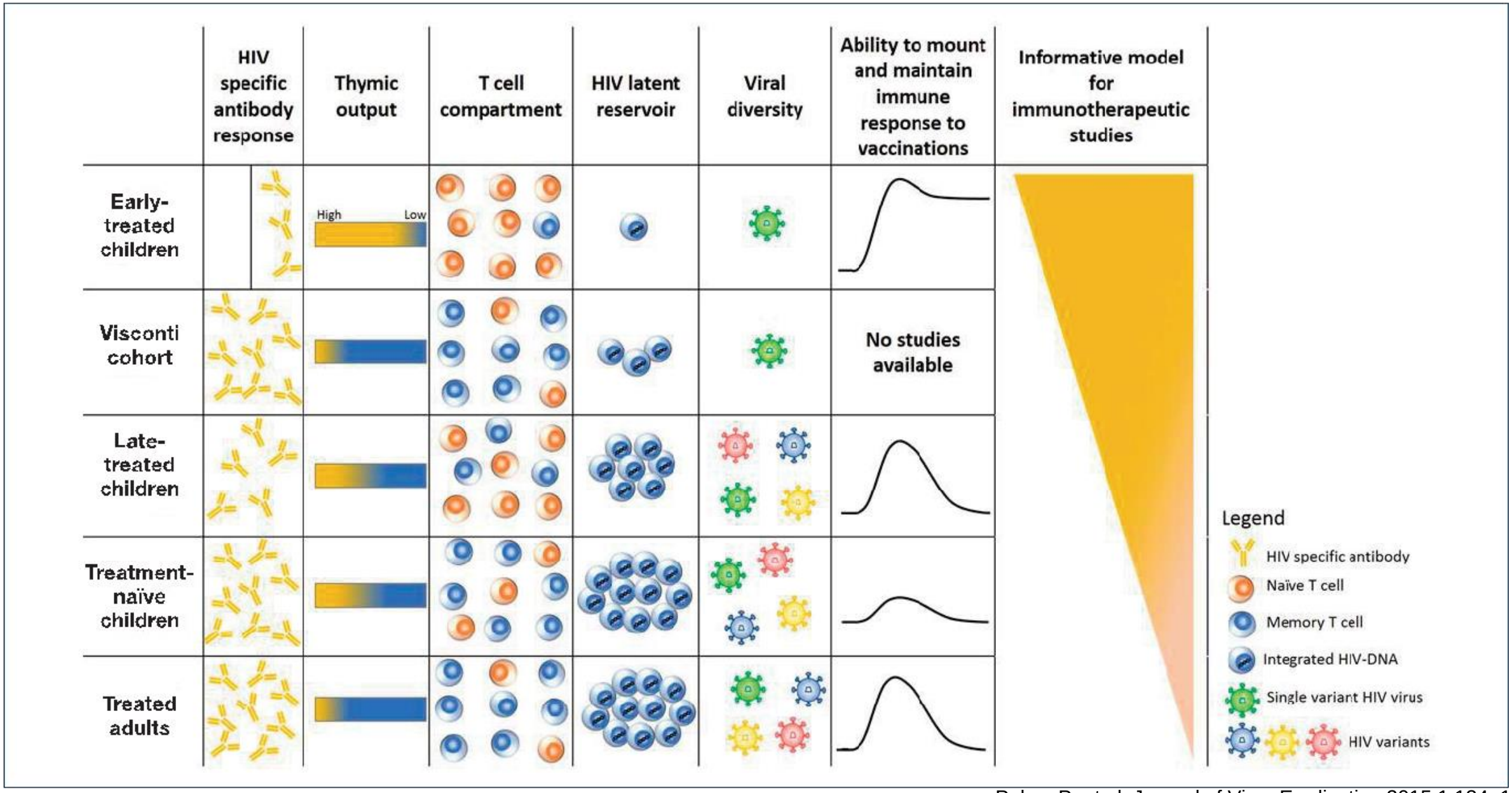


Williams JP, eLife 2014; Etemad B, 2015 CROI; Hurst J, Nature Communications 2015; Frater J, AIDS 2014; Scott-Algara D, 2015 CROI; van Gulck E, Plos One 2012

WHY CHILDREN FIRST

Are there unique virologic features
in perinatally HIV infected
eART treted children that could be leveraged
to develop an effective immunotherapy?

The uniqueness of the early treated children model



Palma P. et al, Journal of Virus Eradication 2015;1:134–139
Palma P et Lancet Infect Dis 2015; 1108-14

EPICAL

The HIV CLINICAL & EXPERIMENTAL PLATFORM

Penta Child Health Research
Bambino Gesù Ospedale Pediatrico
UCL
Hospital Universitario 12 de Octubre
Hospital Universitario Gregorio Marañón
NHS Imperial College Healthcare NHS Trust
University of Miami Miller School of Medicine
Università degli Studi di Padova
Universiteit Stellenbosch University
AHRI Africa Health Research Institute
Johns Hopkins University
Utrecht University
Fondazione per la Ricerca Farmacologica Gianni Benzi ONLUS
University of Massachusetts Medical School
Tor Vergata Università degli Studi di Roma
Columbia University in the City of New York
PHRU
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fundação manhiça moçambique
ISGlobal Barcelona Institute for Global Health
Boston Children's Hospital
Umkhuseli Innovation and Research Management RF NPC
Brigham Health
Brigham and Women's Hospital
RTI International
JCRC Joint Clinical Research Centre

www.epiical.org

Chula Chulalongkorn University

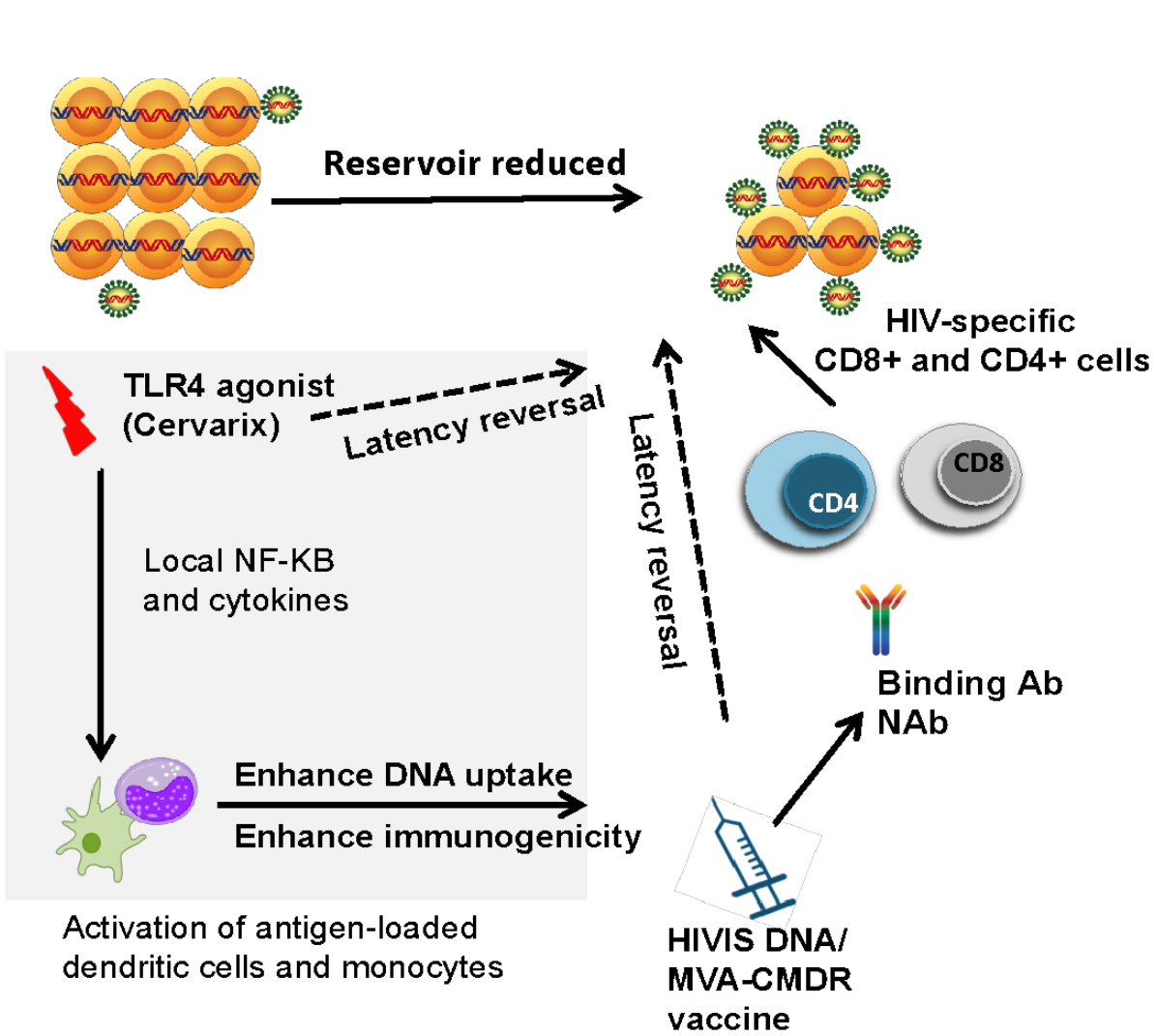
RV534: HVRRICANE

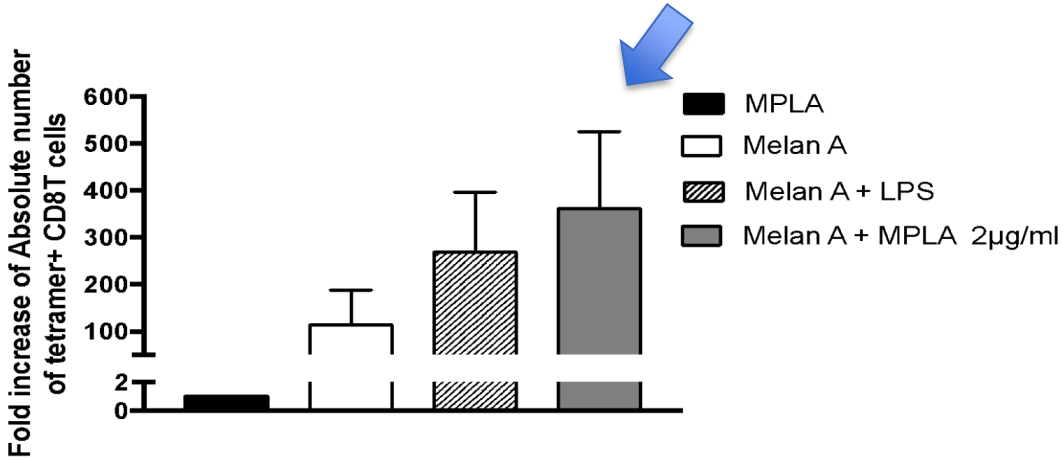
HIV Vaccine to Reduce Reservoir in Children & Adolescents Network (EPIICAL)

Protocol Title: **Phase I, Proof of Concept, Open-Label, Randomized Clinical Trial to Evaluate the Safety and Effects of Using Prime-boost HIVIS DNA and MVA-CMDR Vaccine Regimens with or without Toll-like Receptor 4 Agonist on HIV Reservoirs in Perinatally HIV Infected Children and Youth**

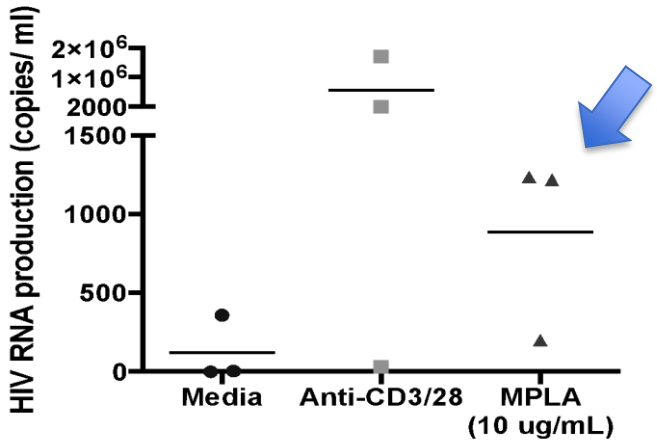
National Institutes of Health

Conceptual Framework





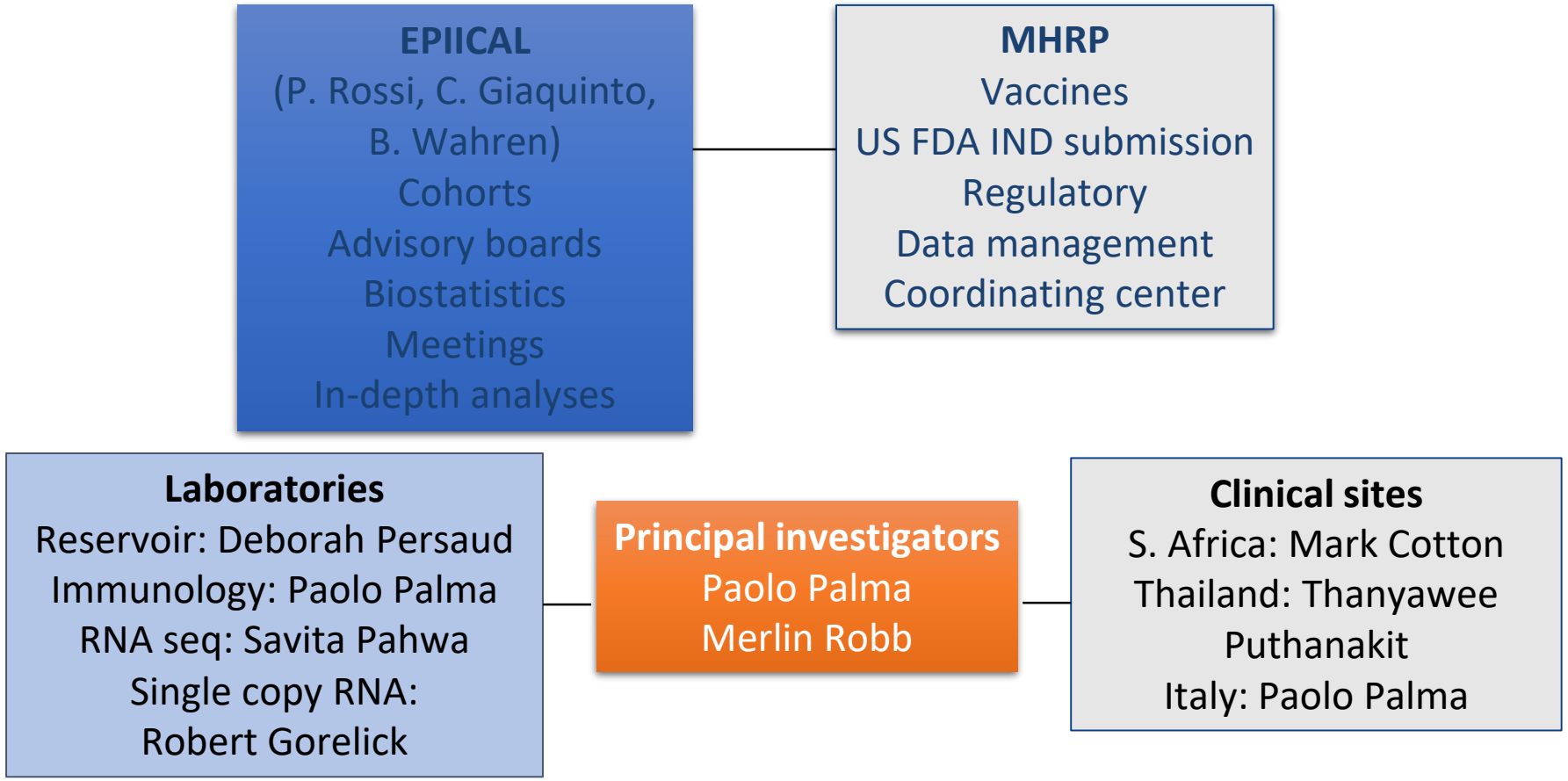
MPLA boosts CD8+ T cell priming



MPLA reactivates latent HIV reservoir

Data generated by
Dr. Lydie Trautmann

Collaborative Study



The PEDVAC trial TIME LINE

Preclinical trials in animals model
Virology198:82-90
AIDS Res Hum Retroviruses.16:1269-80.

Evaluation of immunogenicity of the multiplasmids DNA vaccine (HIVIS) in animal models
J Immunol. 173:7078-89
Vaccine. 16;22:1810-9.

Writing of the PEDVAC protocol and submission to the regulatory authorities

Final acceptance of the protocol by the AIFA, ISS and Hospital Ethical Committee

1998-2000 | 2001-2002 | 2002-2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010/11

First data in HIV infected humans with a single DNA plasmid
Lancet 351:1320-1325

Enrollment of 40 healthy volunters in a randomized trial with the HIVIS vaccine.
J. Inf. Dis 198(10):1482-90

Enrollment of the first pediatric patient in the PEDVAC study

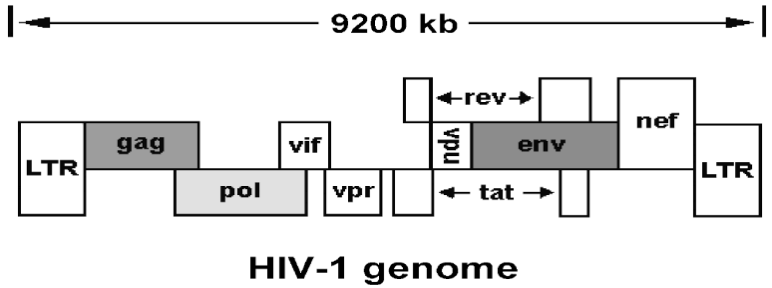
Completion of the vaccine schedule in the arm B- Publication of the preliminary safety data *Vaccine 2011, PLOSone 2014 and Vaccines 2014*

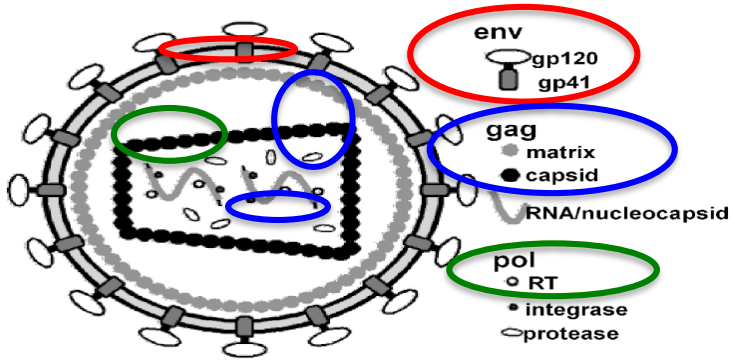
Contents lists available at ScienceDirect

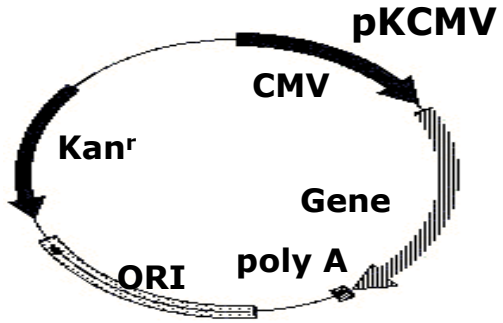
Vaccine

journal homepage: www.elsevier.com/locate/vaccine

The PEDVAC trial: Preliminary data from the first therapeutic DNA vaccination in HIV-infected children







2 Ampoules 1
Plasmids
Env A, B, C e revB

Left arm

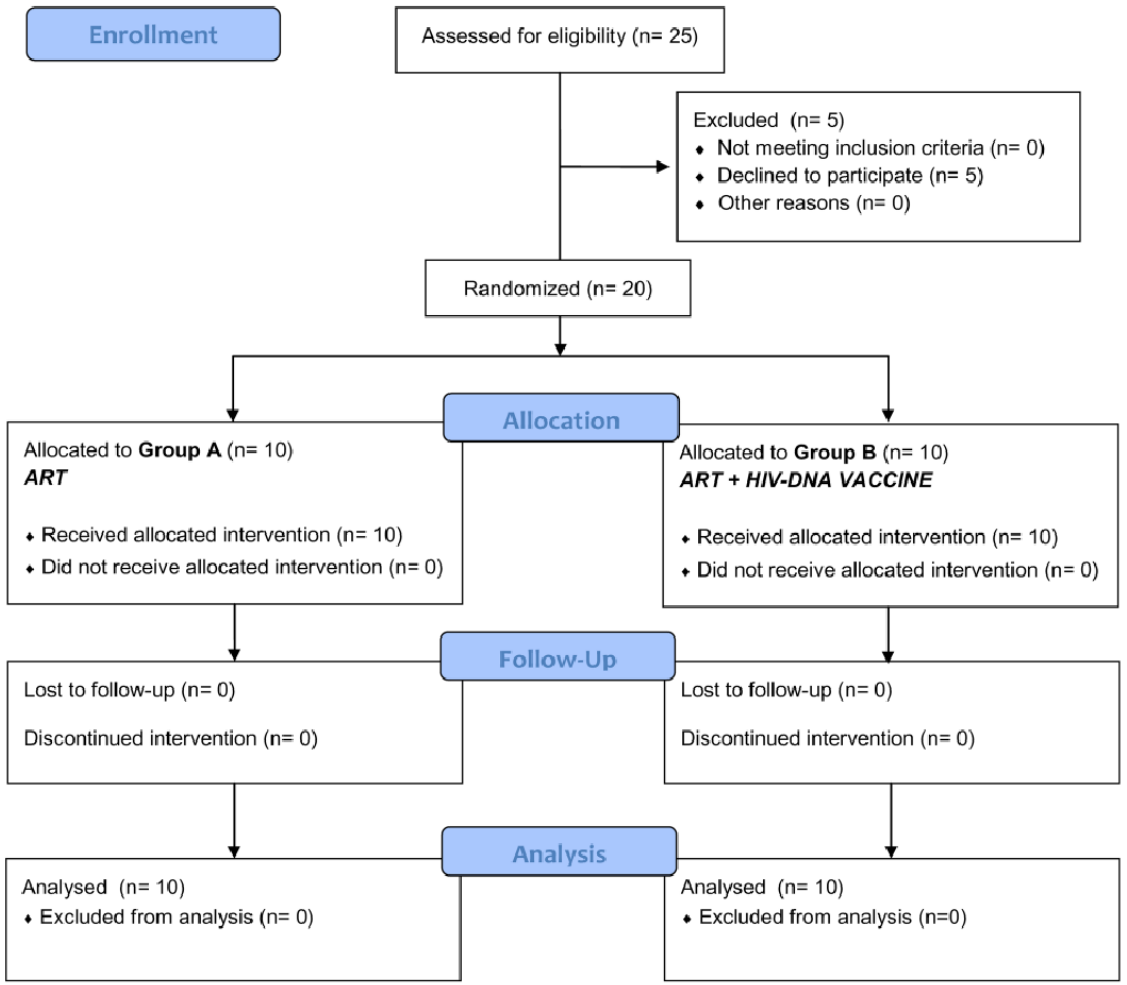
2 Ampoules 2
Plasmids:
Gag A, B e mutRT

Right arm

4 mg DNA i.m injected

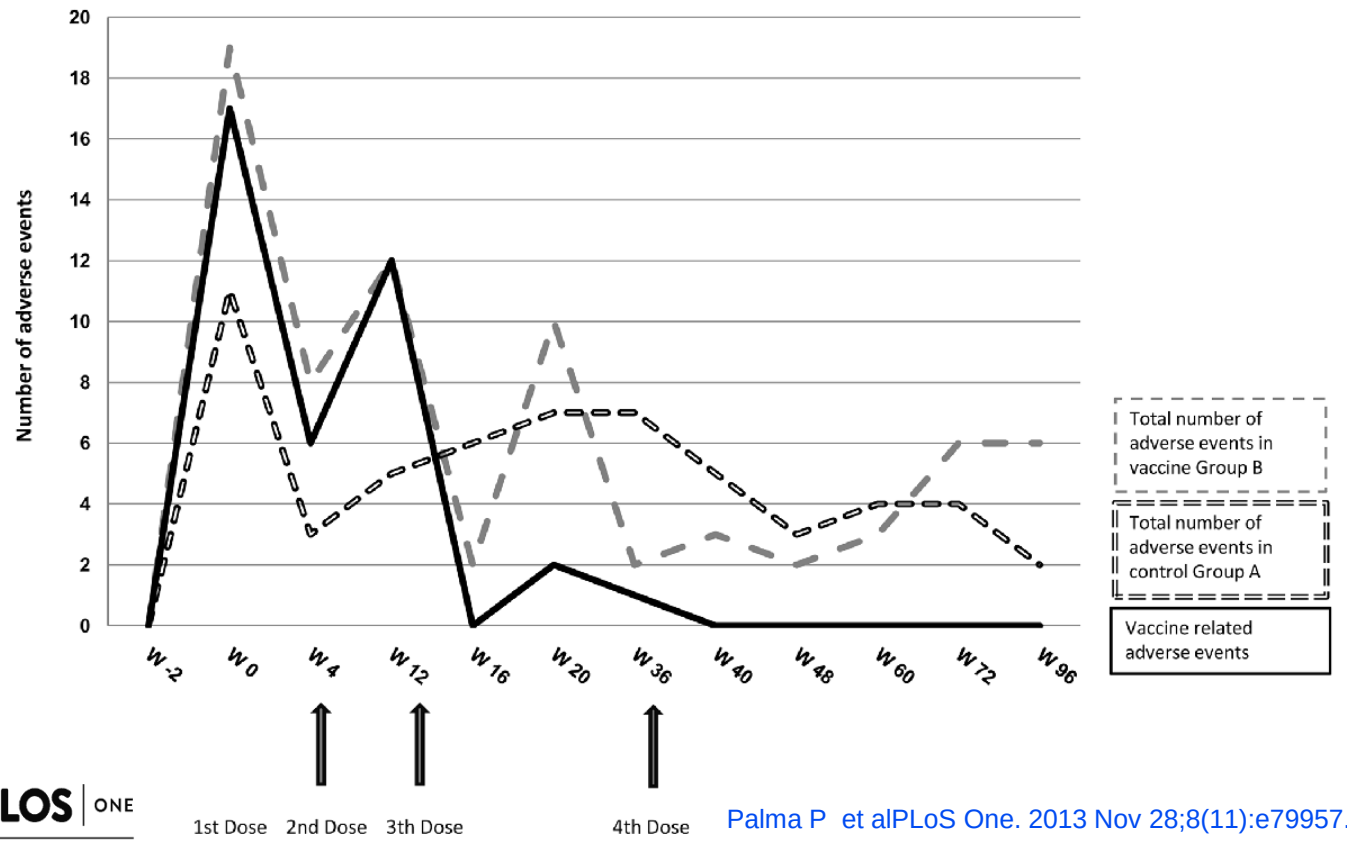
Palma P et al .Vaccine. 2011 Sep 9;29(39):6810-6

Therapeutic DNA Vaccination of Vertically HIV-Infected Children: Report of the First Pediatric Randomised Trial (PEDVAC)



	GROUP A Controls	GROUP B Vaccinees
Female/Male	6/4	6/4
Age (years) median (range)	12,0 (8,1–16,3)	11,5 (6,3–14,3)
CD4+ percentage median (range)	35,5 (28–47)	34 (28–42)
CD4+ no. of cells/mm^3, median (range)	748,5 (423–1188)	798 (497–1094)
Median time in months with HIV<50 copies/ml before study entry (range)	101 (13–156)	69 (12–137)
ART: 2 NRTI/PI	5/10	4/10
ART: 2 NRTI/NNRTI	5/10	6/10
Median time in months with the same ART (range)	12 (12–42)	16,5 (9–46)
Early ART treated children within the first year of life	2/10	2/10

Distribution of adverse events in the Pedvac study



OPEN ACCESS Freely available online

PLOS ONE

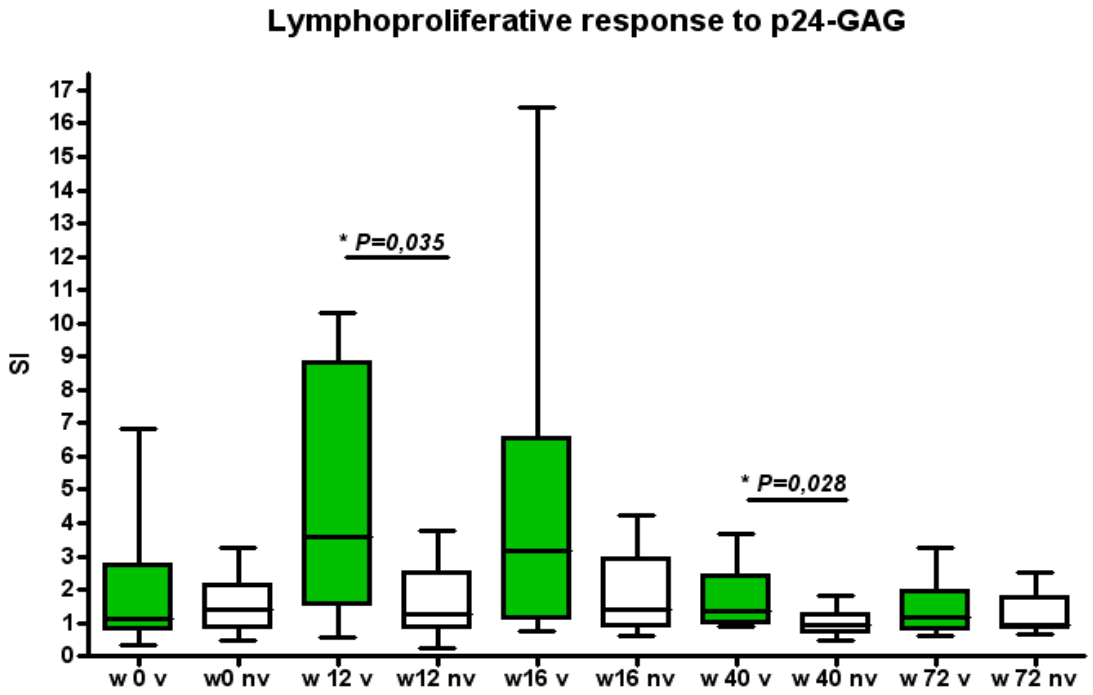
Palma P et alPLoS One. 2013 Nov 28;8(11):e79957.

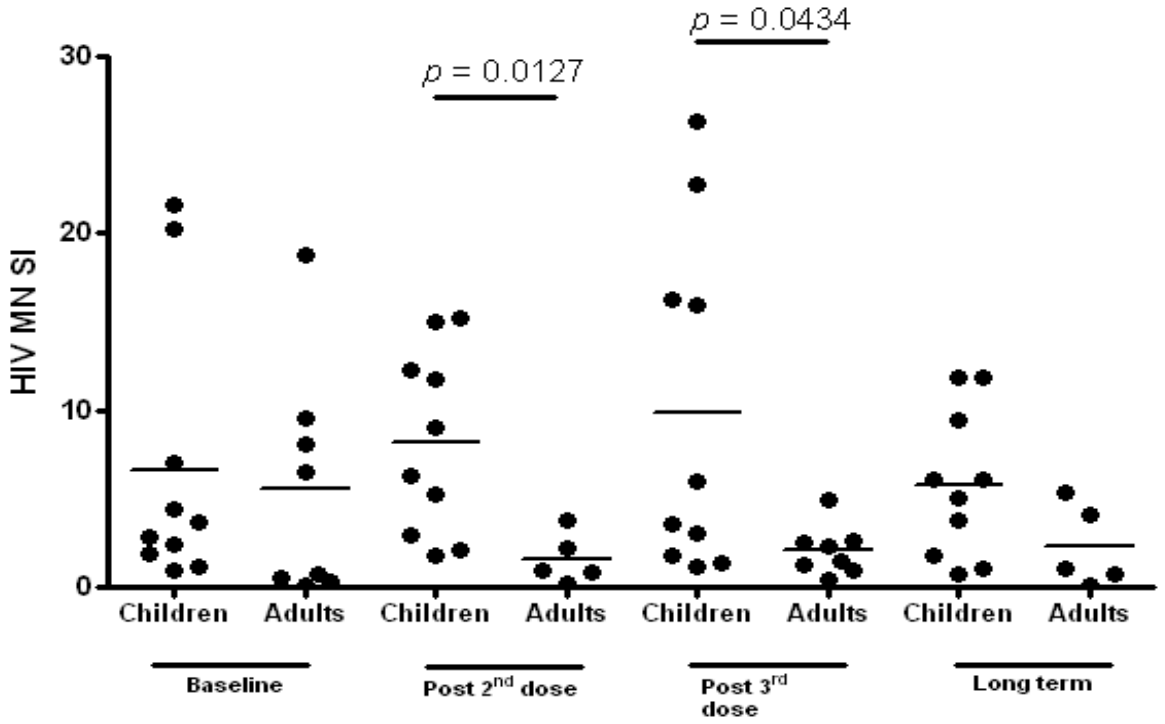
OPEN ACCESS Freely available online

PLOS ONE

Therapeutic DNA Vaccination of Vertically HIV-Infected Children: Report of the First Pediatric Randomised Trial (PEDVAC)

vaccines

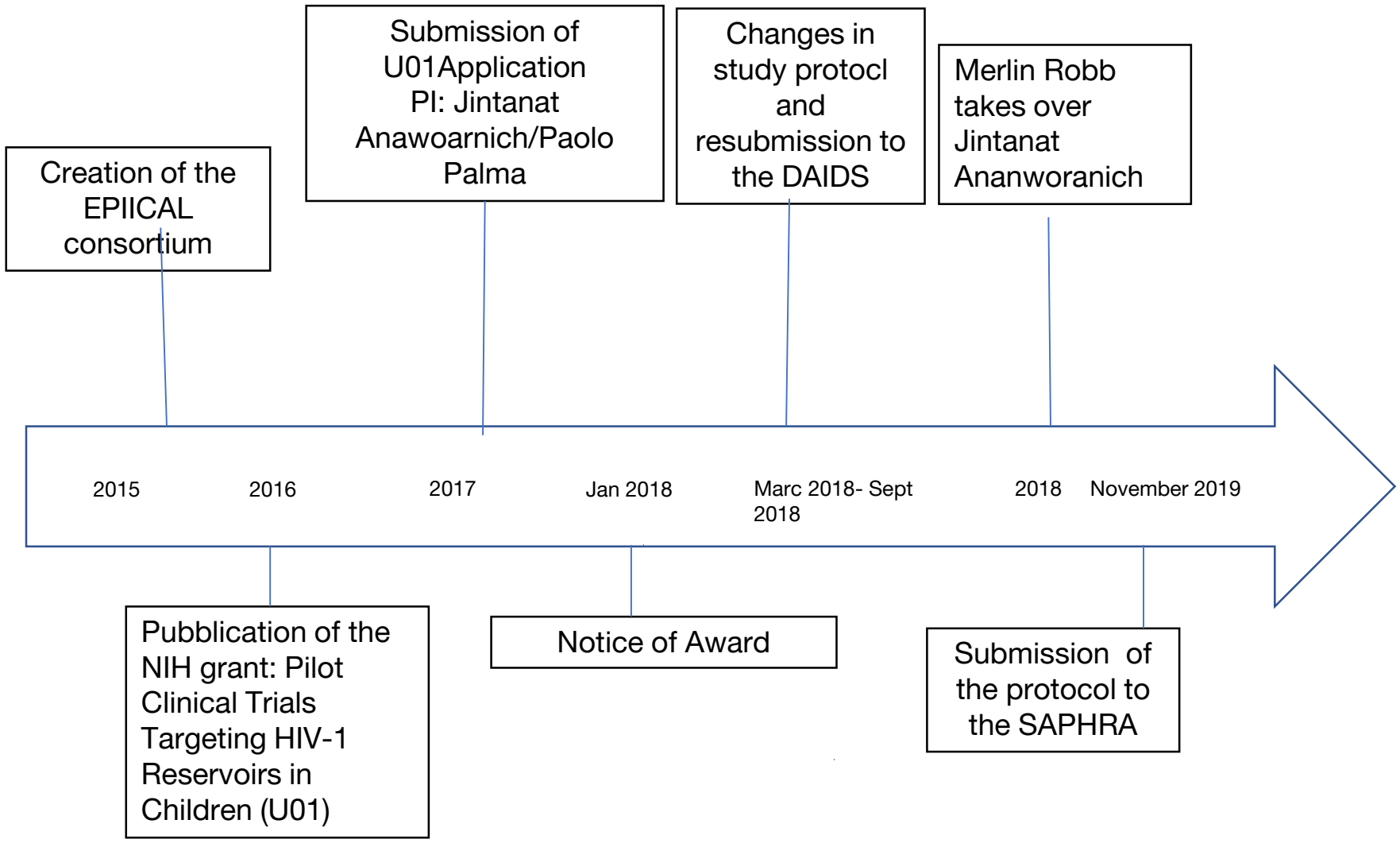




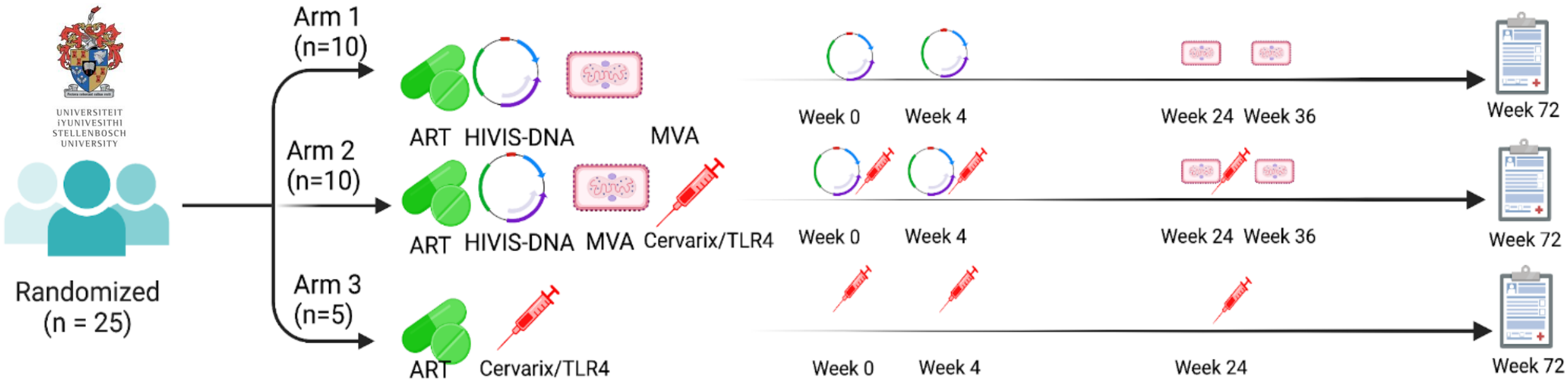
Palma P et al ; PLoS One. 2013 Nov 28;8(11):e79957.

Palma P. et al **Vaccines** (Basel). 2014 Jul 17;2(3):563-80

HURRICANE Time line



HVRRICANE STUDY DESIGN

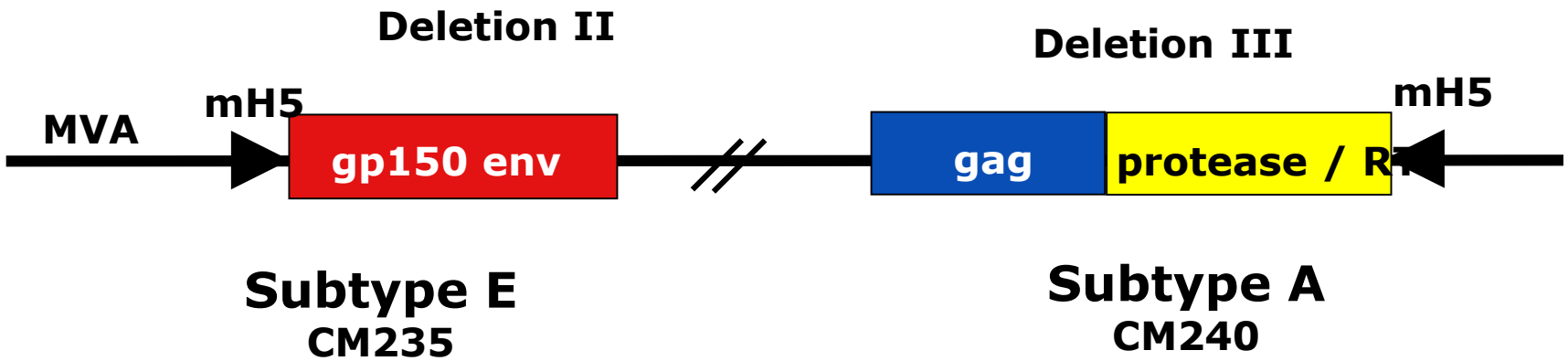


Enrollment Criteria

1. HIV perinatally infected
2. Know their HIV+ status
3. Initiated ART prior to 6 months of age
4. Male and female ≥ 9 years old
5. In generally good health
6. Plasma viral load < 200 copies/ml on ART at screening
7. CD4 count above 400 cells/mm^3 at screening
8. Participants of childbearing potential who are sexually active must be willing to practice effective contraception during the study
9. Negative urine β-HCG (human chorionic gonadotropin) pregnancy test for any female of childbearing age (post-menarche)
10. Availability for follow-up for planned duration of the study
11. Passing a test of understanding is required for participants ≥ 18 years old or the parent(s)/legal representative of participants < 18 years old before consent.
12. Written informed consent from participants ≥ 18 years old or parent(s)/legal representative of participants < 18 years old. Assent by participants aged 9-17 years old will also be required.
13. Laboratory criteria within 8 weeks prior to enrollment

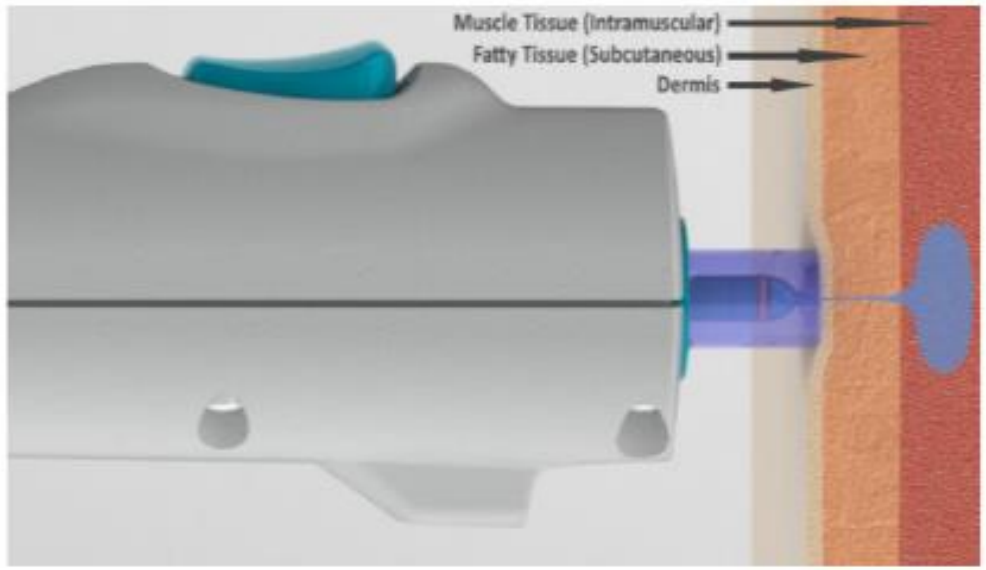
MVA* / CMDR boost

Developed by P Earl and B Moss, Laboratory of Viral Diseases, NIAID, NIH
Produced by Walter Reed Army Institute of Research



*Modified Vaccinia Ankara

Needle-free Injection: How does it work?



- Calibrated spring force allows for injection of vaccine or therapeutic into intramuscular tissue
  - Single use, sterile, disposable needle free syringe
  - Reusable injector (validated to 20,000 uses)
  - Vial adapter

Pharmajet®

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

To do list for the HVRRICANE (RV534) STUDY

first

HIV-specific CD8+ and CD4+ T cell responses:

- Multicolor flow cytometry (BD FACSymphony A3) and ICS upon *in vitro* stimulation with HIV peptide pools
- Fluorospot T upon *in vitro* stimulation with HIV peptide pools

second

Immunophenotyping (BD FACSymphony A3) **and plasma protein profiling** (Olink)

third

Antibody-dependent cellular cytotoxicity (BD FACSymphony A3):

- Infected cell elimination assays against HIV-1 infected 8E5_LAV cells
- Antibody- dependent NK cell activation assays against HIV-1 infected 8E5_LAV cells

fourth

HIV antibodies and neutralization activity

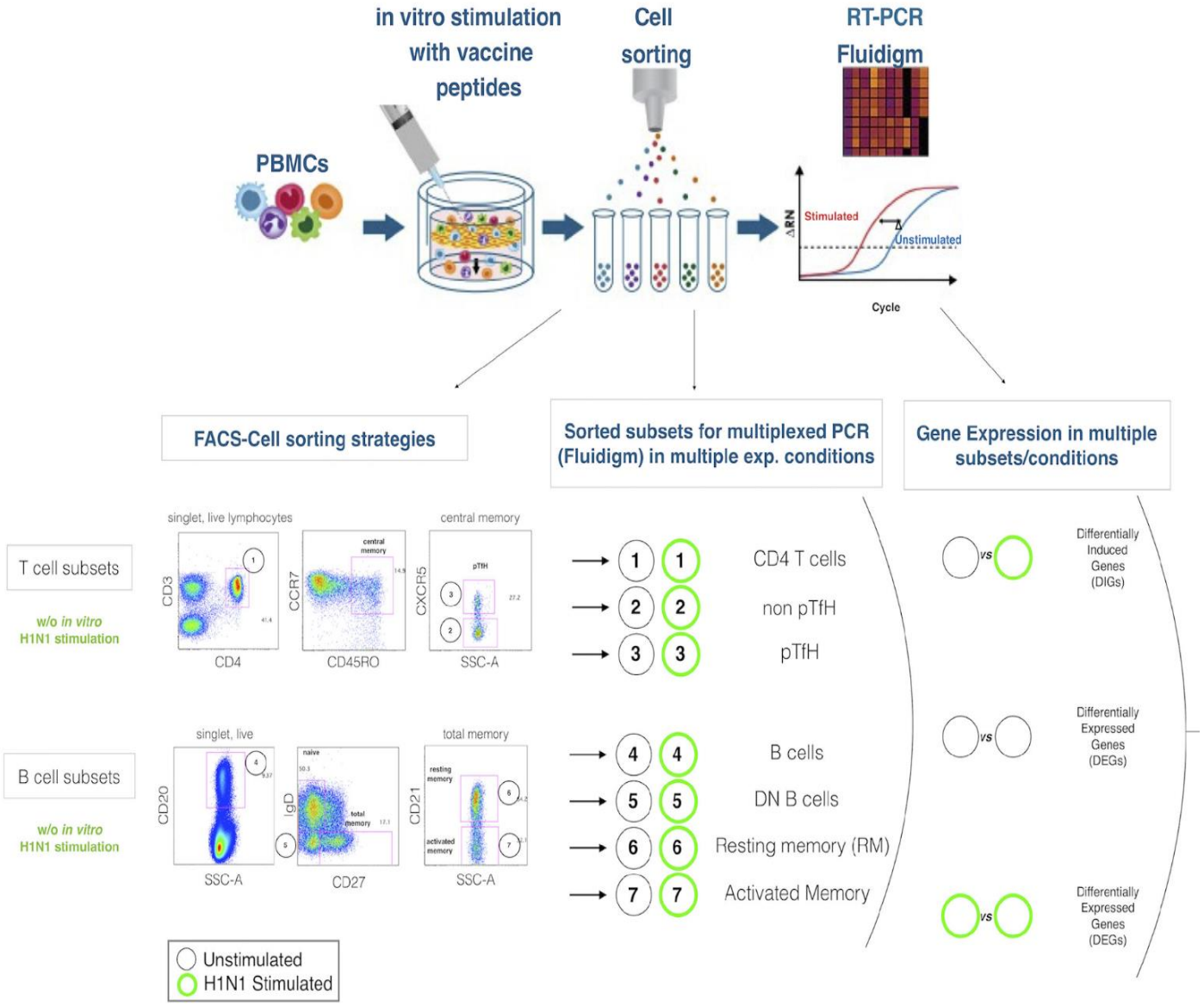
fifth

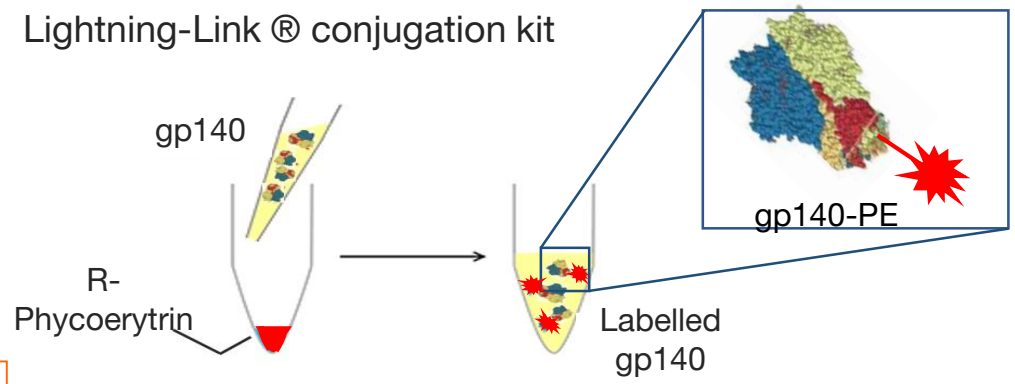
Global gene expression on PBMCs (RNAseq)

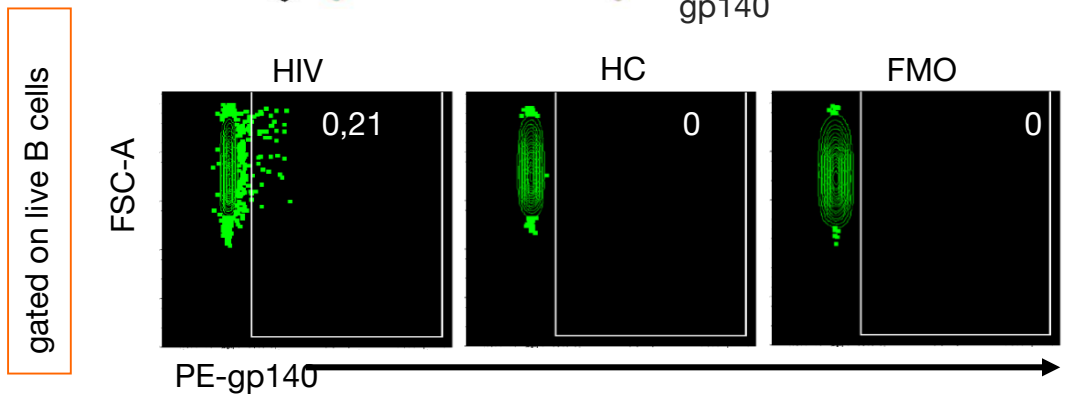
sixth

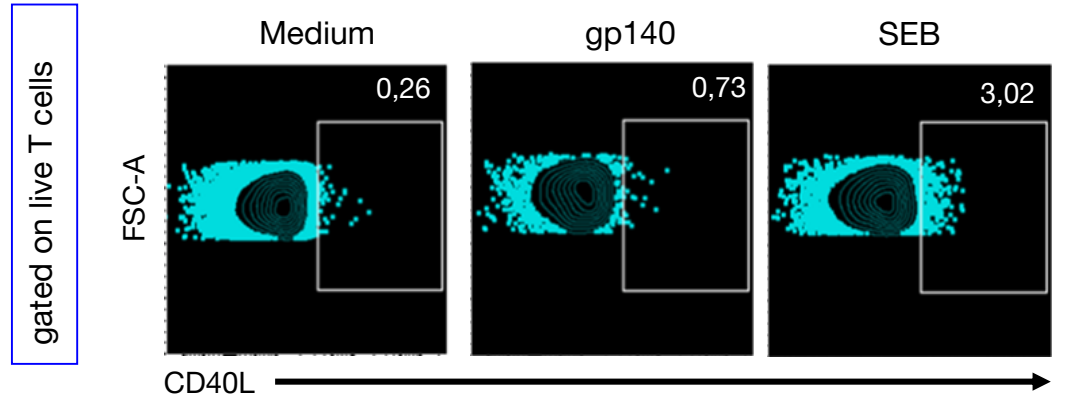
Gene expression of HIV-specific CD8+ (identified as mICAM+ upon *in vitro* stimulation with HIV peptide pools) **and CD4+** (identified as CD40L+ upon *in vitro* stimulation with HIV peptide pools) **T cells** (Fluidigm)

Detection and sorting of HIV specific B and T cell responses and evaluation of their Transcriptomic profile .









Cotugno N et al AIDS. 2020 Apr 1;34(5):669-680.

Rinaldi S et al J Immunol. 2020 Feb 1;204(3):540-549.

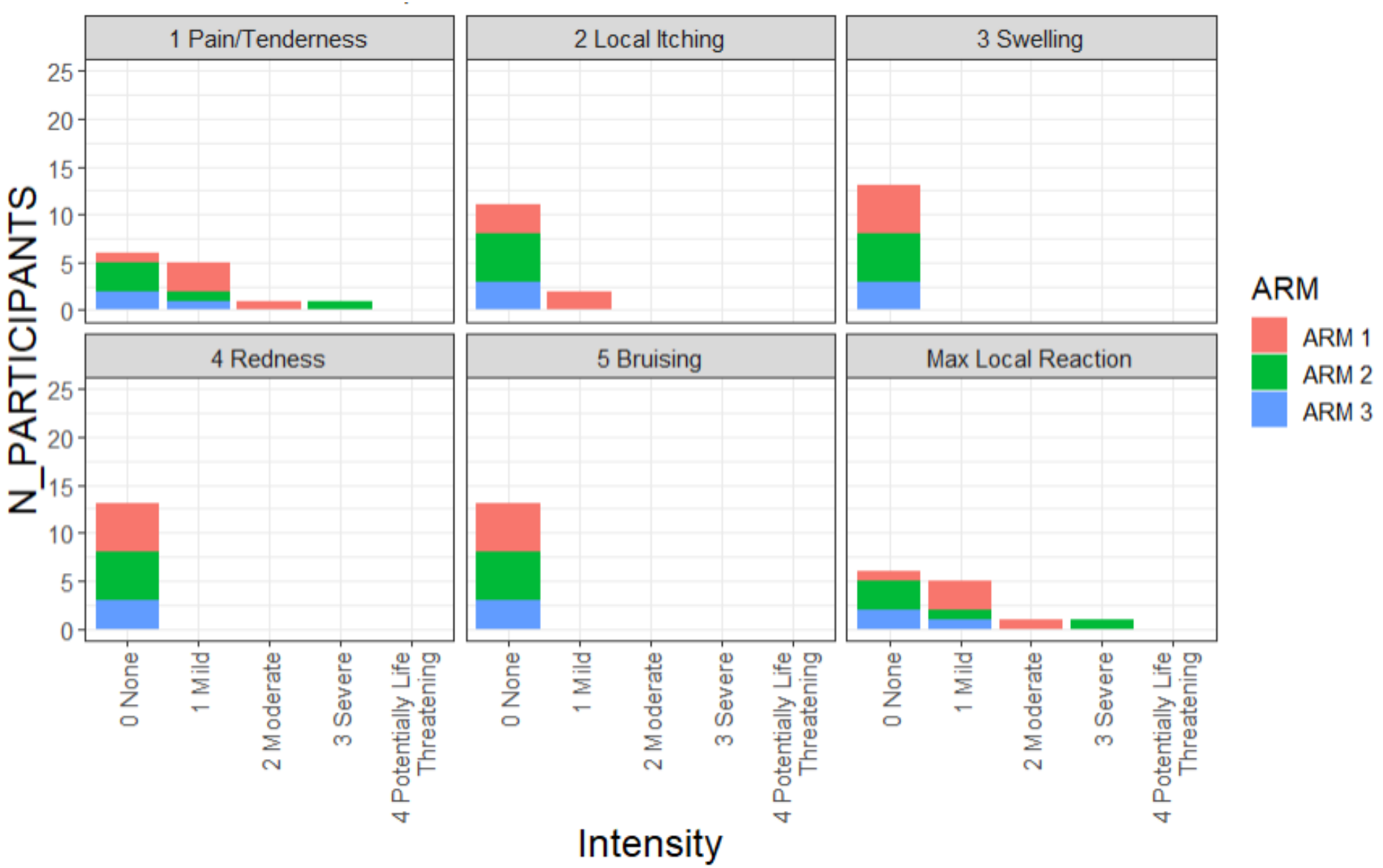
Study Product Administration Summary

(Data as of EOD 26OCT2022)

	Week 0		Week 4		Week 24		Week 36	
Arm (n=planned for each arm)	**Visit n**	**Vaccinated n(%)**	**Visit n**	**Vaccinated n(%)**	**Visit n**	**Vaccinated n(%)**	**Visit n**	**Vaccinated n(%)**
Arm 1 (n=10)	10	10 (100%)	10	10 (100%)	5	5 (50.0%)	0	0 (0.0%)
Arm 2 (n=10)	10	10 (100%)	10	10 (100%)	5	5 (50.0%)	0	0 (0.0%)
Arm 3 (n= 5)	5	5 (100%)	5	5 (100%)	3	3 (60.0%)	0	0 (0.0%)
All Arms (N=25)	**25**	**25 (100%)**	**25**	**25 (100%)**	**13**	**13 (52.0%)**	**0**	**0 (0.0%)**

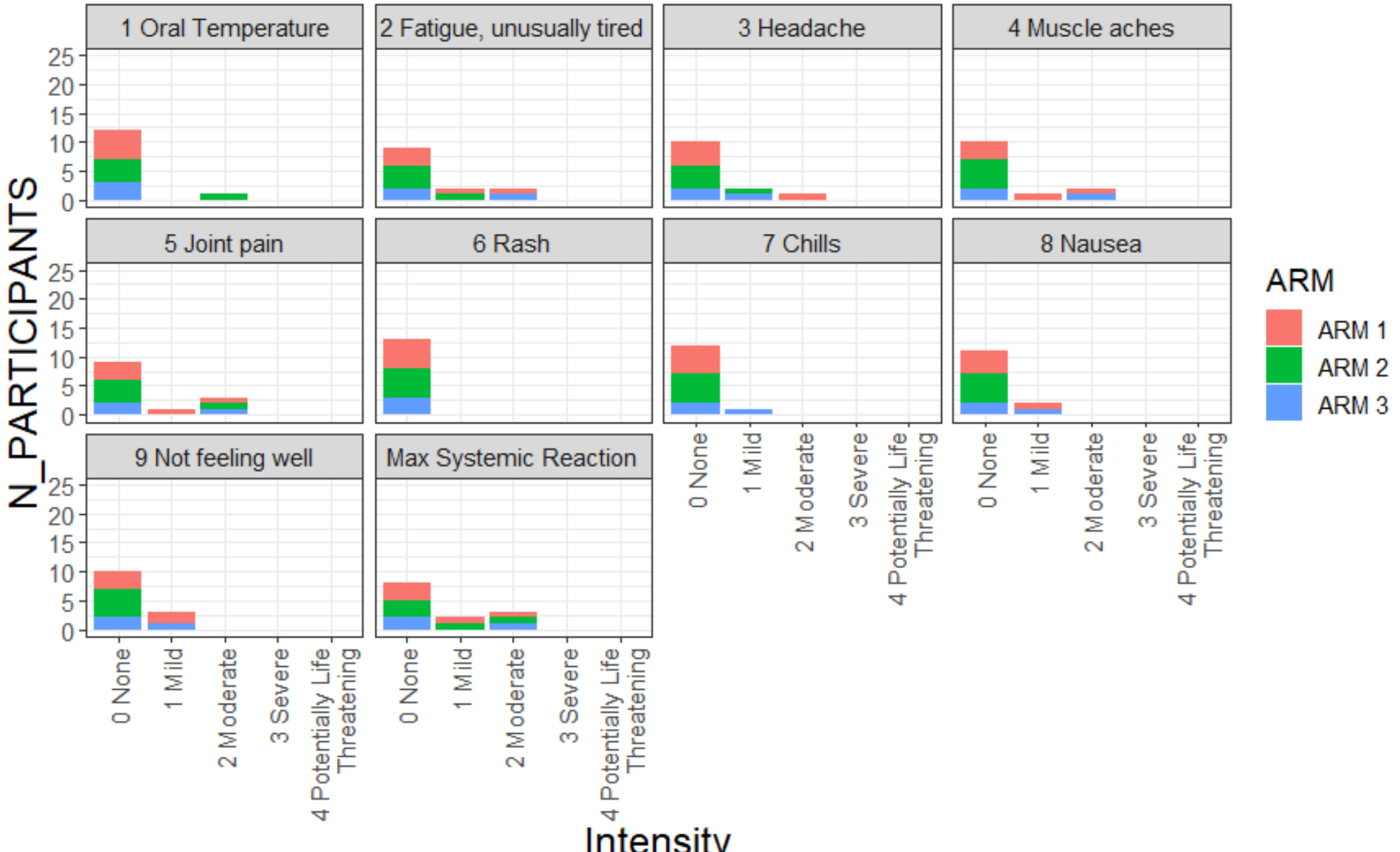
Local Reactions, WK24 (immediate + days 0 to 7)

Data as of EOD 26Oct2022



Systemic Reactions, WK24 (immediate + days 0 to 7)

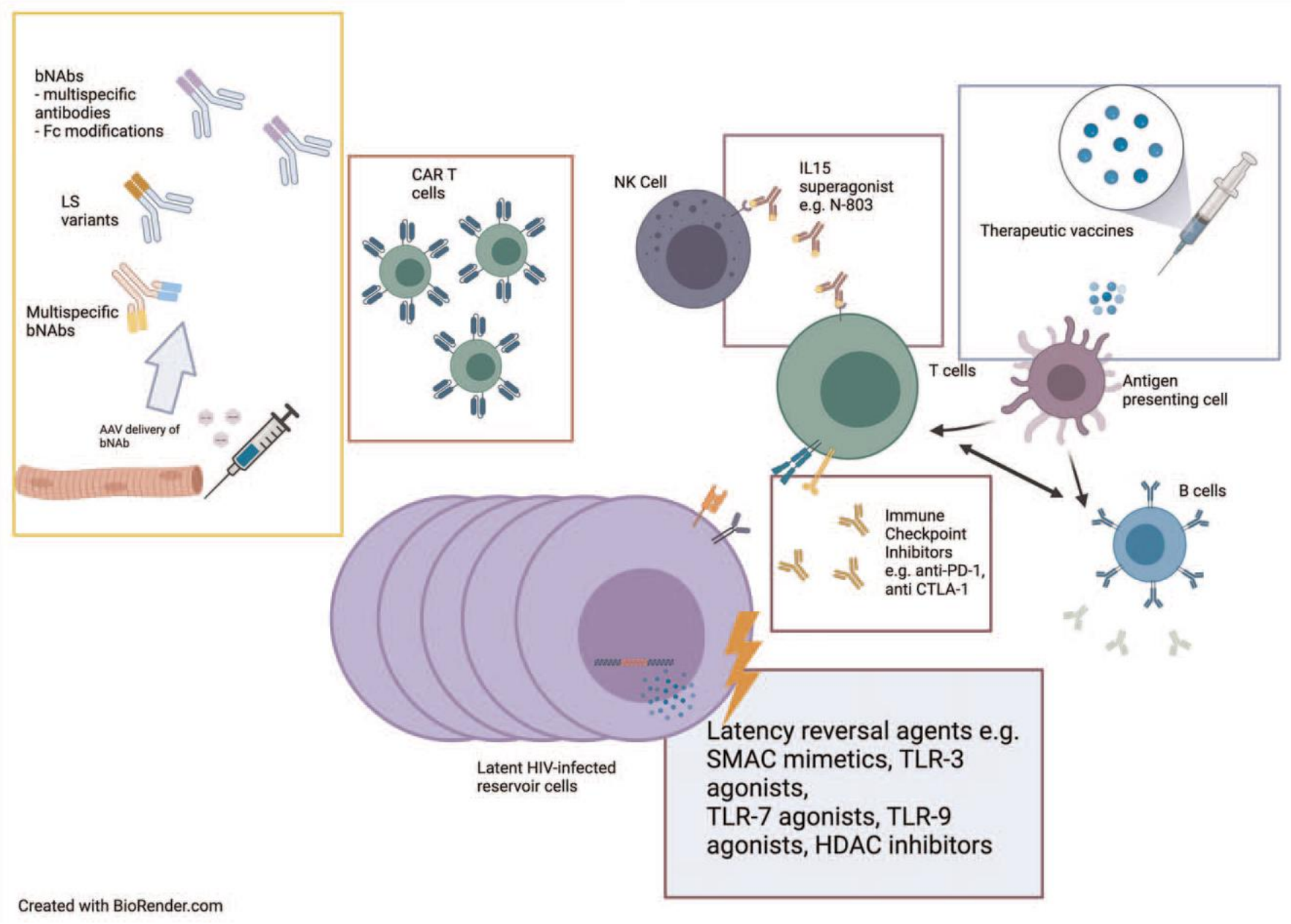
Data as of EOD 26Oct2022



Innovation

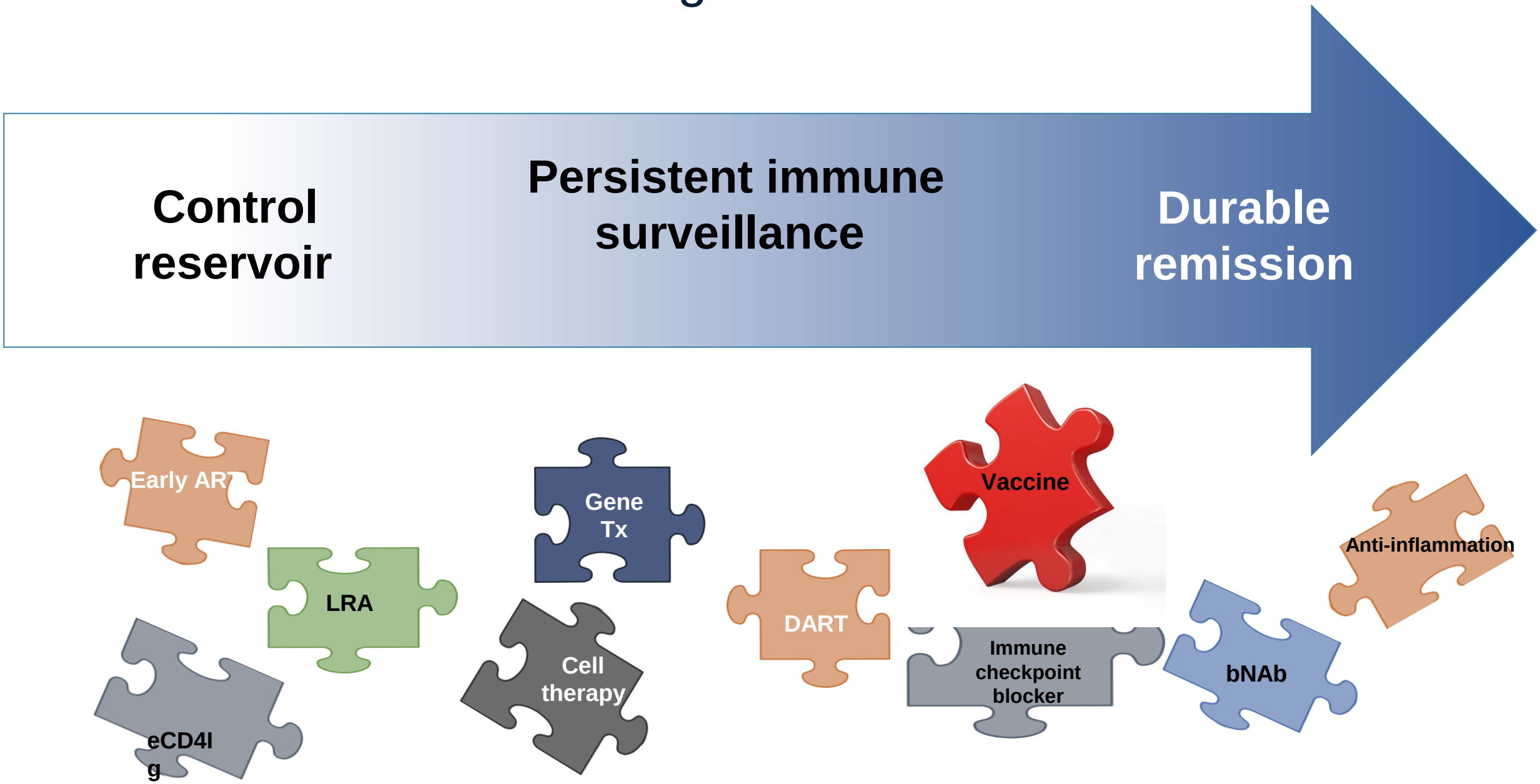
- First prime-boost HIVIS DNA/MVA-CMDR therapeutic vaccines in long term virological suppressed children
- First prime-boost HIVIS DNA/MVA-CMDR therapeutic vaccines in children to explore its impact on the reduction of HIV reservoir
- Novel strategy to deliver HIV-DNA vaccine
  pharmajet stratis needle free device- First time in children
- Novel strategy giving a licensed vaccine to adjuvant HIVIS DNA
  - HPV vaccine, Cervarix with TLR4 agonist
- Support EPIICAL's long-term goal to develop optiized proof of concept vaccine studies in children

Diagram summarising immunotherapeutic strategies targeting the latent HIV reservoir.



Lee, Ming J.; Fidler, S.; Frater, John. Current Opinion in Infectious Diseases: February 2022 - Volume 35 - Issue 1 - p 31-41

Combination Strategies Towards HIV Remission



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Sunee Sirivichayakul
Rungsun Rerknimitr
Sukalya Lerdlum
Sopark Manasnayakorn
Many more

AFRIMS
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Bessara Nantapinit
Pornsuk Visudhiphan
Saowanit Getchalarat
Nampueng Churikanont
Nongluck Sangnoi

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Adit Dhummakupt

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Robert Gorelick

Case Western
Mark Cameron

U Miami
Savita Pahwa
Stefano Rinaldi

MHRP U.S. MILITARY HIV RESEARCH PROGRAM

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NATIONAL INSTITUTES OF HEALTH

Penta Child Health Research

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