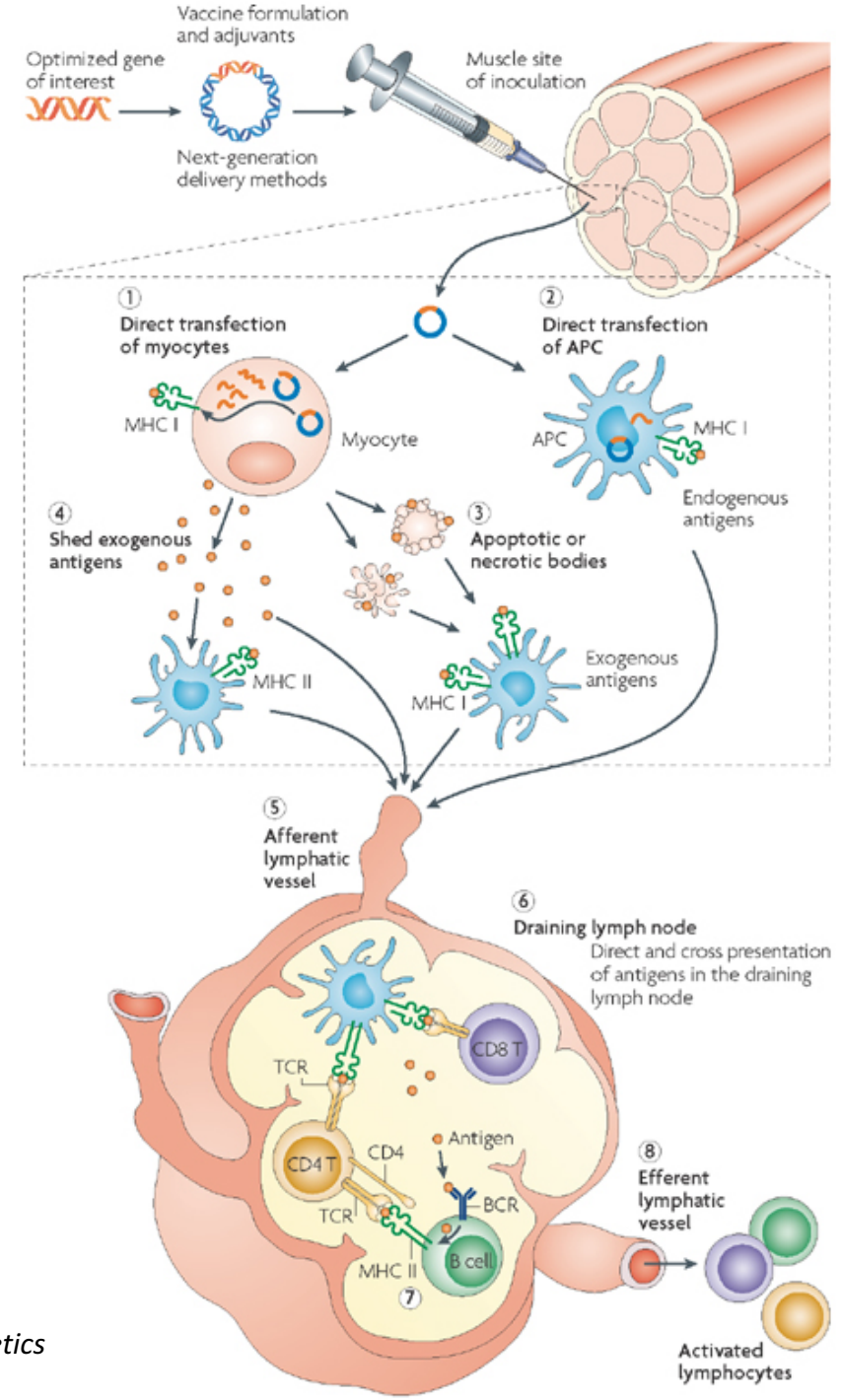
LONG TERM FOLLOW-UP FROM THE PEDVAC STUDY: INSIGHTS ON EARLY TREATED CHILDREN

PENTA INVESTIGATOR'S MEETING (PIM)
Venice, 27th - 30th April 2017

Emma C Manno, MD

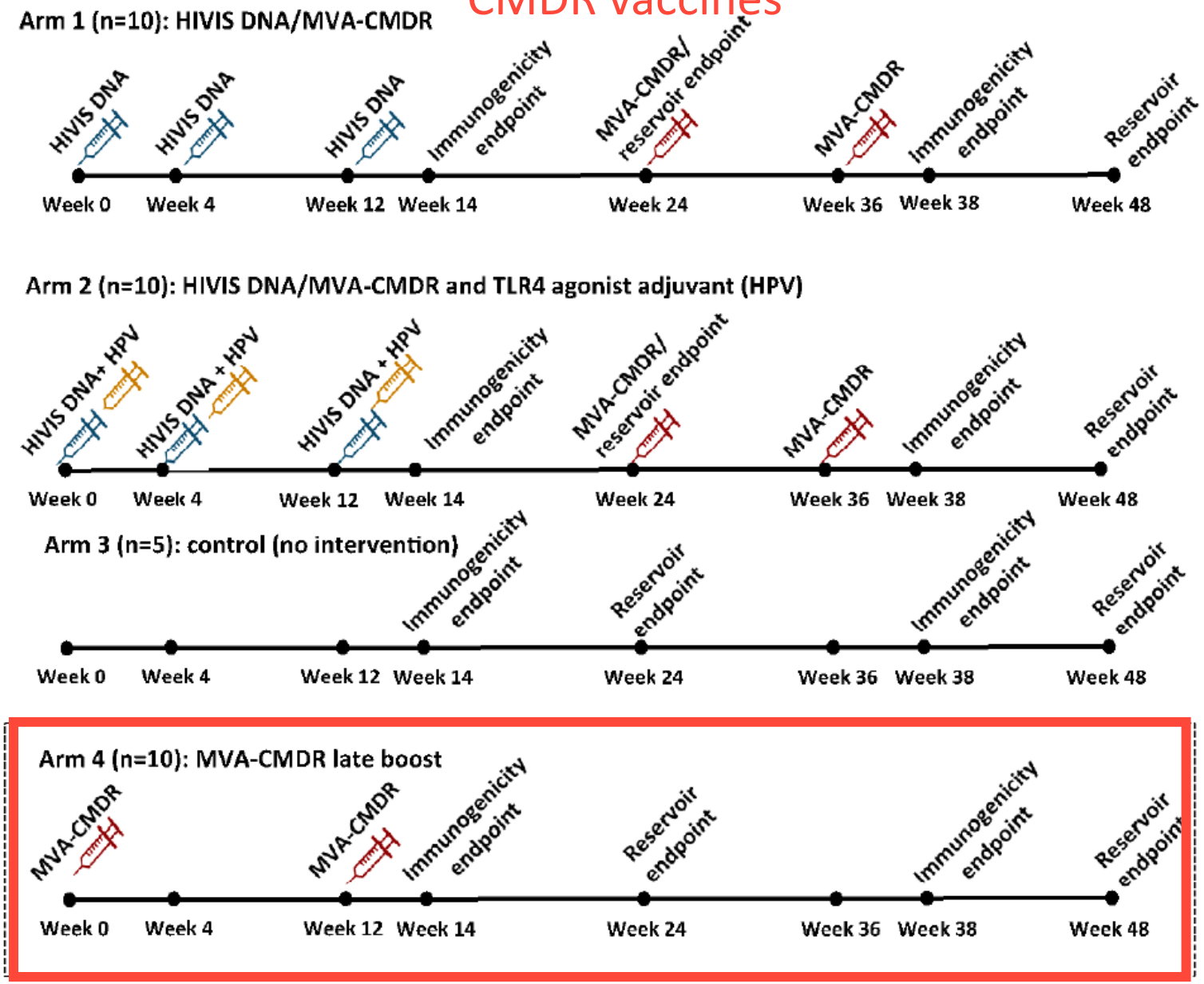
INDUCTION OF CELLULAR AND HUMORAL IMMUNITY BY DNA VACCINATION



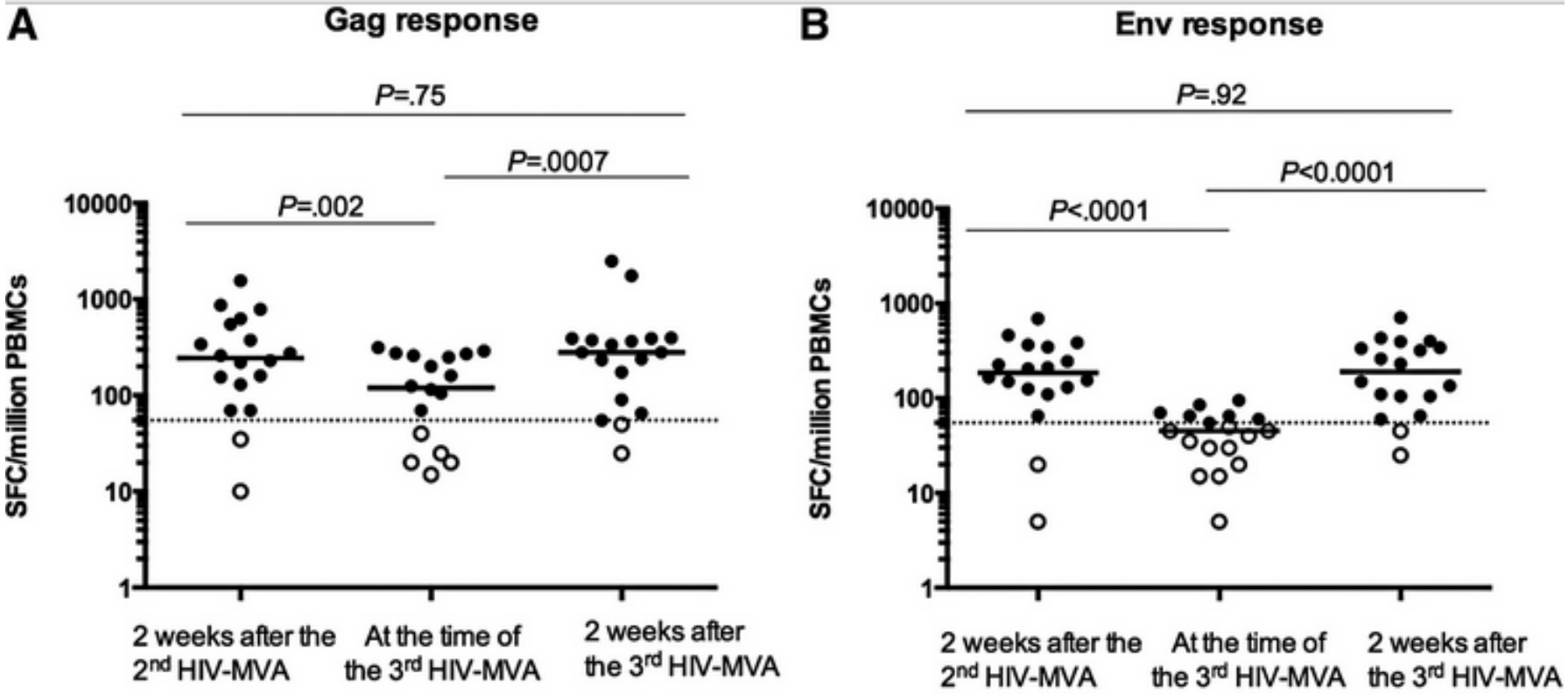
Kutzler and Weiner. DNA Vaccines: Ready for Prime Time? *Nature Reviews Genetics* Vol.9:1-13. 2008

The U01 grant.

Targeting HIV reservoirs in children with HIVIS DNA and MVA-CMDR vaccines



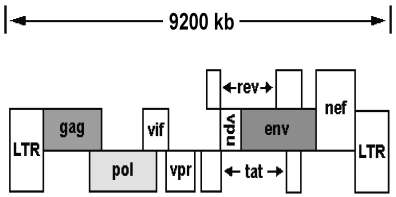
EVIDENCE FOR LATE MVA BOOSTING IN PREAVIUSLY HIVIS-DNA VACCINE VACCINATED INDIVIDUALS



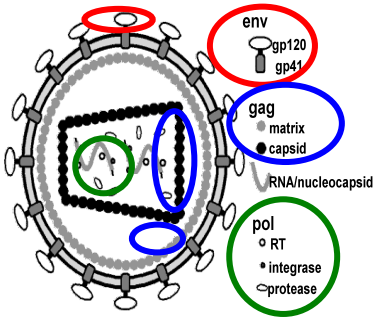
IFN-Y ELISPOT HIV specific responses.

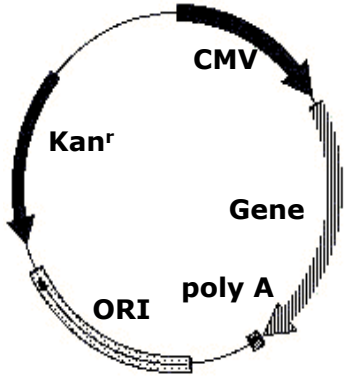
Joachim A et al, *AIDS research and human retroviruses*. 2017.

ARM 4 → PEDVAC STUDY



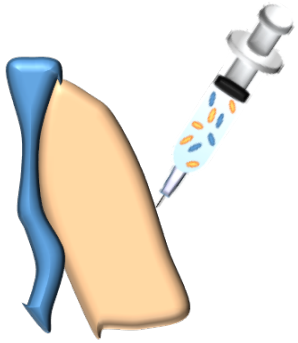
HIV-1 genome





pKCMV

Gag A, B ed mutRT



Env A, B, C e Rev B

W -4	W -2	W 0	W 4	W 12	W 16	W 20	W 36	W 40	W 48	W 60	W 72	W 84	W 96	W 120	W 156

ART

PATIENT DATA AT ENROLMENT

	Controls	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

RESULTS FROM PEDVAC STUDY

Safety

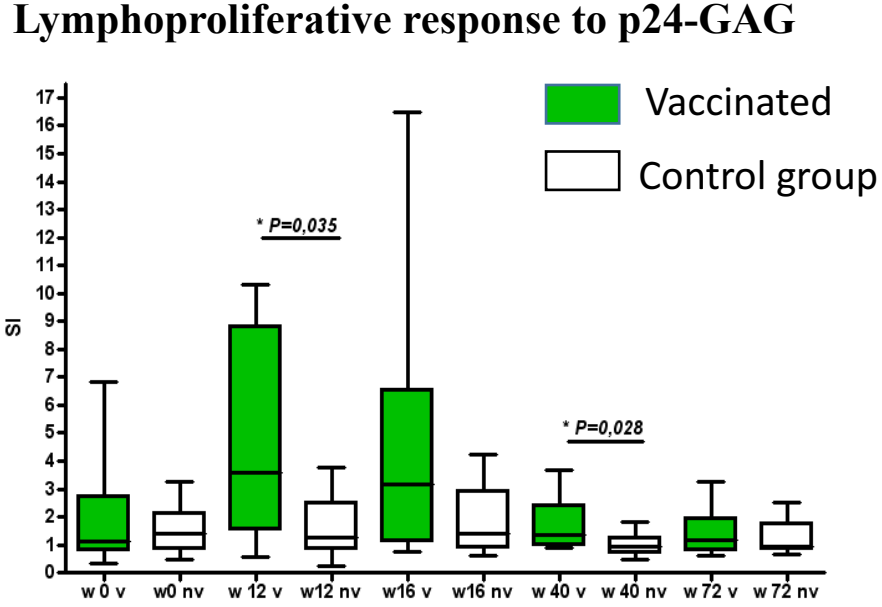
Subjects reporting solicited adverse reactions within 7-days after each vaccination

	1st DNA vaccination	2st DNA vaccination	3st DNA vaccination	4thDNA vaccination
Local	6/10 (60%)	5/10 (50%)	4/10 (40%)	3/10 (30%)
Systemic	6/10 (60%)	2/10 (20%)	5/10 (50%)	4/10 (40%)
Both	3/10 (30%)	1/10 (10%)	3/10 (30%)	1/10 (10%)

- **CD4+ T-cell counts remained stable**

- **No children experienced virological failure**

Immunogenicity



Palma P. et al, *PLOSone* 2014

PEDVAC STUDY: THE FIRST AND UNIQUE TRIAL WITH HIVIS VACCINE IN HIV INFECTED CHILDREN

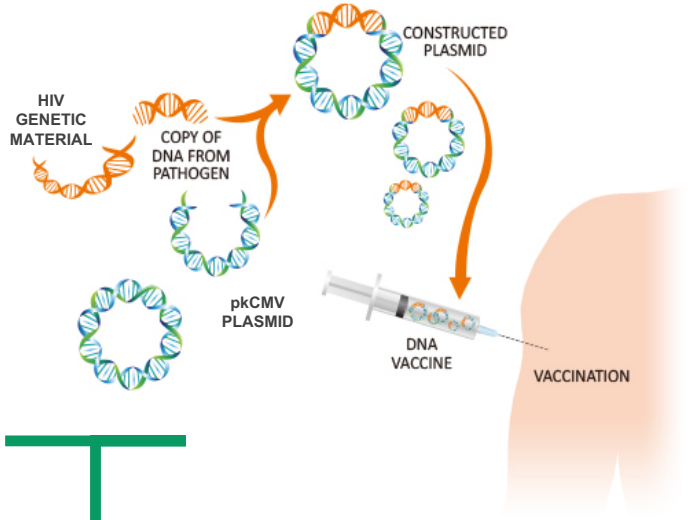
	Infant (0–6 months)				Child (6–16 years)
	PACG 230[72]	PACTG 326[73]	PedVacc 001[74]	PedVac 002[75]	PedVacc[76]
Vaccine type	Prophylactic	Prophylactic	Prophylactic	Prophylactic	Therapeutic
Vaccine compounds	rgp120 (MN) + adjuvant (alum/MF-59)	vCP1452 ± rgp120	MVA.HIVA (HIV-1 clade A gag p24/p17 + CD8 T-cell epitope)	MVA.HIVA (HIV-1 clade A gag p24/p17 + CD8 T-cell epitope)	HIVIS DNA (HIV-1 subtypes A, B, and C, encoded env, rev, gag, and RT)
Number of patients	188	30	48	73	20
Population under study	Exposed infants	Exposed infants	Healthy infants	Exposed infants	Vertically HIV infected children
Study design	Multicentre, phase 1/2, randomised, placebo-controlled study	Multicentre, phase 1/2, randomised, double blinded, placebo-controlled study	Single centre, phase 1, open-label, randomised, no treatment controlled study	Single-site phase 1/2, open-label, randomised-controlled trial	Phase 1/2 open-label controlled, randomised trial
Schedules	Birth and ages 2 or 4, 8, and 20 weeks	Birth and ages 4, 8, and 12 weeks	Aged 20 weeks	Aged 20 weeks	Week 0, 4, 12 with a boosting dose at week 36
Immunogenicity	Induce robust, durable env-specific IgG responses, including anti-V1V2 IgG; higher anti-V1V2 IgG responses in infant recipients of rgp120 (MN) + MF59 than in adult recipients of RV144[77]	Induce robust, durable env-specific IgG responses, including anti-V1V2 IgG	Did not alone induce sufficient HIV-1-specific responses	Not sufficiently immunogenic to induce HIV-1-specific, interferon-γ-producing T cells	Higher HIV-specific cellular immune responses were noted transiently to gag compared with age-matched control group; lymphoproliferative response to the gag virion antigen (HIV-1 MN) were higher in children than in adults[78]

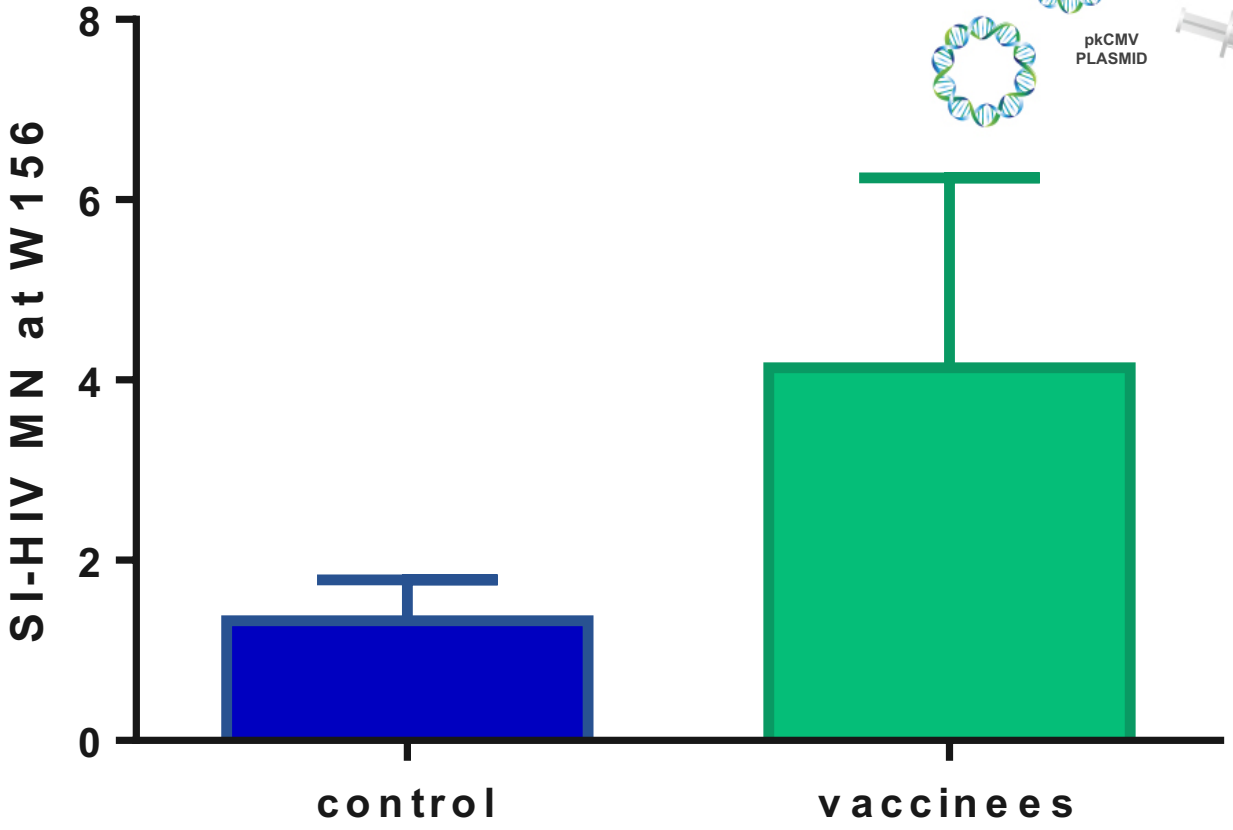
rgp120=recombinant gp120. vCP1452=HIV-1 canarypox vaccine 1452. MVA=modified vaccinia virus Ankara. HIVIS DNA=multiclade multigene HIV DNA vaccine. RT=reverse transcriptase.

Table: **HIV vaccine studies in paediatric settings**

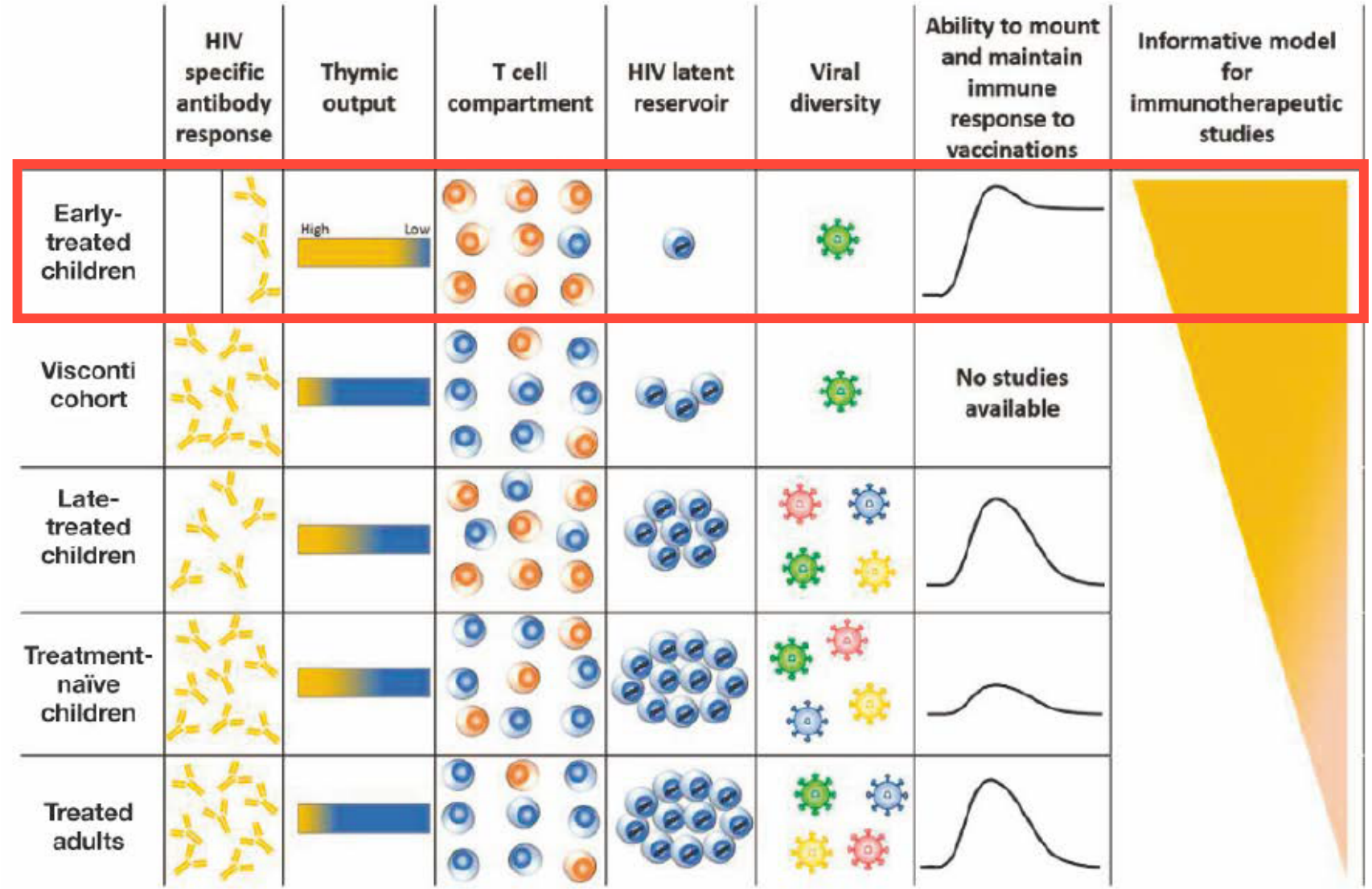
Klein N et al. Lancet *Lancet Infect Dis.* 2015

LONG TERM LYMPHOPROLIFERATIVE RESPONSES (LPR) PERSIST OVERTIME IN VACCINEES GROUP AND ARE DETECTABLE AFTER 156 WEEKS FOLLOW-UP

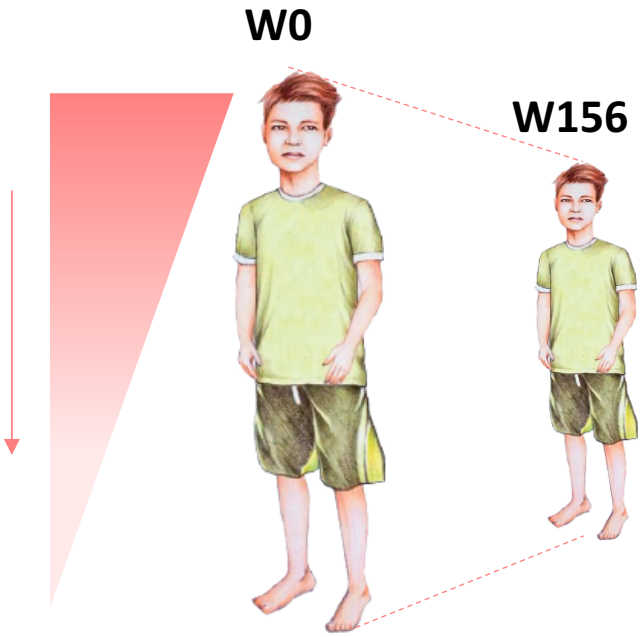


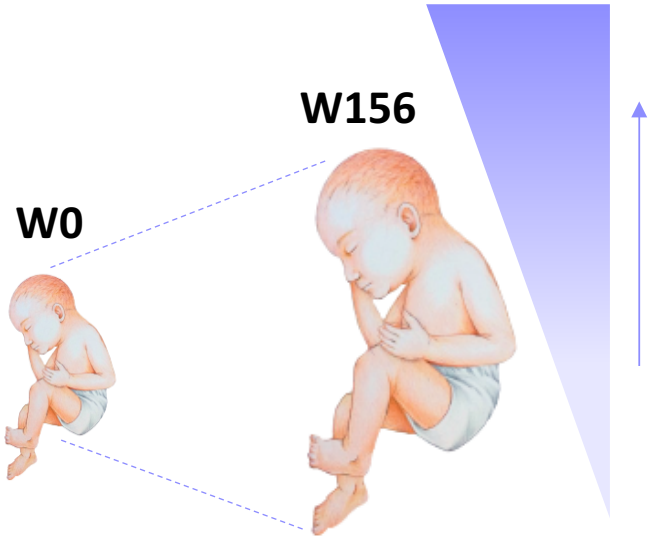


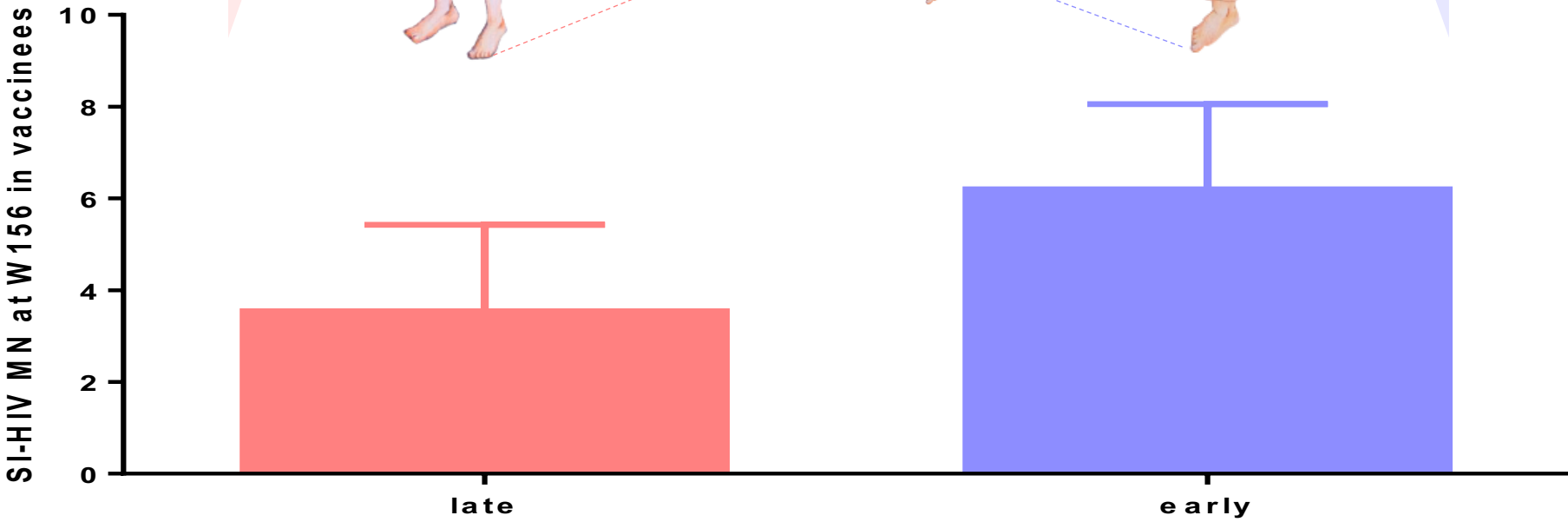
THE UNIQUENESS OF THE EARLY TRATED CHILDREN



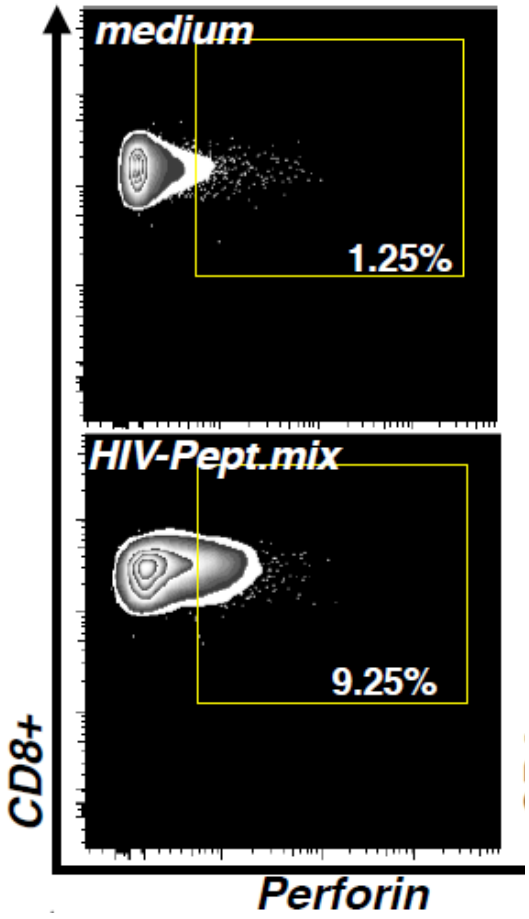
LONG TERM LYMPHOPROLIFERATIVE RESPONSES (LPR) IN VACCINEES IS HIGHER IN EARLY TREATED CHILDREN THAN IN LATE TREATED ONES

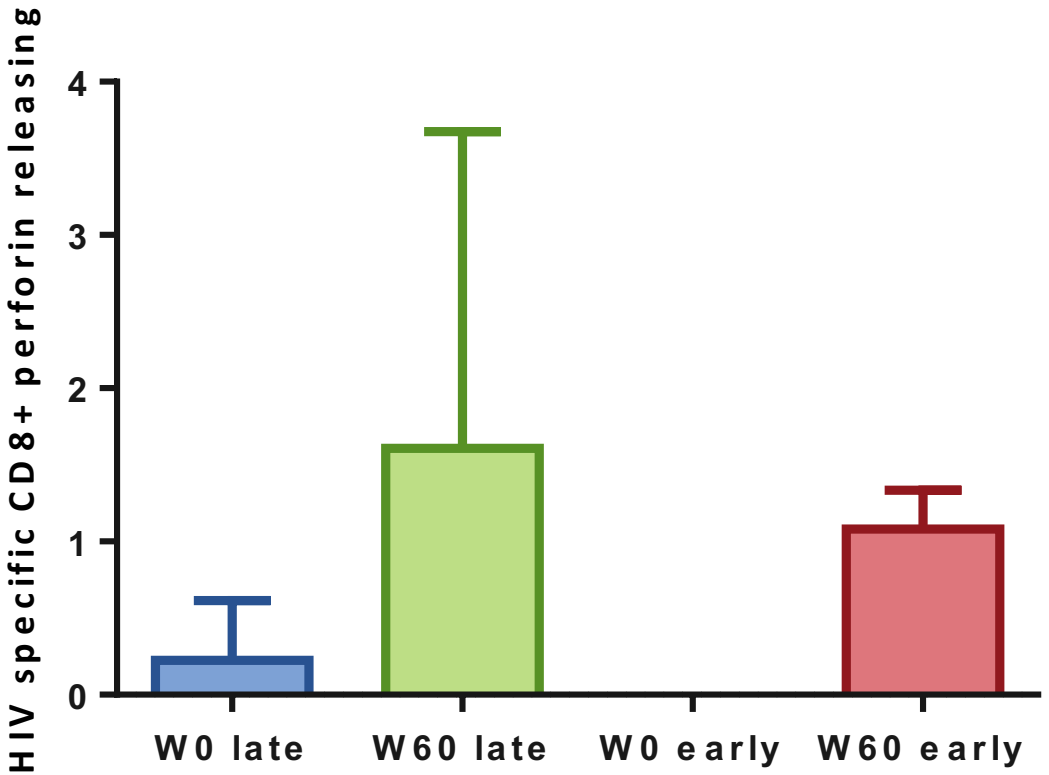




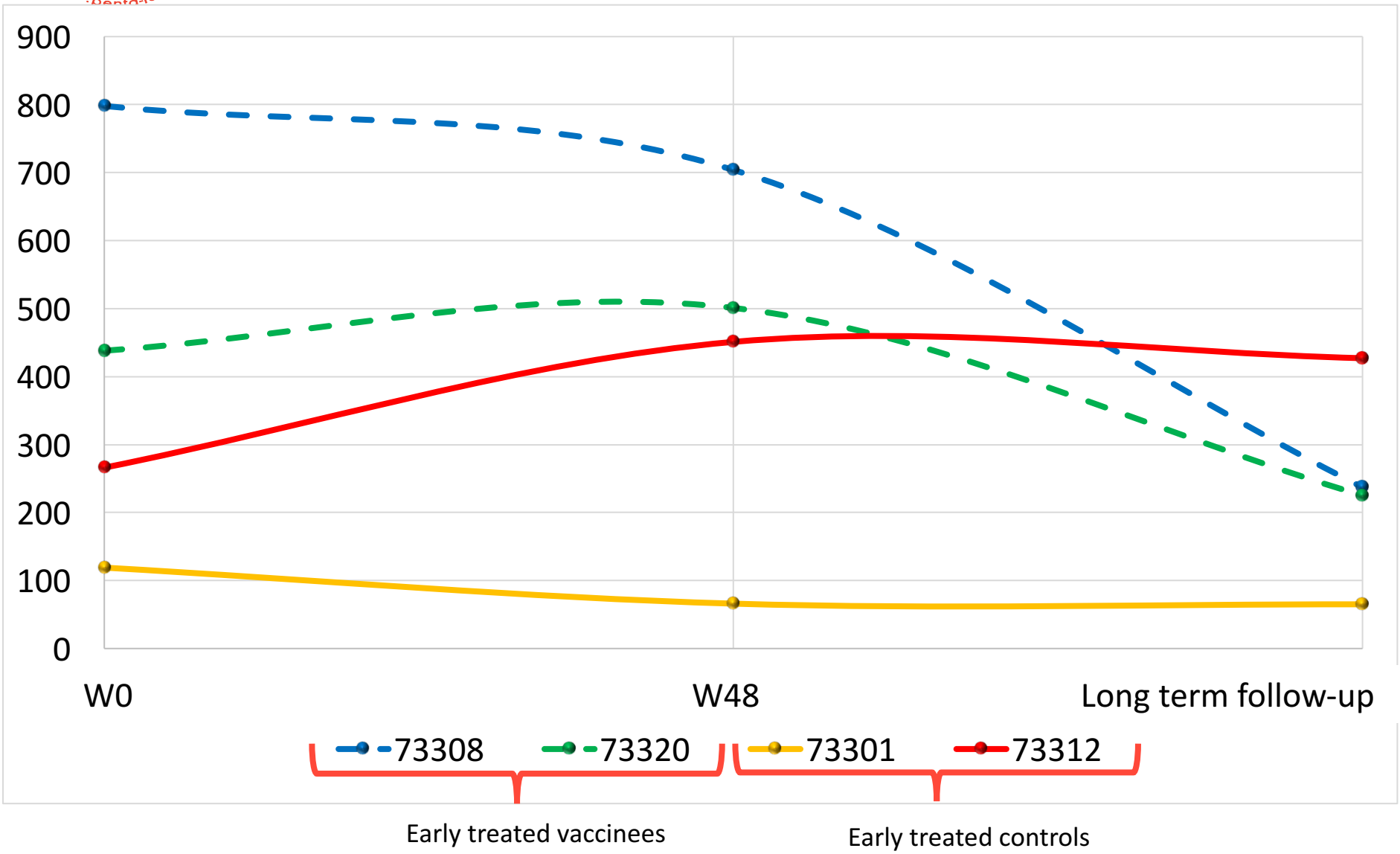


HIVIS ELICIT HIV-SPECIFIC CD8+ PERFORIN RELASING IN EARLY TREATED CHILDREN

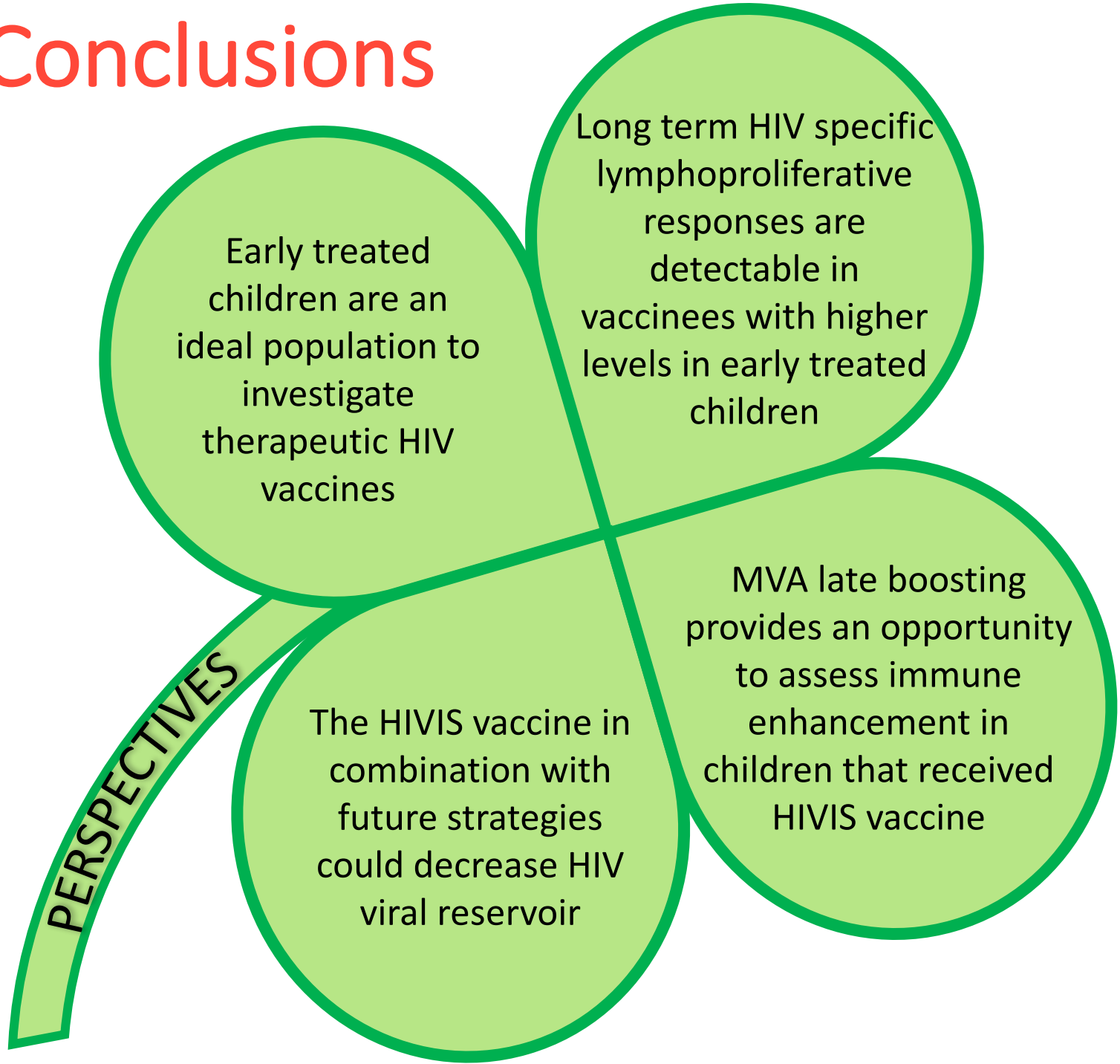




HIV-DNA DYNAMICS IN EARLY TREATED VACCINEES AND CONTROLS



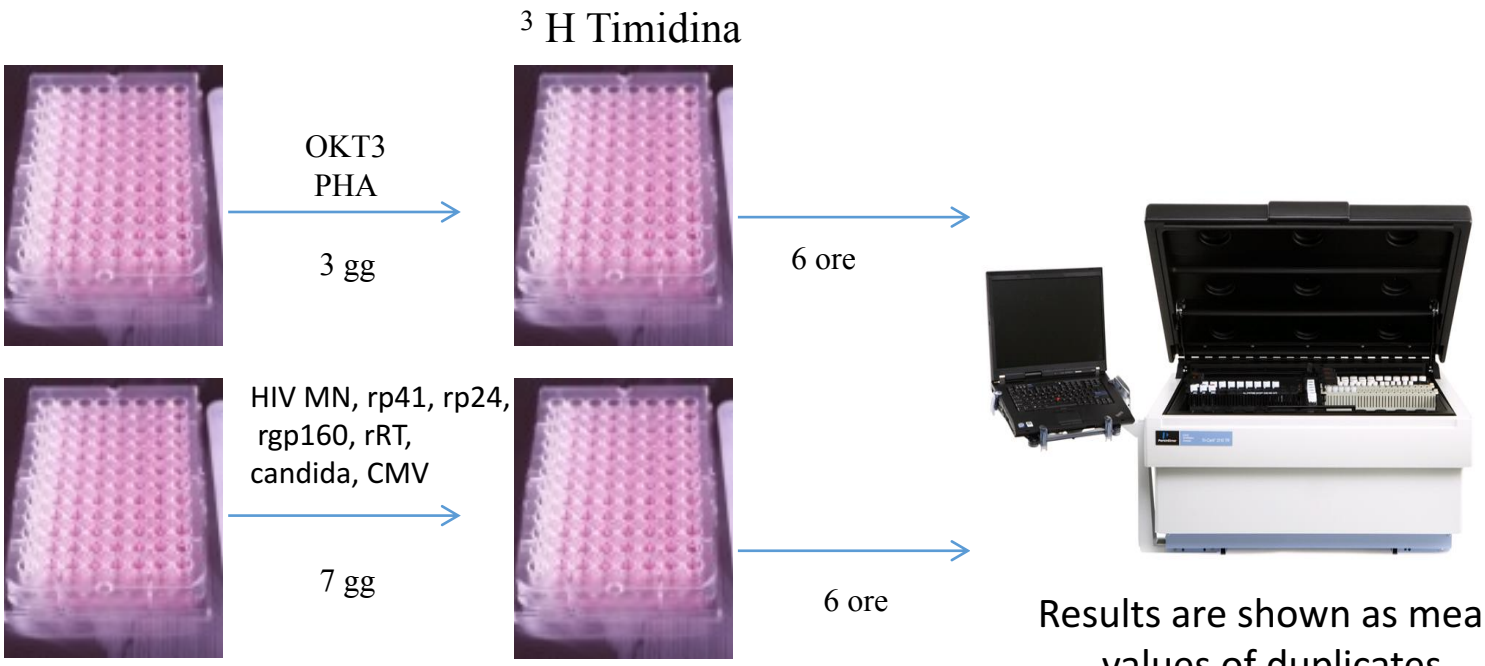
Conclusions



THANKS


Padiglione Giovanni Paolo II
Dipartimento Pediatrico Universitario Ospedaliero
Cattedra di Pediatria
Scuola di Specializzazione in Pediatria

Lymphoproliferation assay

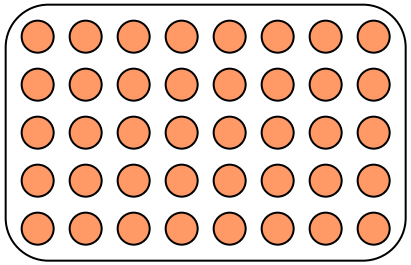


Results are shown as mean values of duplicates and are expressed as counts per minute

Stimulation index (SI): the ratio between the average counts of PBMC stimulated with antigen and the negative control. SI was considered as positive when ≥3

Intracellular Cytokine Staining Assay

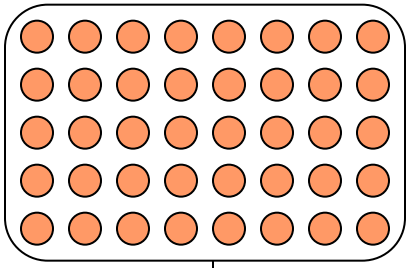
Heparinized fresh whole blood



Anti CD49d e anti CD3+
Protein Pool RT, p17/24 Clade B,
P17/24 Clade C, gp140 Clade C,
gp140 Clade A

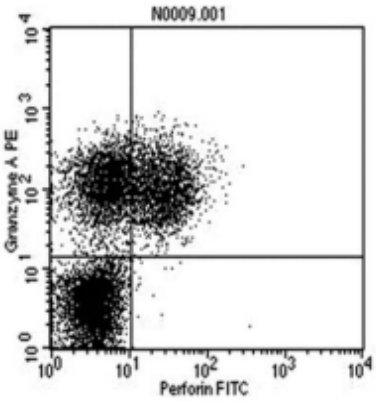
Incubate 16h

Brefeldina A

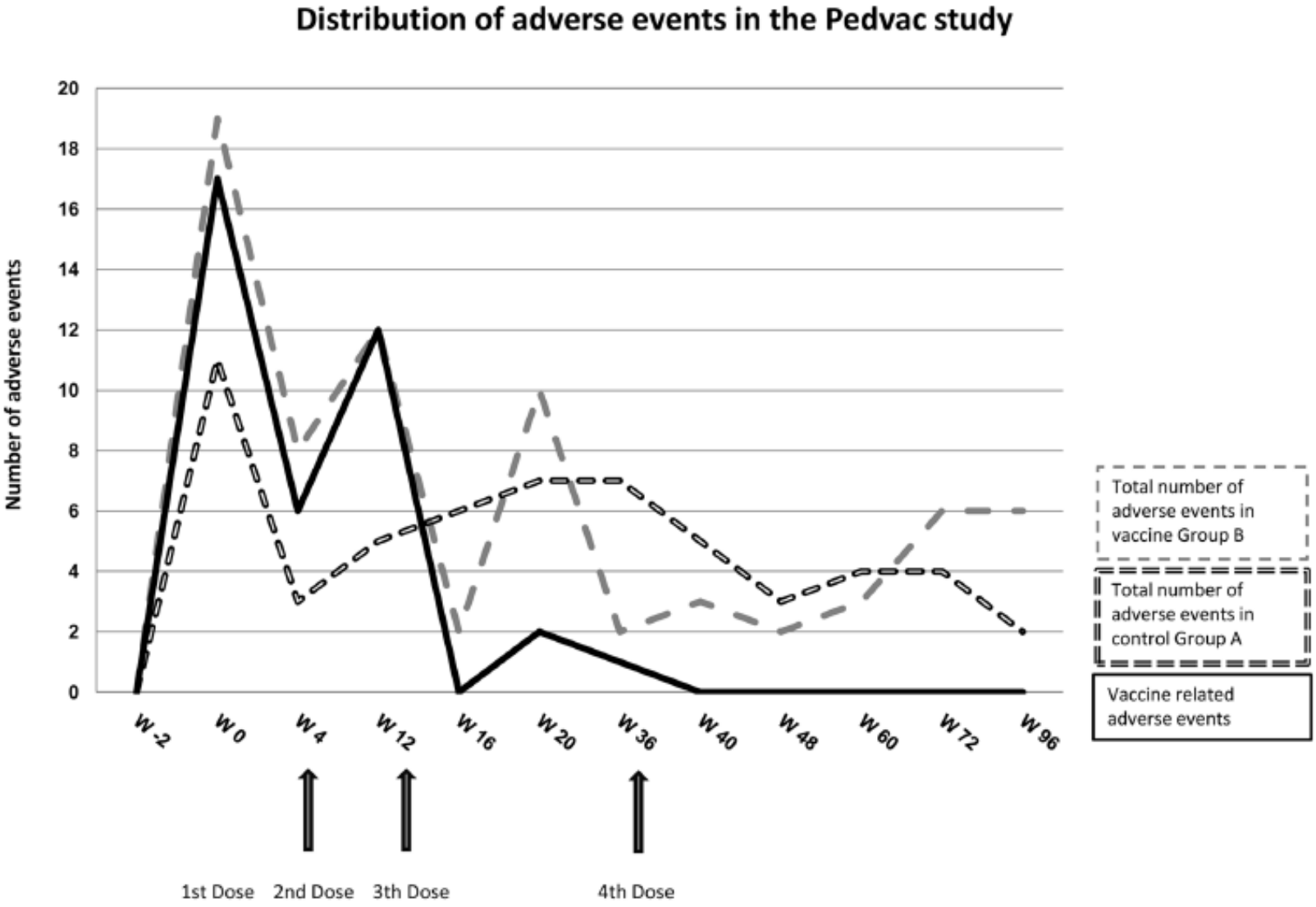


14 h

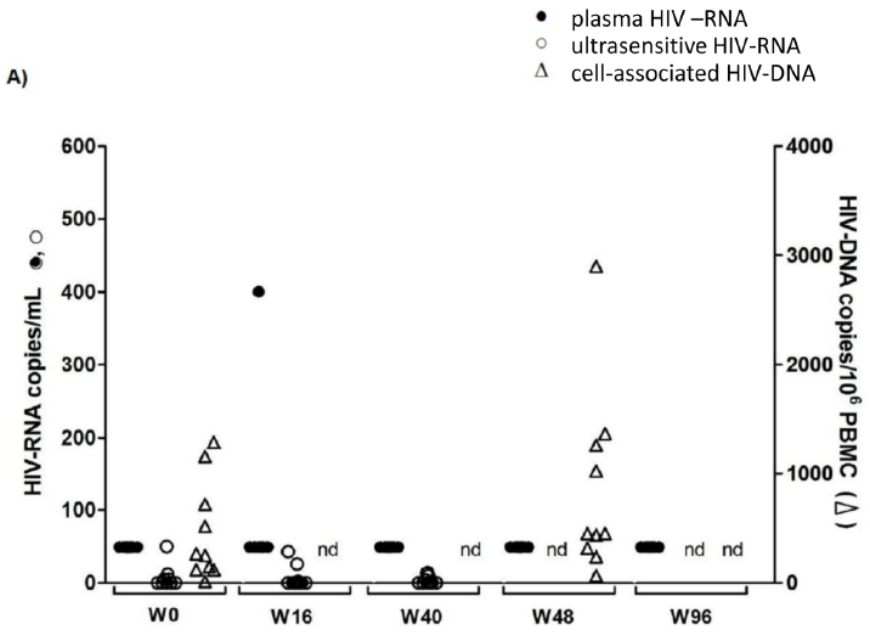
Anti CD3+,
anti CD4+,
anti CD8+

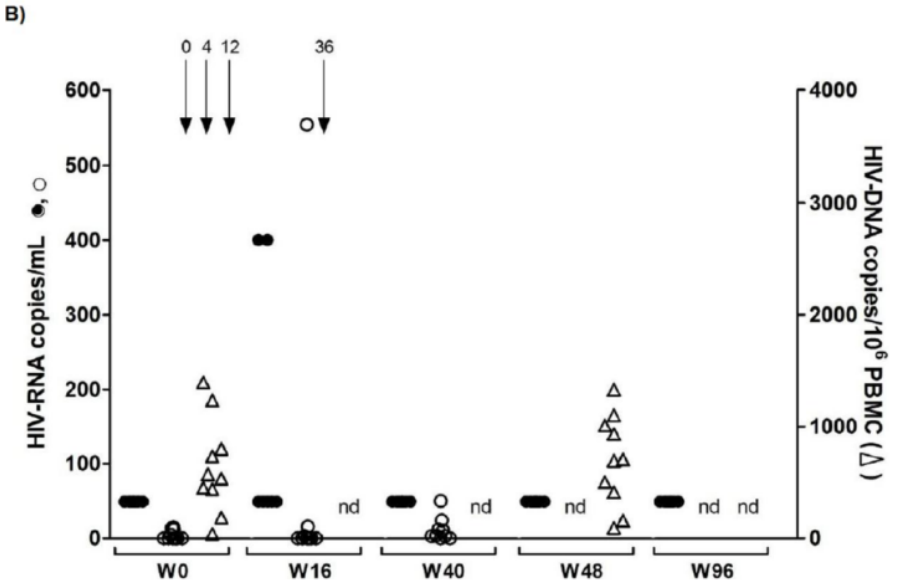


- Formaldeide
- Siero bovino 1%
- IFNγ

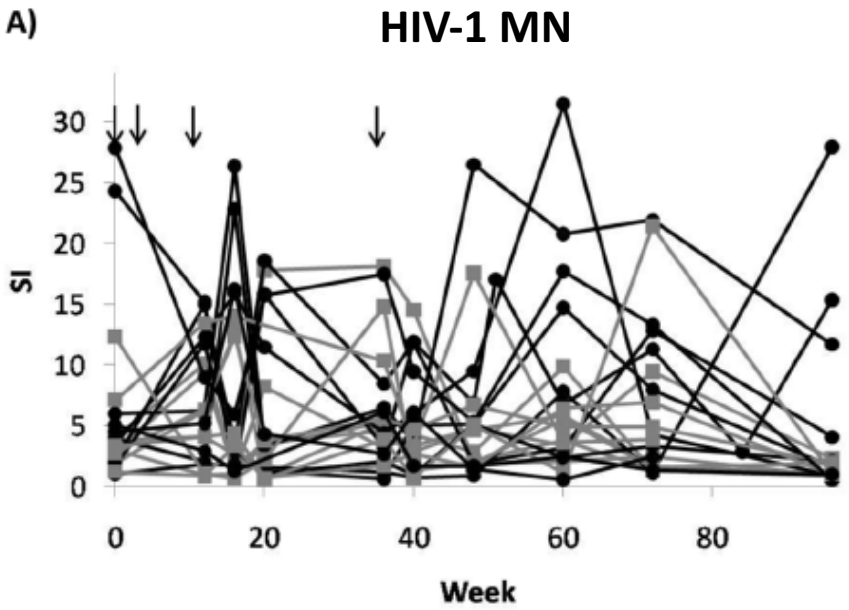

Distribution of adverse events in the Pedvac study
Number of adverse events
20
18
16
14
12
10
8
6
4
2
0
W -2
W 0
W 4
W 12
W 16
W 20
W 36
W 40
W 48
W 60
W 72
W 96
1st Dose
2nd Dose
3th Dose
4th Dose
Total number of adverse events in vaccine Group B
Total number of adverse events in control Group A
Vaccine related adverse events

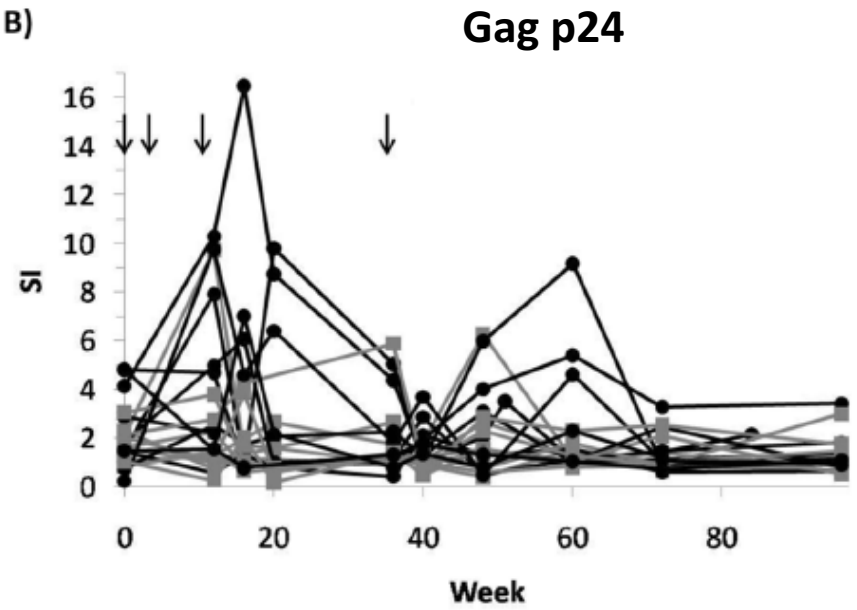
VIRAL DYNAMIC

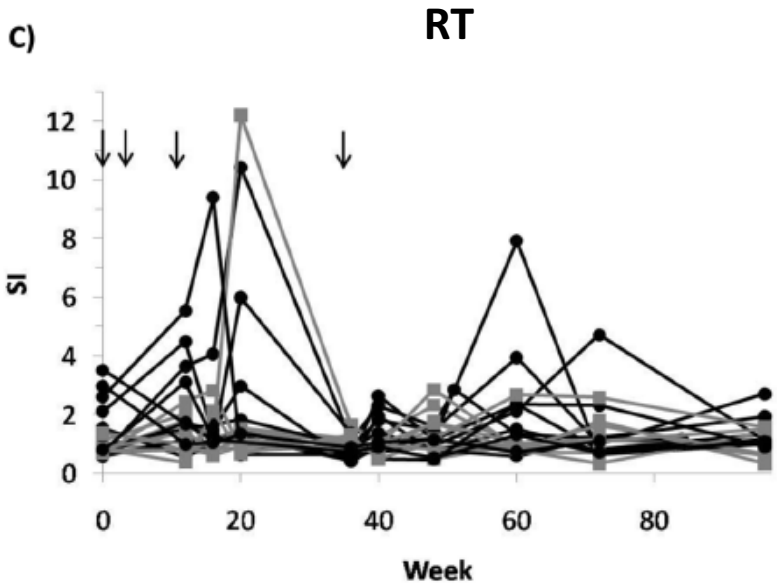




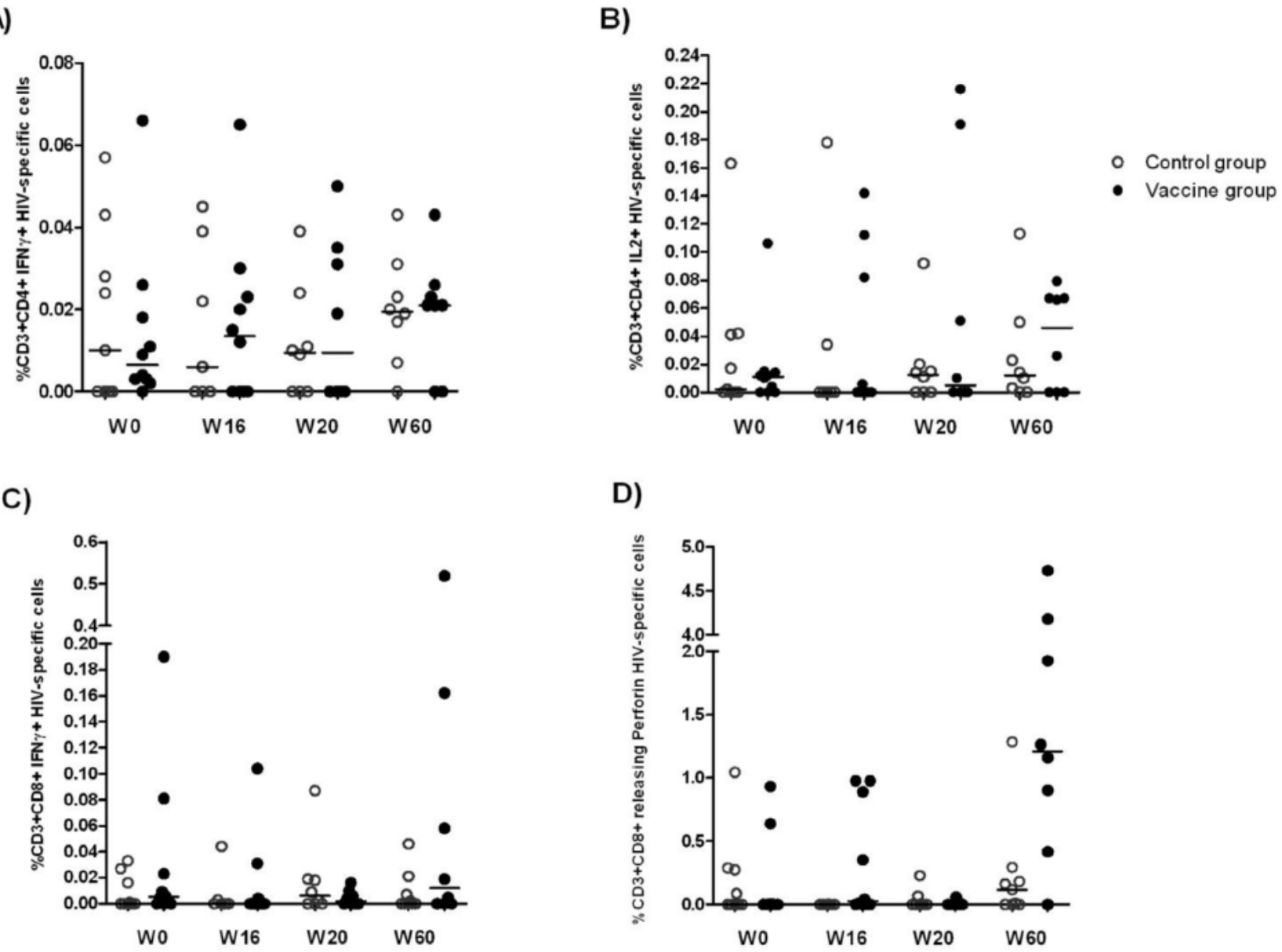
LYMPHOPROLIFERATIVE RESPONSES



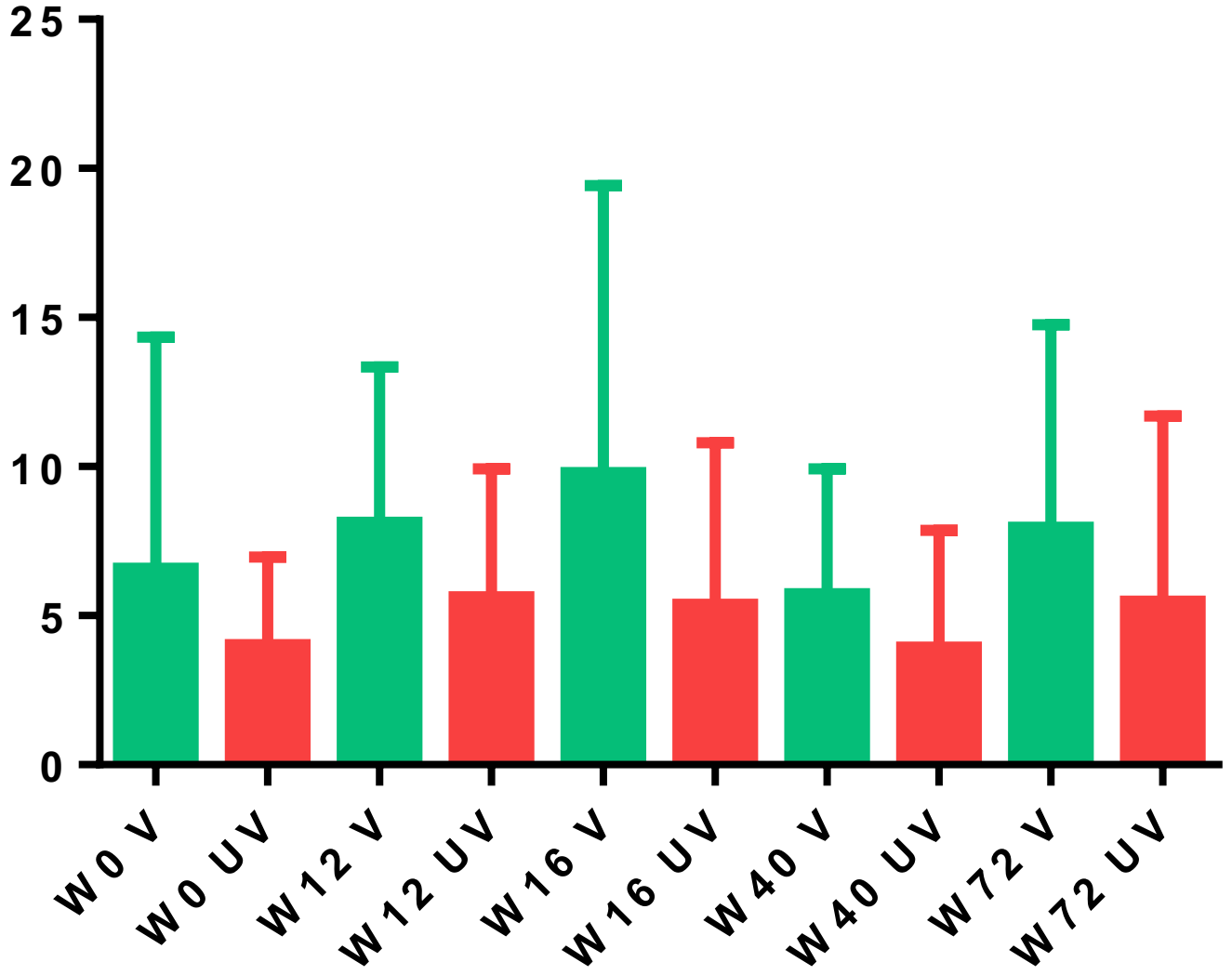




HIV-SPECIFIC CD4+ AND CD8+ T-CELLS ANALYZED BY ICS



LYMPHOPROLIFERATIVE RESPONSE TO MN



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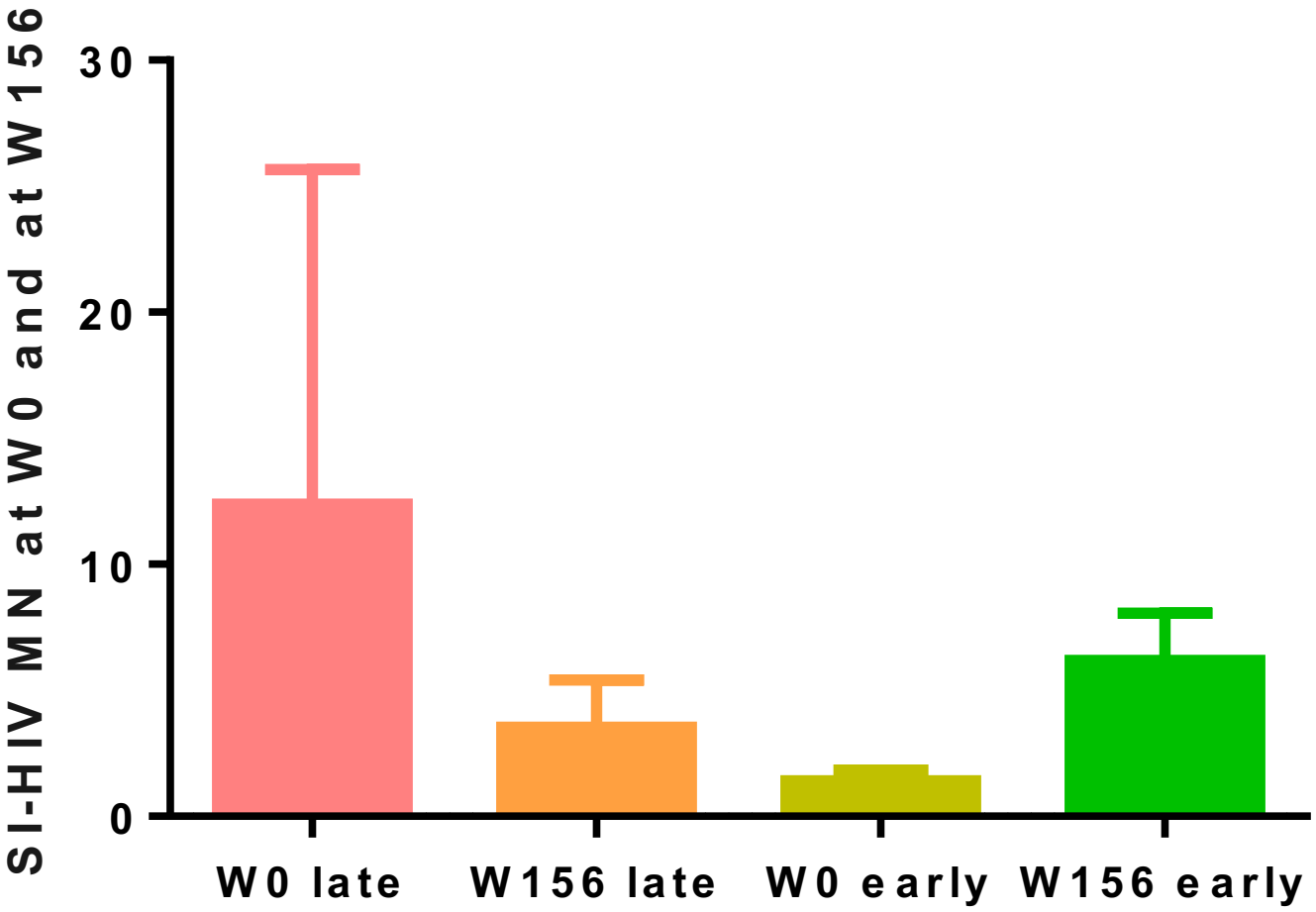
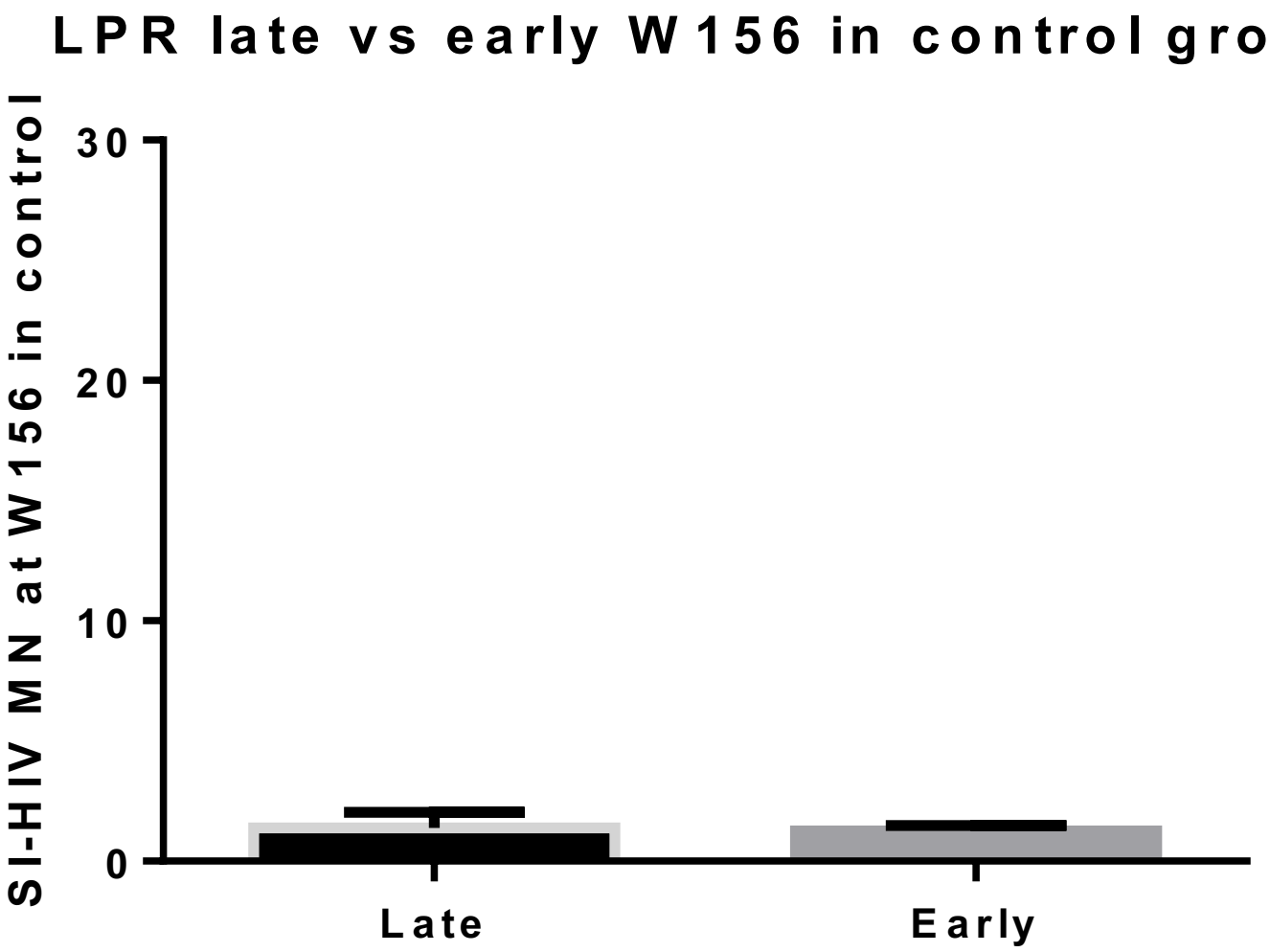


LONG TERM LYMPHOPROLIFERATIVE RESPONSES (LPR) IN CONTROL: NO DIFFERENCE BETWEEN LATE AND EARLY



THE EFFECT OF HIVIS DNA VACCIN ON TOTAL HIV DNA