The “window of opportunity”: harnessing the pediatric immune landscape for life long vaccine-elicited protection

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Neonatal immune development

Infant humoral immunity development

- Transferred maternal IgG
- Transient IgG deficiency
- IgM
- IgG
- IgA
- Th1
- Treg
- Th2
- Early B cell development

Birth 2 4 6 12 24 36 month

Weaning
Frequent opportunities for pediatric vaccine dosing

Vaccination Schedule 2016

<table>
<thead>
<tr>
<th>Disease</th>
<th>Vaccine</th>
<th>Birth</th>
<th>6 weeks</th>
<th>10 weeks</th>
<th>14 weeks</th>
<th>6 months</th>
<th>9 months</th>
<th>12 months</th>
<th>15 months</th>
<th>18 months</th>
<th>6 years</th>
<th>9 &amp; 10 years</th>
<th>12 years</th>
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<td>Polio</td>
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<td>Diphtheria, Tetanus, Pertussis, Polio, Haemophilus Influenza, Hepatitis B</td>
<td>Hexaxim OR Infarrix Hexa</td>
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<td>Pneumococcal</td>
<td>Prevenar 13 OR Synflorix</td>
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<td>Rotavirus</td>
<td>RotaTeq OR Rotarix</td>
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<td>Measles</td>
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<td>Measles Mumps Rubella</td>
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<td>Hepatitis A</td>
<td>AVALIX® Avaxim®</td>
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<td>Chickenpox</td>
<td>Varilrix</td>
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<td>Tetanus, Diphtheria + Pertussis, Polio</td>
<td>Td OR ADACEL QUADRA®</td>
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<tr>
<td>Human Papilloma Virus</td>
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<tr>
<td>Influenza</td>
<td>VAXIGRI®</td>
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<tr>
<td>Respiratory Syncitial Virus</td>
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**State Epi Vaccines**: These vaccines are available free from Government supplied clinics

**Recommended Optional Vaccines**: Some of the vaccines in this schedule are only available from private clinics

New bacterial vaccine recommended due to increased risk of importation polio

If no HepB at birth must be given at 6, 12 & 16 weeks

New meningococcal vaccine. Must not be given together with any other vaccine.

Rotavirus will be phased out in 2014/15 and replaced by Measbio.

Can be given at 9 months if no single measles vaccine available.

For individuals 2-55 years administer one dose

Can be given at 12 years if not given at 6 years.
Opportunity to direct the microbiome development for optimal vaccine-elicited immune responses.
B cell receptor somatic hypermutation and CDR3 lengths rapidly change in first year of life

Somatic hypermutation

IgG CDR3 length

Li Yin, UF
Johns Sleasman, Duke
Maureen Goodenow, NIH
Kristina DeParis, UNC
Pediatric HIV Env immunization to induce broad responses that persist into adolescence/adulthood
Pediatric HIV immunization for lifelong immunity

Modeling studies suggest that a vaccine that protects prior to sexual debut would significantly reduce both adolescent/adult and subsequent infant HIV-1 infections.
High coverage of multi-dose vaccines initiated in infancy (U.S.)

Vaccine-specific coverage* among children 19-35 months, National Immunization Survey, 1994-2014

- Infant HepB vaccine (3 doses)
- Adolescent HPV vaccine (females, 3 doses)
Persistence of Env vaccine-elicited responses >2yrs in rgp120/MF59 pediatric vaccine trials

- **Durable responses >2 yrs to rgp120/MF59**

- 22 fold higher V1V2 IgG response in Env/MF59 immunized infants vs RV144 vaccinees

- 56% of infants still had responses at **2 years**

Fouda et al, JID, 2014
Isolation of HIV Env-reactive mAbs from a Chiron rgp120/MF59 vaccinated infant

46 gp140 positive memory B cells

37 mAb pairs

24 gp140 reactive mAbs, all IgG1

0 gp41 reactive

20 gp120 reactive mAbs

1 V3 reactive mAb

12 CD4 bs reactive mAbs (YU2 core/not mutant)

7 mAbs fine specificity undetermined

Giny Fouda, Tony Moody
Comparison of infant and adult vaccine-elicited Env-specific mAbs at peak response

**Infant:** Chiron SF2 gp120 + MF59, 4 doses over 6 mo

**Adult:** GSK PRO HIV002 clade B gp120 W6.10/Nef-Tat + ASO1B, 4 doses over 6 mo

Giny Fouda
Moody et al, JV, 2012
Infant immune landscape and bNAb development

- HIV-1-infected infant frequently produce bnAbs (Goo and Overbaugh et al. Nature Medicine; 2014; Goulder et al CROI 2016)

- Infant nAbs have low SMH (Simonich and Overbaugh et al. Cell 2016)
B cell lineage design vaccines and the pediatric immune landscape

CH505 Envelopes selected from individual with broad neutralizing activity as vaccine immunogens

Collaboration between: Duke CHAVI-ID, IMPAACT, IDRI, HVTN

(Williams, Han, Haynes et al., In preparation)
### Study design of IMPAAACT CAP523

Immunization of HIV-exposed uninfected infants with CH505 Env immunogens (24 participants per group)

1) Sequential immunization with a single Env immunogen
2) Sequential immunization with combination of Env immunogens

<table>
<thead>
<tr>
<th>Group</th>
<th>Birth</th>
<th>2 wks</th>
<th>2 mo</th>
<th>4 mo</th>
<th>9 mo</th>
<th>18mo, 2yrs, 3yrs, 4yrs</th>
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<tbody>
<tr>
<td>G 1</td>
<td>TF</td>
<td>w53</td>
<td>w78</td>
<td>w100</td>
<td>w100</td>
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<td>w53, 78</td>
<td>w78, 100</td>
<td>w100</td>
<td>w 100</td>
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<tr>
<td>G 3</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
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</table>
What are the differences in the adult and infant antibody responses to the same HIV Env vaccine?
**Adult and infant HIV rgp120 vaccine study population**

**PACTG 230:** HIV exposed infants vaccinated with either rgp120 (SF-2)/MF-59 (Chiron) or rgp120 (MN)/alum (VaxGen)
- 4 vaccine doses between **birth and 20 weeks** of age

**AVEG 201:** Uninfected adults with different exposure risk immunized either with the Chiron or VaxGen vaccine
- 4 vaccine doses between **0 and 52 weeks**

<table>
<thead>
<tr>
<th>Study</th>
<th>Age group</th>
<th>Placebo</th>
<th>rgp120/MF59</th>
<th>rgp120/alum</th>
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</thead>
<tbody>
<tr>
<td>AVEG 201</td>
<td>Adults</td>
<td>10</td>
<td>42</td>
<td>49</td>
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<tr>
<td>PACTG 230</td>
<td>Infants</td>
<td>16</td>
<td>45</td>
<td>47</td>
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</table>
Magnitude of Env-specific IgG is higher in rgp120/MF59 vaccinated infants (wk 24) than adults (wk 54)

**MN gp120**

<table>
<thead>
<tr>
<th>Frequency of responders at peak immunogenicity</th>
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<tbody>
<tr>
<td><strong>Placebo</strong></td>
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<tr>
<td>adults</td>
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<tr>
<td>MN gp120</td>
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<tr>
<td>gp70 B case V1V2</td>
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</tbody>
</table>
Infant rgp120/MF59 ab responses remain higher than peak adult response 6 mo after last vaccine dose

<table>
<thead>
<tr>
<th>Frequency of response</th>
<th>Placebo adults</th>
<th>Placebo infants</th>
<th>rgp120/MF59 adults</th>
<th>rgp120/MF59 infants</th>
<th>rgp120/alum adults</th>
<th>rgp120/alum infants</th>
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</thead>
<tbody>
<tr>
<td>MN gp120</td>
<td>0</td>
<td>8</td>
<td>69</td>
<td>77</td>
<td>85</td>
<td>68</td>
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<tr>
<td>gp70 B case V1V2</td>
<td>0</td>
<td>0</td>
<td>38</td>
<td>95</td>
<td>2</td>
<td>27</td>
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</table>

Giny Fouda
Youyi Fong
rgp120/MF59 induces a higher proportion of V1V2 IgG3 responders in infants than in adults.

gp70 B case A V1V2 IgG

<table>
<thead>
<tr>
<th></th>
<th>Infant Chiron</th>
<th>Adult Chiron</th>
<th>Infant VaxGen</th>
<th>adult VaxGen</th>
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<tbody>
<tr>
<td>Percent responders at week 0</td>
<td>10</td>
<td>20</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Percent responders at week 24/54</td>
<td>40</td>
<td>40</td>
<td>5</td>
<td>5</td>
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</table>
Summary I – Infant vs adult HIV Env vaccine immunogenicity

- Infants vaccinated with rgp120/MF-59 have higher magnitude gp120 and V1V2 IgG responses compared to adults at peak immunogenicity and 6 months later.

- Infant vaccination with rgp120/MF-59 induces a higher frequency of V1V2 IgG3 responders than in adults.

- Infant rgp120-induced antibody responses are durable for >2 yrs.
What is the optimal HIV Env viral vector prime-boost regimens for infants?

Sallie Permar, MD, PhD
Koen Van Rompay, DVM
Kristina De Paris, PhD
Preclinical MVA-rgp120 vaccine optimization in infant rhesus monkeys

- Env Protein Only (n=5)
- Conventional (n=5)
- Co-Administration (n=5)
- Extended Interval (n=5)

Legend:
- MVA-HIV Env : IM
- MVA-SIV gag/pol : IM
- HIV Env Protein : IM/IN

 NX
Infant monkey vaccine-elicited plasma gp120-specific IgG kinetics

Consensus 6 gp120 IgG Plasma Concentration

Early Response

Persistence

Extended Interval
Protein Only
Co-Administration
Conventional

Weeks (Age)

ng/mL

0 1 2 3 4 5 6

Weeks

= Shorter Interval Immunizations

= Extended Interval Immunizations
Infant monkey vaccine-elicited plasma V1V2 IgG responses

Clade C V1V2 Epitope Plasma IgG

Exact Wilcoxon rank-sum test
**Infant monkey MVA/rgp120 HIV vaccine optimization**  
**tier 1 neutralizing antibodies: MW965, Clade C**

<table>
<thead>
<tr>
<th>Date</th>
<th>Conventional</th>
<th>Co-Administration</th>
<th>Protein Only</th>
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<tr>
<td></td>
<td>45035 45042 45054 45081 45082</td>
<td>45038 45047 45069 45083 45091</td>
<td>45519 45521 45522 45532 45535</td>
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<tr>
<td>Wk 0</td>
<td>&lt;20 &lt;20 &lt;20 &lt;20 &lt;20</td>
<td>&lt;20 &lt;20 &lt;20 &lt;20</td>
<td>21 22 &lt;20 24 30</td>
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<tr>
<td>Wk 3</td>
<td></td>
<td>&lt;20 &lt;20 &lt;20 &lt;20</td>
<td>&lt;20 &lt;20 27 41 &lt;20</td>
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<td>Wk 6</td>
<td>&lt;20 &lt;20 &lt;20 &lt;20 &lt;20</td>
<td>118 345 51 359 &lt;20</td>
<td>384 57 1370 216 63</td>
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<td>Wk 8</td>
<td>205 548 29 112 90</td>
<td>829 163 279 1517 393</td>
<td>1948 1061 1198 412 659</td>
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<td>Wk 10</td>
<td>248 295 &lt;20 92 138</td>
<td>714 89 129 673 147</td>
<td>1350 1126 598 294 1593</td>
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<tr>
<td>Wk 12</td>
<td>318 226 29 85 218</td>
<td>314 425 107 60 58</td>
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<td>Wk 14</td>
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<tr>
<td>Wk 15</td>
<td>331 128 47 89 333</td>
<td>233 159 121 381 37</td>
<td>746 1205 297 146 1158</td>
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<td>Wk 20</td>
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<tr>
<td>Wk 24</td>
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**Neutralization ID$_{50}$ + Persistence**

Protein-only group achieved higher magnitude and durable tier 1 virus neutralization responses
Infant monkey MVA/rgp120 HIV vaccine optimization tier 1 neutralizing antibodies: MW965, Clade C

<table>
<thead>
<tr>
<th>Date</th>
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<tr>
<td></td>
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<td>Wk 0</td>
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<td>&lt;20</td>
<td>&lt;20</td>
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<td>Wk 6</td>
<td>118</td>
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<td>Wk 16</td>
<td>150</td>
<td>244</td>
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<tr>
<td>Wk 18</td>
<td>162</td>
<td>150</td>
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</table>

Extended vaccine intervals (q3->q6 weeks) may increase neutralizing Ab responses.
Infant monkey vaccine-elicited ADCC responses against vaccine and heterologous strain gp120

SHIV C = SHIV1157ipd3N4
Splenic and Oral Lymph Node T Follicular Helper Cells

**Spleen**

IL-4 Production in TFH Cells

![Graph showing IL-4 production in spleen with p=0.0079 comparison between Protein only, Conv., and Co-Administration groups.](image)

**Oral LN**

IL-4 Production in TFH Cells

![Graph showing IL-4 production in oral lymph nodes with p=0.0159 comparison between Protein only, Conv., and Co-Administration groups.](image)

Exact Wilcoxon rank-sum test
HIV gp120-Specific B cells in GI tract dependent on extended vaccine intervals/age

**Antigen-Specific B cells**

*Axillary LN*

*Rectal biopsies*

Normalized % gp120-Specific B Cells

**Exact Wilcoxon rank-sum test**
HIV Env-specific IgA in stool higher magnitude after extended vaccine intervals

Maximum gp120-specific IgA in Stool

Exact Wilcoxon rank-sum test
Harnessing the microbiome diversification of the infant GI tract for elicitation of optimal vaccine responses
Diversion of HIV-1 Env vaccine elicited immune responses by gut microbiota cross-reactive pre-existing antibodies

Williams et al, Science 2015
Infant rhesus monkey stool bacterial diversity over time

- **Week 0**
  - Predominant: Prevotella
  - Other: Succinivibrio, S24-7, Bifdobacterium, Megasphaera

- **Week 14**
  - Predominant: Prevotella
  - Other: Succinivibrio, S24-7, Bifdobacterium, Megasphaera

- **Week 24**
  - Predominant: Prevotella
  - Other: Succinivibrio, S24-7, Bifdobacterium, Megasphaera

- **Week 35**
  - Predominant: Prevotella
  - Other: Succinivibrio, S24-7, Bifdobacterium, Megasphaera
Bacterial taxa cluster in their kinetics of infant stool microbiome population.
Correlation of magnitude of vaccine-elicited humoral immune responses and bacterial taxa
Summary II – Infant vs adult HIV Env vaccine immunogenicity

- Infant immunization + microbiome manipulation may be a strategy to avoid “diverting” B cell lineages and promote protective B cell lineages

- Infants have robust and durable antibody responses to rgp120-MF59 immunization

- Extended interval infant prime-boost vaccination results in high GI tract ab responses

- Abundance of certain bacteria in the infant GI tract (Firmicutes) may be associated with the magnitude of B cell responses to infant HIV Env vaccination
Mother/infant NHP HIVRAD Collaborators

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Hannah Itell
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Olaf Mueller

Moody Laboratory
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Lawrence Armand
Whitney Binz
Thad Gurley
Tarra Von Holle
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Alexis Theime
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Jamie Peacock
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LSUHSC: Pam Kozlowski & lab

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David Martinez

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Elizabeth McFarland
William Borkowsky
Petronella Muresan

SCHARP
Youyi Fong

GSK
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Marguerite Koutsoukos

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Sanjay Phogat

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- Duke School of Medicine
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- UNC School of Medicine
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