VRC01 in Children and Adults

Barney S. Graham, MD, PhD
2015 HPTN and IMPAACT Annual Meeting
Arlington, VA
June 17, 2015
Clinical Use of HIV Antibodies

Prevention

• Breastfeeding Infants
• High risk young adults
• Discordant couples
• High risk MSM

Treatment

• Acute affect on viremia
• Treatment interruption/sparing
• Impact on viral reservoir
• Combined with ARV (functional cure)

Maximize Coverage (breadth)
Potent enough

Maximize potency
Avoid escape
Potential Targets for Neutralization

**N332 Glycan Supersite:**
- PGT121, PGT128
- 10-1074

**V1V2 Glycan:**
- PG9, PG16
- PGT141-145
- CAP256-VRC26.25
- PGDM1400

**CD4 Binding Site:**
- VRC01, PG04, CH31, 3BNC117, 12A12, VRC13, VRC01-LS, VRC07-523-LS, Z258-N6

**Trimer (gp120/41):**
- 8ANC195
- PGT151
- 35022

**gp41 MPER:**
- 2F5, 4E10
- 10e8

Huang et al. Nature 2014
## VRC01 Clinical Development

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>June: Initiated development of VRC01 as clinical product</td>
</tr>
<tr>
<td>2011</td>
<td>Jan 19: VRC01 Pre-IND meeting</td>
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<tr>
<td>2011</td>
<td>May 29: IRB Submission: VRC 601 [HIV Infected Cohort]</td>
</tr>
<tr>
<td>2012</td>
<td>Aug 7: IND Submission</td>
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<tr>
<td>2012</td>
<td>Sept 6: VRC receives FDA safe to proceed notification</td>
</tr>
<tr>
<td>2013</td>
<td>Oct 1: IRB Submission: VRC 602 [Healthy Vol Cohort]</td>
</tr>
<tr>
<td>2013</td>
<td>Nov 20: IRB Approval: VRC 602</td>
</tr>
<tr>
<td>2013</td>
<td>Sept 30: VRC01 First IV Infusion (1 mg/kg IV)</td>
</tr>
<tr>
<td>2013</td>
<td>Nov 12: VRC 601 First SC Infusion (5 mg/kg SC)</td>
</tr>
<tr>
<td>2013</td>
<td>Dec 9: VRC 602 First Infusions (5mg/kg IV), (5mg/kg SC)</td>
</tr>
<tr>
<td>2014</td>
<td>Aug 29: HVTN 104 opened</td>
</tr>
<tr>
<td>2014</td>
<td>April 10: IMPAACT P1112 opened</td>
</tr>
<tr>
<td>2015</td>
<td>April 21: Therapeutic IND safe-to-proceed</td>
</tr>
</tbody>
</table>

### Key Events
- **VRC01 Pre-IND meeting**
- **IND Submission**
- **FDA safe to proceed notification**
- **IRB Submission: VRC 602** [Healthy Vol Cohort]
- **VRC01 First IV Infusion (1 mg/kg IV)**
- **VRC 601 First SC Infusion (5 mg/kg SC)**
- **HVTN 104 opened**
- **Therapeutic IND safe-to-proceed**

### Meetings and Conferences
- **Panel of Experts: Bethesda July 2010**
- **International Consultation: Entebbe January 2013**
- **Passive Immunization and Vaccine Design: Bethesda August 2014**
## Phase I Dose Escalation

### VRC 601
**HIV-Infected**

<table>
<thead>
<tr>
<th>Group</th>
<th>N =23 infused</th>
<th>Day 0 +/- Day 28*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>1 mg/kg IV</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>5 mg/kg IV</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>5 mg/kg SC</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>20 mg/kg IV</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>40 mg/kg IV*</td>
</tr>
</tbody>
</table>

17 clinical visits and 28 PK blood draws per subject

### VRC 602
**Healthy Uninfected Volunteer**

<table>
<thead>
<tr>
<th>Group</th>
<th>N=28 infused</th>
<th>Day 0 +/- Day 28*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>5 mg/kg IV</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>20 mg/kg IV*</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>40 mg/kg IV</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>5 mg/kg or Placebo SC</td>
</tr>
</tbody>
</table>

16 clinical visits and 28 PK blood draws per subject
VRC01 Pharmacokinetics in Healthy Volunteers

T1/2  15 days
VRC01 Concentration Following Repeat Dosing

VRC01 Concentration (mcg/mL)

- 5 mg/kg IV
- 20 mg/kg IV
- 40 mg/kg IV
- 5 mg/kg SQ

28 Days After Dose 1
28 Days After Dose 2

10 mcg/mL
VRC01 Pharmacokinetics 
Aviremic, Viremic & Uninfected Subjects
Anti-VRC01 Abs Were Not Detected VRC 602

A. Positive and Negative Controls

B. Subcutaneous VRC01 Administration

C. Intravenous VRC01 Administration
Phase I Trials Summary

- VRC01 has been safe and well tolerated
  - No infusion reactions
- Half-life is 15 days
- Anti-VRC01 antibody has not been detected in subjects to date
- Post-infusion VRC01 retains broad and potent neutralizing activity
- VRC01 reduced VL by >1 Log in 6/8 viremic subjects
- No effect on aviremic viral reservoir detected
Clinical Development Plans for Prevention

- **VRC: Phase I** safety and PK in HIV-infected adults
- **VRC: Phase I** safety and PK in healthy HIV-uninfected adults
- **IMPAACT: Safety and PK** in high-risk US infants, Route: SC
- **HVTN: Multi-dose safety and PK** in US adults, Route: IV and SC
- **IMPAACT: Phase IIb** in high-risk breastfeeding infants
- **Phase IIb efficacy** in high-risk adults

**PMTCT**

**Adults**

**Phase**
- 1
- 1b
- 2b

**HIV-infected**

**HIV-uninfected**
VRC01 Clinical Development Plans: Therapy

Phase I safety and PK in HIV-infected adults

- USMHRP
  - Acute infection: Viral Reservoir
- USMHRP
  - Acutely treated: Treatment Interruption
- ACTG & NIAID
  - Chronic infection: Treatment Interruption
- ACTG & IMPAACT
  - Chronic infection: Viral Reservoir

Duration of infection prior to treatment
### VRC01 Efficacy Study
**HVTN 703/HPTN 081 (AMP Study)**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>IV Treatment</th>
<th>n=</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>North + South American MSM</td>
<td>VRC01 10 mg/kg</td>
<td>800</td>
<td>Every 8 wks x 10 doses</td>
</tr>
<tr>
<td></td>
<td>VRC01 30 mg/kg</td>
<td>800</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo Control</td>
<td>800</td>
<td></td>
</tr>
<tr>
<td>Sub-Saharan African women</td>
<td>VRC01 10 mg/kg</td>
<td>500</td>
<td>Every 8 wks x 10 doses</td>
</tr>
<tr>
<td></td>
<td>VRC01 30 mg/kg</td>
<td>500</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo Control</td>
<td>500</td>
<td></td>
</tr>
</tbody>
</table>

**3900 HIV uninfected subjects**

- 2400 men in N. and S. America (18 sites)
- 1500 women in sub-Saharan Africa (9 sites)

10 mg/kg IV and 30 mg/kg IV based on Phase I studies and NHP prevention data

≈50 kg of VRC01 to be provided by VRC
Vaccine Production Program

15mL

15 Liters

50 Liters

2000 Liters

Gaithersburg, Md

Frederick, Md

Scale-Up
HVTN 703/HPTN 081

• Conducted by DAIDS Networks Internationally (HVTN and HPTN)
• 2:1 active:control allocation
• 10 infusions over 20 months per subject=39,000 infusions total
  • “Toyota Lean Thinking” consultation completed early 2015
• Frequent HIV testing—positive test ends infusion schedule
  • F/U for virology and safety continues
• Open to accrual in November 2015 in US
  – May 2016 in South America and Sub-Saharan Africa
VRC01 Clinical Trials Summary
Projected Activity 2015-2019

2015 2016
Phase I: HIV- Adults
HVTN 104: US (Enrollment Ongoing)

2017
Phase I: HIV+ Adults
NIAID Intramural: VRC 601 (Enrollment Complete)

Phase I: HIV- Adults
NIAID Intramural: VRC 602 (Enrollment Complete)

Phase I: HIV- Adults
HVTN 104: US (Enrollment Ongoing)

Phase I: HIV+ Adults (ATI)
ACTG A5340: US

Phase I: HIV Long Term+ Adults (Reservoir Study)
ACTG A5342: US

Phase I: HIV+ Adults Acutely Treated and Stable (ATI)
MHRP RV397: Thailand

Phase I: HIV+ Adults Acutely Infected (Acute Treatment)
MHRP RV398: Thailand, Kenya, Tanzania, Uganda

Phase I: HIV+ Stable Adults (ATI)
NIAID ATI: US

Phase I: HIV Long Term+ Children (Reservoir Study)
IMPAACT: US

Phase IIb: MSM/TG and Women (Prevention in High Risk)
HVTN 703/HPTN 081: US / International

2018 2019
HIV- Negative Subjects (Prevention)
HIV+ Positive Subjects (Treatment)

Phase I: HIV+ Adults Acutely Treated and Stable (ATI)
MHRP RV397: Thailand

Phase I: HIV+ Adults (ATI)
ACTG A5340: US

Phase I: HIV+ Adults Acutely Treated and Stable (ATI)
MHRP RV397: Thailand

Phase I: HIV+ Adults Acutely Infected (Acute Treatment)
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Phase I: HIV+ Stable Adults (ATI)
NIAID ATI: US

Phase I: HIV Long Term+ Children (Reservoir Study)
IMPAACT: US

Phase I: Infants of HIV+ Mothers
IMPAACT P1112: US / International

Phase II: Infants of HIV+ Mothers
IMPAACT Network: International
VRC01 Clinical Trials
(Global Collaborations)

Therapeutic, Adult Prevention, MTCT Prevention

**ACTG 5340**
**ACTG 5342**
**HVTN 104**
**IMPAACT P1112**
**HVTN 703/HPTN 081**
**NIAID ATI/IMPAACT Rx**
(USA – Multiple Sites)

**IMPAACT P1112**
(Puerto Rico)

**RV 397**
(Thailand)
**RV 398**
(Uganda, Kenya, Tanzania)

**HVTN 703/HPTN 081**
(South America)

**HVTN 703/HPTN 081**
(Sub-Saharan Africa)

**IMPAACT P1112**
(South Africa, Zimbabwe)

**USA**
**Puerto Rico**
**South Africa**
**Zimbabwe**
**Thailand**
**Uganda**
**Kenya**
**Tanzania**
**Sub-Saharan Africa**
**South America**
Neutralization of 186 HIV Env Pseudoviruses

% of viruses resistant to neutralization, IC80 >50 µg/ml

- Dotted line shows median IC80 of all viruses (includes those not neutralized)
- Solid line shows median IC80 of viruses sensitive to neutralization (excludes those not neutralized)
Percent of Viruses Neutralized (IC80 <1 mcg/ml)

Antibody Percent Viruses Neutralized

Number of Viruses Tested, Breakdown by Clade

<table>
<thead>
<tr>
<th>Antibody</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>AE</th>
<th>AG</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>25</td>
<td>40</td>
<td>54</td>
<td>7</td>
<td>20</td>
<td>14</td>
<td>26</td>
<td>186</td>
</tr>
<tr>
<td>B</td>
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<td></td>
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<td>C</td>
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<tr>
<td>OTHER</td>
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</tr>
</tbody>
</table>

Other = Clade AC/ACD/AD/BC/CD/G

Antibodies that did not neutralize an entire clade were assigned a value of "2" for graphing purposes.

Other: AC/ACD/AD/CD/G
Neonatal Fc (FcRn) Mutations Extend Half-Life

- Fc region binds with high affinity to FcRn at acidic pH (<6.5) in endosome
- Protects antibody from endosomal degradation
- IgG released back into circulation at physiological pH (7.4)
- Results in prolonged circulating half life

Zalevsky et al. Nat. Biotechnol, 2010
Summary

• VRC01 is being advanced in both preventive and therapeutic trials in both children and adults

• Other bNAbs to multiple epitopes are being produced for evaluation alone and in combination to improve:
  – potency
  – breadth
  – durability
Acknowledgements

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Study Volunteers

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