Antibody Mediated HIV Prevention

The AMP Studies

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Disclosures

- No financial disclosures
Passive Antibody Protection

- Long history of use of antibodies against viral infections
- Passive Antibody Prevention of HIV/SHIV in NHP for over 20 years
  - Polyclonal IgG protects Chimps from HIV infection
  - Polyclonal IgG protects against SHIV challenge
  - Use of mAbs (2F5, 2G12, F105) and protection against mucosal challenge
  - Protection with newer generation mAbs (PGT121, 3BNC117, 10-1074, VRC01, VRC07)
- NHP studies tell us that physiologically achievable levels of mAb could prevent HIV-1 infection
- There are no human data regarding passive protection by HIV-1 monoclonal antibodies
Can Antibodies be used to Prevent HIV in Humans?
Many Unanswered Questions

- Can antibodies prevent HIV-infection in humans?
- What level of mAb is needed to protect?
- Where and how does the mAb work:
  - lumen, epithelial surface,
  - mucosal or lymphoid tissue
- Are Fc-mediated effector functions (ADCC, ADCVI) needed for protection?

Adapted from J Mascola CROI 2016
VRC01

- CD4bs is functionally conserved
- Neutralizes 80 - 90% of diverse viruses, all clades

<table>
<thead>
<tr>
<th>IC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>Number of viruses</th>
<th>VRC01</th>
<th>b12</th>
<th>VRC01</th>
<th>b12</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC&lt;sub&gt;50&lt;/sub&gt; &lt; 1 μg/ml</td>
<td>190</td>
<td>91%</td>
<td>41%</td>
<td>72%</td>
<td>17%</td>
</tr>
<tr>
<td>IC&lt;sub&gt;50&lt;/sub&gt; 1-50 μg/ml</td>
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<td>IC&lt;sub&gt;50&lt;/sub&gt; &gt; 50 μg/ml</td>
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</table>
VRC01: Safety and Tolerability

- Studied in Phase 1 trials: VRC601, VRC602, HVTN104
  - **VRC 601***: dose escalation and PK study of IV and SC in HIV infected individuals
  - **VRC 602**: dose escalation and PK study of IV and SC in HIV uninfected individuals
  - **HVTN 104**: safety and PK study of VRC01 in HIV uninfected individuals
- >100 participants; >250 IV infusions of VRC01
- Overall, safe and well-tolerated

Can a passively infused monoclonal antibody prevent HIV-1 infection in high risk adults?

Two harmonized protocols:

**HVTN 704/HPTN 085**
(2700 MSM and TG in the Americas)

**HVTN 703/HPTN 081**
(1500 Women in sub-Saharan Africa)
AMP Sites

- HVTN 704/HPTN 085, MSM + TG
- HVTN 703/HPTN 081, Women
AMP Study Objectives

• **Safety & Tolerability of VRC01 Infusion**
  • Reactogenicity, AEs, SAEs, discontinuation rates

• **Efficacy to prevent HIV Infection**
  • HIV infection by Week 80 in those HIV-negative at enrollment

• **Develop a marker(s) of VRC01 that correlates with the level and antigenic specificity of efficacy and to provide insight into mechanistic correlates of protection**
  • Serum VRC01 concentration
  • Serum mAb mediated neutralization and Fc effector functions to panels of HIV-1 Envs
  • Breakthrough HIV viral sequences in infected people
  • VRC01 neutralization sensitivity of, & effector functions against, HIV strains from infected trial participants
AMP Study Objectives

• To determine whether and how the can prevent HIV infection
• To develop a marker(s) of VRC01 that correlates with the level of protection against HIV infection
• To provide insight into the mechanistic correlates of protection

Application: Help design candidate HIV vaccines and define immunogenicity study endpoints in Phase I/II trials for evaluating these candidate vaccines
Week 80 is the last study visit for the primary endpoint analysis of prevention efficacy. Week 92 is the last study visit for the co-primary endpoint analysis of safety and tolerability.

*An interim safety assessment will be performed through the Week 24 visit for the first 450 enrolled participants. Infusions for those 450 participants will continue while the interim safety assessment is conducted. Following enrollment of the 450th participant, enrollment can continue, subject to the following condition: No more than 25% of the total study population may be enrolled before the interim safety report is complete, reviewed by the DSMB, and submitted to the US FDA. Enrollment will then continue only if the safety record for the run-in subgroup is deemed satisfactory.
**SSA Women AMP Schema: HVTN 703/HPTN 081**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N*</th>
<th>W0</th>
<th>W8</th>
<th>W16</th>
<th>W24</th>
<th>W32</th>
<th>W40</th>
<th>W48</th>
<th>W56</th>
<th>W64</th>
<th>W72</th>
<th>W80*</th>
<th>W92†</th>
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</thead>
<tbody>
<tr>
<td>Group 1</td>
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<tr>
<td>VRC01 10 mg/kg</td>
<td>500</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
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<td>Group 2</td>
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</tr>
<tr>
<td>VRC01 30 mg/kg</td>
<td>500</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
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<td>Group 3</td>
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<tr>
<td>Control</td>
<td>500</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
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<tr>
<td>Total:</td>
<td>1500</td>
<td>(500 VRC01 30 mg/kg; 500 VRC01 10 mg/kg; 500 control)</td>
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</table>

*Week 80 is the last study visit for the primary endpoint analysis of prevention efficacy.
†Week 92 is the last study visit for the co-primary endpoint analysis of safety and tolerability.

*An interim safety assessment will be performed through the Week 24 visit for the first 300 enrolled participants. Infusions for those 300 participants will continue while the interim safety assessment is conducted. Following enrollment of the 300th participant, enrollment can continue, subject to the following condition: No more than 25% of the total study population may be enrolled before the interim safety report is complete and reviewed by the DSMB. Enrollment will then continue only if the safety record for the run-in subgroup is deemed satisfactory. Data from VRC01 administration in HVTN 704/HPTN 085 may inform the safety assessment in HVTN 703/HPTN 081.*
The AMP Study Highlights

- Placebo controlled trial of VRC01 mAb (IV), given on Q2 month schedule, 2 harmonized trials

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>MSM &amp; TG in the Americas</th>
<th>Women in sub-Saharan Africa</th>
<th>TOTAL</th>
<th>Infusions</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRC01 10 mg/kg</td>
<td>900</td>
<td>500</td>
<td>1400</td>
<td>10</td>
<td>~22 months</td>
</tr>
<tr>
<td>VRC01 30 mg/kg</td>
<td>900</td>
<td>500</td>
<td>1400</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>900</td>
<td>500</td>
<td>1400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2700</td>
<td>1500</td>
<td>4200</td>
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</table>
Primary Endpoint – HIV-1 Infection

- Week 80
- Diagnosed via the HVTN algorithm
- Independent adjudication committee confirms each HIV-1 infection endpoint within 24-hour turn-around
Select Eligibility Criteria

- General and Demographic Criteria
  - 18-50 years of age
- HIV-Related Criteria: HIV uninfected
- Risk behavior related criteria:
  - In the Americas: male or TG who has had condomless anal intercourse with \( \geq 1 \) male or TG partner(s) or any anal intercourse with \( \geq 2 \) male or TG partners
  - In Africa: female who has had vaginal or anal intercourse with a male partner in the past 6 months
  - All volunteers in a mutually monogamous relationship with an HIV(-) partner for > 1 year are excluded.
- Volunteers with clinically significant medical conditions are excluded
AMP Study Procedures

- **IV**: receive an IV over a 30-60 minute period every 8 weeks (10 times total)
- **Blood Draw**: get a blood draw at the clinic every 4 weeks (includes an HIV test)
- **STI Testing**: get STI testing at enrolment and Q6 months thereafter
- **Questionnaires**: complete questionnaires about sexual behavior & general health every 4-8 weeks
- **Comprehensive HIV Prevention Package**

**STUDY DURATION**: about 22 months
AMP Monitoring

- Monitoring for harm, non-efficacy, high efficacy
- Monitoring for futility to assess prevention efficacy
- Safety assessment/slow down once enrollment reaches
  n=450 participants/300 participants
What Happens with Success?

- We define the level of plasma mAb needed to protect against infection (e.g., 5 - 10 ug/ml)
- Translate that into:
  - Single dose administration of mAbs to achieve this level
  - Incentive to develop next generation mAb (more potent, longer half life)
  - Options for genetic immunization to provide medium to long-term protective antibody levels
  - Knowledge that neutralizing mAb can protect will guide vaccine field
Site Activation Status - HVTN 704/HPTN 085
Study Opened March 31, 2016

<table>
<thead>
<tr>
<th>Sites activated (67%)</th>
<th>Sites not activated</th>
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<tbody>
<tr>
<td>Activation n/a training June 5-10</td>
<td>Iquitos, Lima-Barranco CRS, Lima-San Miguel CRS, Lima Via Libre CRS, Rio-IPEC-Fiocruz CRS</td>
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AMP 1 - OUR FIRST PARTICIPANT
# Activation Status - HVTN 703/HPTN 081

**Study Opened May 9, 2016**

<table>
<thead>
<tr>
<th>Sites activated (20%)</th>
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<td>Soweto CRS, eThekwini CRS, Vulindlela CRS</td>
<td>Groote Schuur CRS, Chatsworth CRS, Gabarone, Parirenyatwa CRS, Seke South CRS, Spilhaus CRS, WRHI CRS, Kisumu CRS</td>
</tr>
</tbody>
</table>

**Activation n/a training August 1-5**

Blantyre CRS, Lilongwe, Maputo CRS, Mbeya CRS
Enrollment Updates as of 13 June 2016

703/081 African Women
- 9 enrolled
- 4 randomized

704/085 MSM + TG
- 142 enrolled
- 9 randomized
## Conclusions – Why Antibodies?

<table>
<thead>
<tr>
<th>Px Option</th>
<th>Current Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal gel</td>
<td>☐ Results of FACTS 001 from Q1 2015</td>
</tr>
<tr>
<td>Rectal gel</td>
<td>☐ First phase II just finished</td>
</tr>
<tr>
<td>Vaginal ring</td>
<td>☐ Two phase IIs</td>
</tr>
<tr>
<td>Oral PrEP</td>
<td>☐ WHO recommends for all at substantial risk as of Sept 2015</td>
</tr>
<tr>
<td>Long-acting Injectable ARV</td>
<td>☐ Phase II studies; will there be a phase III in 2017</td>
</tr>
<tr>
<td>Preventive vaccines</td>
<td>☐ P5 – licensure: Research trials launch in 2016</td>
</tr>
<tr>
<td></td>
<td>☐ Janssen Ad26/mosaic, early stages</td>
</tr>
<tr>
<td>Antibodies</td>
<td>☐ HVTN/HPTN with VRC01</td>
</tr>
</tbody>
</table>
Conclusions – Why Antibodies?

• Reasonable likelihood that antibodies will work
• Likely to be safe and well tolerated (human mAbs)
• Potential that single shot – confer long lasting protection
• If we achieve clinical efficacy, mAbs could be developed for larger scale use

• **Goal:** A single shot injectable antibody product given one every 3 - 4 months, that safely and effectively protects high risk individuals from HIV-1 infection
Thank you

Some of this slide set was adapted from versions created by Dr. J Mascola, Dr S Karuna and Dr. S Edupuganti
AMP Protocol Team

- Chairs: Larry Corey & Mike Cohen
- co-Chairs: Sri Edupuganti & Nyaradzo Mgodi
- Protocol Team Leader & Core Medical Monitor: Shelly Karuna
- DAIDS Medical Officers: Marga Gomez & David Burns
- Statisticians: Allan DeCamp, Deborah Donnell, Peter Gilbert, Michal Juraska, Nidhi Kochar
- Laboratory Representatives: John Hural, Sue Eshleman, On Ho, David Montefiori, Vanessa Cummings, Estelle Piwowar-Manning
- VRC Representatives: Julie Ledgerwood, Barney Graham, John Mascola
- Investigator Representatives: Ken Mayer, LaRon Nelson, Manuel Villaran, Sinead Delany-Moretlwe
- Social & Behavioral Scientist: Michele Andrasik
- DAIDS Protocol Pharmacist: Scharla Estep
- Regional Medical Liaison: Simba Takuva
- Clinical Safety Specialist: Maija Anderson
- Protocol Development Manager: Carter Bentley
- FHI360/HPTN LOC Director: Niru Sista
- Senior Research Clinician: Phil Andrew
- Clinical Research Manager: Liz Greene
- Clinical Trials Manager: Carissa Karg
- SDMC Representatives: Lynda Emel, Gina Escamilla, Evangelyn Nkwopara
- Regulatory Affairs Representative: Meg Brandon
- Communications Representatives: Jim Maynard & Eric Miller
- Community Engagement Representatives: Gail Broder, Jonathan Lucas, Jontraye Davis
- Clinic Coordinators: Deb Dunbar, Lilian Saavedra, Elaine Sebastian
- CAB Representatives: Likhapha Faku, Mark Hubbard, Jim Wick
- Community Educators/Recruiters: DaShawn Usher & Luciana Kamel
- Technical Editor: Erik Schwab
ACKNOWLEDGEMENTS

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