Women and AMP in Africa
Study Design Discussion

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University of Zimbabwe - University of California San Francisco Collaborative Research Program
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Can a passively infused monoclonal antibody prevent HIV-1 infection in high risk adults?

Two harmonized protocols:
The AMP Studies:

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

HVTN 703/HPTN 081
(1500 Women in sub-Saharan Africa)
The AMP Studies

Being conducted by the HIV Vaccine Trials Network and the HIV Prevention Trials Network, in partnership with their combined clinical trial sites.
AMP Study Research Sites
(As of January, 2017)
The AMP Study: Objectives & Endpoints

- **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**
  - Serum VRC01 concentration
  - Serum mAb effector functions
  - Breakthrough HIV infection sequences
  - VRC01 neutralization sensitivity of, & effector functions against, HIV strains from infected trial participants
The Main AMP Study Questions

- Is the VRC01 antibody **safe** to give to people?
- Are people able to “tolerate” the antibody without becoming too uncomfortable?
- Does the antibody **lower** people’s chances of getting infected with HIV?
- If the antibody does lower people’s chances of getting infected with HIV, **how much** of it is needed to provide protection from HIV?
## Study Schema for The AMP Studies

**HVTN 704/HPTN 085**

**REGIMEN**

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>MSM &amp; TG in the Americas</th>
<th>Women in sub-Saharan Africa</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRC01 10 mg/kg</td>
<td>900</td>
<td>500</td>
<td>1300</td>
</tr>
<tr>
<td>VRC01 30 mg/kg</td>
<td>900</td>
<td>500</td>
<td>1300</td>
</tr>
<tr>
<td>Control</td>
<td>900</td>
<td>500</td>
<td>1300</td>
</tr>
<tr>
<td>Total</td>
<td>2700</td>
<td>1500</td>
<td>4200</td>
</tr>
</tbody>
</table>

**HVTN 703/HPTN 081**

- 10 infusions total - given every 8 weeks
- Study duration: ~22 months

**REGIMEN**

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<td>Total</td>
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<td>1500</td>
<td>4200</td>
</tr>
</tbody>
</table>
**MSM+TG AMP Schema: HVTN 704/HPTN 085**

<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>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>VRC01 10 mg/kg</td>
<td>900</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Group 2</td>
<td>VRC01 30 mg/kg</td>
<td>900</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Group 3</td>
<td>Control</td>
<td>900</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Total:</td>
<td></td>
<td>2700 (900 VRC01 30 mg/kg; 900 VRC01 10 mg/kg; 900 control)</td>
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<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</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 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>
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<td>500</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
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<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>Control</td>
<td>500</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
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<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td></td>
<td>1500</td>
<td>(500 VRC01 30 mg/kg; 500 VRC01 10 mg/kg; 500 control)</td>
<td></td>
<td></td>
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<td></td>
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* 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.*
A Model for Discussing HIV Risk

HIV (free virus and/or infected cells)

Protective barrier

Susceptible cells
A Model for Discussing HIV Risk

Columnar epithelium
- Infection
- Transcytosis
- Transmigration

Stratified epithelium
- Physical abrasion
- Langerhans cell
- Macrophage

Shattock and Moore 2003
## What increases the risk of HIV infection?

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased amount of HIV</td>
<td>Increased viral production</td>
</tr>
<tr>
<td></td>
<td>Type of body fluid</td>
</tr>
<tr>
<td>Breakdown of natural barrier</td>
<td>Trauma</td>
</tr>
<tr>
<td></td>
<td>Inflammation</td>
</tr>
<tr>
<td></td>
<td>Immune, genetic factors</td>
</tr>
<tr>
<td></td>
<td>(?) Hormonal contraception</td>
</tr>
<tr>
<td>Larger pool of susceptible cells</td>
<td>Inflammation</td>
</tr>
<tr>
<td></td>
<td>Genetic factors</td>
</tr>
</tbody>
</table>
Why are young women so vulnerable to HIV?

- Low sexual frequency but high risk sex
- Partners are recently infected men 5-10 years older
- Low condom use
- Biologic vulnerability of the genital tract, potentially including:
  - Ectopy - larger surface area of vulnerable cells exposed?
  - Increased HIV co-receptors in cervical cells
  - Recent HSV-2 infection
  - Intra-vaginal practices
  - Trauma during sex

Caelum, C, 2016
Changes in the vaginal mucosa during different stages of a woman's life

Prepuberal girls
- High pH
- Diverse microbiota
- Low levels of estrogen
- Squamous epithelium
- Low levels of glycogen
- Thin vaginal mucosa

Adult women
- Low pH
- $H_2O_2$
- L. iners
- L. crispatus
- Mucus
- Degradation to glucose
- Thick vaginal mucosa
- Deposition of glycogen

Postmenopausal women
- High pH
- Diverse microbiota
- Low levels of estrogen
- Mucus
- L. crispatus
- L. iners
- Low levels of glycogen
- Thin vaginal mucosa
Rationale for 2 Cohorts

• As these are Test-of-Concept trials we selected the two populations in which novel biomedical interventions are needed
  • MSM + TG
  • Heterosexual women in sub-Saharan Africa
• We suspect that route of acquisition and genital tract immunology and anatomy may influence the distribution of VRC01 and potential efficacy
Rationale for 3 Arms

• The primary analysis compares the combined VRC01 group vs. control, therefore having similar sample size as a 2-arm trial
• Assessment of PE at two doses provides data for modeling how PE would change given a new dose and/or schedule
• Multiple doses improves assessment of correlates of protection
Two Dose Groups: Overlapping Serum Concentrations

10 and 30 mg/kg VRC01 Group Overlap

<table>
<thead>
<tr>
<th>VRC01 Conc (mcg/mL)</th>
<th>10 mg/kg</th>
<th>30 mg/kg</th>
<th>Overlap</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50 mcg/mL</td>
<td>10% PYRs</td>
<td>50% PYRs</td>
<td>10% PYRs</td>
</tr>
<tr>
<td>10-50 mcg/mL</td>
<td>40% PYRs</td>
<td>40% PYRs</td>
<td>40% PYRs</td>
</tr>
<tr>
<td>&lt;10 mcg/mL</td>
<td>50% PYRs</td>
<td>10% PYRs</td>
<td>10% PYRs</td>
</tr>
</tbody>
</table>

Total Overlap = 60% PYRs or Person Years at Risk
Trial Design Rationale

- Passive administration of VRC01 antibody will reduce acquisition of HIV infection in high risk populations.
- Doses selected will determine the activity of the antibody across a range of serum concentration in diverse populations across multiple geographic regions of the world.
- Level of VRC01 antibody required for protection will vary by type of sexual exposure.
- Concentration of antibody in serum will be directly associated with the rate of protection; that is, higher levels of antibody will give greater rates of protection than lower levels.
- Breakthrough isolates will have greater resistance to neutralization and will exhibit molecular signatures associated with escape from neutralization.
Assumptions for Sample Size Calculations

- The two trials have identical statistical designs and analysis plans
- Each trial powered to detect 60% (vs. 0%) prevention efficacy
- Incidence
  - 5.5% annual HIV-1 incidence in the sub-Saharan African women placebo group
  - 3% annual HIV-1 incidence in the MSM+TG placebo group
- ~30 month uniform accrual period
- Q4-weekly visits for HIV-1 diagnostic tests
- 10% annual dropout incidence in each study group
Sample size selection for SSA women

Sub-Saharan African Women
1-sided $\alpha=0.025$
5.5% annual placebo incidence
10% annual drop-out rate
HIV-1 testing every 4 weeks

Total Sample Size for 90% Power

PE (Prevention Efficacy)
Sample size & power calculations are robust over a range of HIV incidence & dropout assumptions: WOMEN
HVTN 704/HPTN 085: Select Eligibility Criteria

• Men & transgender people who have sex with men, 18-50 years of age
  ▪ HIV uninfected
  ▪ Risk behavior related criteria:
    ▪ Male or TG who has had condomless anal intercourse with ≥ 1 male or TG partner(s) or any anal intercourse with ≥ 2 male or TG partners 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
HVTN 703/HPTN 081: Select Eligibility Criteria

- Heterosexual Women, 18-40 years of age
- HIV uninfected
- Risk behavior related criteria:
  - 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 (urine and rectal swabs) about every 6 months
- **Questionnaires:** complete questionnaires about sexual behavior & general health every 4-8 weeks

**STUDY DURATION:** about 22 months
AMP Studies: Summary

• 1st large scale, phase 2b studies with an IV intervention for HIV prevention in men & women
• 1st efficacy trials with an anti-HIV mAb
• Cross-Network collaboration: HVTN & HPTN
• Global trials in 2 cohorts on 4 continents
  • 2700 MSM + TG in North & South America (Clade B)
  • 1500 Women in sub-Saharan Africa (Clades C, A, D)
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, Erica Lazarus
- Social & Behavioral Scientist: Michele Andrasik
- DAIDS Protocol Pharmacist: Katherine Shin
- Regional Medical Liaisons: Simba Takuva & Robert De La Grecca
- 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
- Regulatory Affairs Representative: Meg Brandon
- Communications Representatives: Jim Maynard & Eric Miller
- Community Engagement Representatives: Gail Broder, Jonathan Lucas, Jontraye Davis
- Clinic Coordinators: Deb Dunbar, Ana Rimachi, Christie Heiberg
- CAB Representatives: Likhapha Faku, Mark Hubbard, Jim Wick
- Community Educators/Recruiters: DaShawn Usher & Luciana Kamel
- Technical Editor: Erik Schwab
THANK YOU