Introduction to the Science of HVTN 703/HPTN 081

March 2016

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OUTLINE: AMP Science

• HIV Prevention in sub-Saharan Africa
• The AMP Study: a brief introduction
• Antibodies: what they are & how they work
• Antibody Vocabulary: bnAbs, mAbs
• The AMP Study Antibody: VRC01
• And it all comes together: The AMP Study
  • What questions does the AMP Study help answer?
  • What does the AMP Study ask of a participant?
• Questions???
Where is the HIV Prevention Field?
The Context for the AMP Study

• Despite many advances in prevention and treatment, the global HIV epidemic continues.

• Millions of new HIV infections occur every year.

• The current prevention toolbox is insufficient to curb the epidemic.

• We cannot treat our way out of the epidemic.
HIV in SSA: the Epidemic Goes On

People living with HIV in sub-Saharan Africa, 2013

- 11% Rest of the region
- 1% Botswana
- 1% Lesotho
- 2% Côte d’Ivoire
- 2% Democratic Republic of the Congo (the)
- 2% Cameroon
- 3% Ethiopia
- 4% Malawi
- 4% Zambia
- 6% Zimbabwe
- 6% United Republic of Tanzania (the)
- 6% Uganda
- 6% Kenya
- 6% Mozambique
- 25% South Africa
- 13% Nigeria

Source: UNAIDS 2013 estimates

UNAIDS Gap Report, 2014
## HIV in SSA AMP Countries

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Botswana</td>
<td>300 000</td>
<td>23.4</td>
<td>160 000</td>
<td>15 000</td>
<td>4 200</td>
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<td>1, 600 000</td>
<td>6.2</td>
<td>800 000</td>
<td>220 000</td>
<td>62 000</td>
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<td>Malawi</td>
<td>910 000</td>
<td>10.0</td>
<td>430 000</td>
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<td>Mozambique</td>
<td>1, 400 000</td>
<td>11.3</td>
<td>750 000</td>
<td>200 000</td>
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<td>SA</td>
<td>5, 600 000</td>
<td>17.3</td>
<td>2, 900 000</td>
<td>460 000</td>
<td>270 000</td>
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<td>Tanzania</td>
<td>1, 800 000</td>
<td>5.6</td>
<td>760 000</td>
<td>230 000</td>
<td>84 000</td>
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<tr>
<td>Zimbabwe</td>
<td>1,200 000</td>
<td>14.9</td>
<td>600 000</td>
<td>200 000</td>
<td>58 000</td>
</tr>
</tbody>
</table>
HIV in SSA: the Epidemic Among Women

- In 2013, of the 24.7 million people HIV infected in SSA >50% were women
- Young women are twice as likely to be infected as young men
- Women have fewer HIV prevention options than men

Source: UNAIDS 2013 estimates

UNAIDS Gap Report, 2014
What Do We Have to Address the Epidemic?

- Education and behavior modification
- Condoms, and other barrier methods
- Treatment/prevention of drug/alcohol abuse
- Clean syringes, i.e. needle exchange programs
- Interruption of mother-to-child transmission
- Circumcision for female-to-male transmission
- HIV/STI Testing
- Antiretroviral treatment as prevention
- Post-exposure prophylaxis (PEP)
- Pre-exposure prophylaxis (PrEP)*
- Topical microbicides†
- Vaccination†

*Daily Truvada®; alternate regimens still in research
†Still in research

With thanks to Carl Dieffenbach & Jeff Schouten
## Consider an Analogy

<table>
<thead>
<tr>
<th>PREGNANCY PREVENTION</th>
<th>HIV PREVENTION</th>
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</thead>
<tbody>
<tr>
<td>Education &amp; behavior modification</td>
<td>Education &amp; behavior modification</td>
</tr>
<tr>
<td>Condoms</td>
<td>Condoms</td>
</tr>
<tr>
<td>Birth control pill</td>
<td>PrEP</td>
</tr>
<tr>
<td>“Morning-after pill”</td>
<td>PEP</td>
</tr>
<tr>
<td>Spermicide</td>
<td>Topical microbicides</td>
</tr>
<tr>
<td>Implantable birth control</td>
<td>Antibody-mediated Prevention (bnAbs)</td>
</tr>
<tr>
<td>Vasectomy/Tubal Ligation</td>
<td>Vaccination</td>
</tr>
</tbody>
</table>
What is Missing to Address the Epidemic?

Thanks to Mike Cohen for this slide. Cohen et al, JCI, 2008; Cohen IAS 2008
HIV Prevention in SSA Women: The Gap

- HIV-1 prevention interventions demonstrated to be effective in reducing HIV-1 risk are inadequate
  - **Condom use, HIV/STI testing** - Require participation/consent of male partner
  - **PrEP** - Achieving high adherence, especially among young SSA women, has been a central challenge (VOICE, Fem-PrEP)
  - **Microbicides** - Data suggest young SSA women wanted a product they could use to reduce their risk, but that microbicides did not fit into the realities of their daily lives (VOICE, FACTS 001)

- Inadequate prevention options for women unable to negotiate safe sex practices
- Developing HIV-1 prevention options that SSA women can use remains a global concern
The HVTN 703/HPTN 081 AMP Study: Filling the Gap

AMP = Antibody Mediated Prevention

This is the idea of using an antibody made by scientists and giving it to people directly, i.e. using an intravenous (IV) infusion, to prevent HIV infections.
Who is Doing the AMP Study?

The study is being conducted by two groups, the HIV Vaccine Trials Network and the HIV Prevention Trials Network.

Another name for The AMP Study in SSA is HVTN 703/HPTN 081
AMP Research Sites
AMP sub-Saharan Africa Sites

- Gabarone, Botswana
- Kisumu, Kenya
- Blantyre, Malawi
- Lilongwe, Malawi
- Maputo, Mozambique
- Harare (3 clinics), Zimbabwe

- Cape Town, RSA
- Durban (2 clinics), RSA
- Johannesburg, RSA
- Soweto, RSA
- Vulindlela, RSA
- Mbeya, Tanzania
The HVTN 703/HPTN 081 AMP Study: Defining a new path forward

This is the first trial to assess if antibodies can be used to prevent HIV infection in women in sub-Saharan Africa, similar to how antibodies are used to prevent other infectious diseases.
There is a Long History of Using Antibodies to Prevent Viral Infections

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>PRODUCT DESCRIPTION</th>
<th>INDICATION</th>
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<tbody>
<tr>
<td>Measles</td>
<td>Concentrated human gamma globulin</td>
<td>Prevention</td>
</tr>
<tr>
<td>Polio</td>
<td>Concentrated human gamma globulin</td>
<td>Prevention</td>
</tr>
<tr>
<td>CMV</td>
<td>Cytomegalovirus Immune Globulin</td>
<td>Prevention</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Immune serum globulin (ISG)</td>
<td>Prevention (travel)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Hepatitis B Immune Globulin</td>
<td>Post Exposure</td>
</tr>
<tr>
<td>Rabies</td>
<td>Rabies Immune Globulin</td>
<td>Post Exposure</td>
</tr>
<tr>
<td>RSV</td>
<td>mAb (palivizumab) for prophylaxis of high risk infants</td>
<td>Prevention in High Risk Infants</td>
</tr>
<tr>
<td>VZ</td>
<td>Varicella Zoster Immune Globulin</td>
<td>Post Exposure</td>
</tr>
</tbody>
</table>

And, most effective vaccines induce antibodies that neutralize the pathogen.

Thanks to John Mascola for this slide.
What is an Antibody?

B-cells produce antibodies
How Does an Antibody Work?

**NEUTRALIZATION**
Binds to HIV & blocks its attachment to host cells

**OPSONIZATION**
(“buttering the toast”)
Binds to HIV, then binds to a macrophage; the macrophage then eats the HIV

**SENSITIZATION**
(“the lookout for the hitman”)
Binds to HIV, then binds to an NK cell; the NK cell then spills its “poison” to kill HIV
Neutralizing Antibodies

HIV gp120

Antibody

Antibody bound to HIV gp120

Thanks to Lisa Donohue for these images.
Neutralization Animation Goes Here
What is a BROADLY Neutralizing Antibody?

A “bnAB”: an antibody that neutralizes a lot of different types of strains of HIV.

And why do we care...?
HIV Diversity Within an Individual

Usually 1 HIV strain in a new infection
(“Transmitted-founder”)
Replicates within about 24hrs
 Produces BILLIONS of new virions a day
Mutations with viral replication
Rapidly develop multiple lineages or “quasispecies”
HIV-1 Diversity Worldwide

HIV-1 group M: 9 subtypes & several circulating recombinant forms

HIV genomes differ by 10-30%

Human genomes differ by about 0.1%

Hemelaar et al. 2004. WHO/UNAIDS.
What is a Monoclonal Antibody (mAb) to HIV?

- A single type ("clone") of antibodies often found in the blood of long-term non-progressors, then made in a lab
- Bind to different parts of the HIV gp120 envelope protein

N332 Glycan Supersite:  
PGT121, PGT128  
10-1074

V1V2 Glycan:  
PG6, PG16, CH01-04, PGT141-45, CAP256-VRC26

CD4 Binding Site:  
VRC01, PG04, CH31, VRC07, 3BNC117, 12A12, CH103

Trimer (gp120/41):  
8ANC195, PGT151, 35022

gp41 MPER:  
2F5, 4E10, 10e8

Thanks to the Subramaniam, Kwong, and Wilson groups.
OUTLINE: AMP Science

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- Antibody Vocabulary: bnAbs, mAbs
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- Questions???
VRC01: The AMP Study Antibody

- Broadly Neutralizing (“bnAb”)
- Monoclonal (“mAb”)
- Antibody
- Discovered by scientists at the US NIH
- In the lab, it has been able to block HIV in about 90% of the different types of HIV that it has been tested against.

Gray: gp120
Red: CD4 binding site (CD4bs)
Purple & Green: VRC01 attached to the CD4bs

Photo: NIAID/NIH Vaccine Research Center (VRC)
VRC01 Attaches to the CD4 Binding Site on gp120

The GP 120 Protein

Red lines = linear epitopes
Red circle = the CD4 binding site

Image credit: NIAID
Why Evaluate VRC01?

- Promising antibody for HIV prevention
  - Broadly neutralizing & potent in lab studies
  - Good results in early studies
  - May supplement other prevention approaches

- Move the HIV vaccine search forward
  - Teach us the amount of antibody a vaccine may need to elicit to prevent HIV
  - Help us find a safe, effective HIV vaccine more efficiently
VRC01 is a BROADLY NEUTRALIZING Antibody

Tested Against 190 Different “Types” or Strains of HIV

Wu et al. Science. 2010
VRC01 is a Potent Antibody

Fraction neutralized

IC50 cutoff (ug/ml)

Thanks to David Montefiori & CAVD and Bob Bailer & NVITAL Laboratory
VRC01 in Preclinical (NHP) Trials

20 mg/kg infusion of VRC01

RECTAL CHALLENGE
4/4 PROTECTED

VAGINAL CHALLENGE
4/4 PROTECTED

0/4 protected

1/4 protected
VRC01 in Phase 1 Clinical (Human) Trials: Safe and Well-tolerated

- 3 Phase 1 trials: VRC601, VRC602, HVTN 104
- Safe, well-tolerated in >100 participants, >250 infusions
  - No related serious “adverse events”
  - Mild adverse events only, which included mild lab changes in liver & kidney tests
How Could VRC01 be a Prevention Tool?

- Cover a period of risk for newborns (during & right after birth, during breastfeeding)
- Cover the “tail” of long-acting PrEP injection
- Cover the ramp-up period of an HIV vaccine regimen
- Combine with other mAbs in a prevention “cocktail”
How Could VRC01 Help Us Find an HIV Vaccine?

No HIV vaccine has (yet) been able to teach the body to make (enough) neutralizing antibody to prevent HIV.

- How much neutralizing antibody is enough?
- How good are non-human “models” in the lab and in practical (NHP) studies?

Answering these questions can help us find a safe, effective HIV vaccine more quickly & less expensively.
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?
PrEP in the AMP Study

- **US:** PrEP as part of risk reduction counseling, including referral to PrEP providers & Truvada at no drug cost for interested ppts
- **South America:** PrEP Demonstration Projects for interested ppts
- **Sub-Saharan Africa:** WHO PrEP guidelines issued but PrEP not yet available in the public sector; work with stakeholders; respect in-country leadership & follow in-country guidelines as they evolve
# AMP Study Design: HVTN 703/HPTN 081, version 1

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## 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>
<th>Notes</th>
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<tbody>
<tr>
<td>VRC01 10 mg/kg</td>
<td>800</td>
<td>500</td>
<td>1300</td>
<td>10 infusions total &amp; Infusions every 8 weeks</td>
</tr>
<tr>
<td>VRC01 30 mg/kg</td>
<td>800</td>
<td>500</td>
<td>1300</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>800</td>
<td>500</td>
<td>1300</td>
<td>Study duration: ~22 months</td>
</tr>
<tr>
<td>Total</td>
<td>2400</td>
<td>1500</td>
<td>3900</td>
<td></td>
</tr>
</tbody>
</table>
Study Schema for the AMP Study in sub-Saharan Africa

Planned version 2.0 of HVTN 703/HPTN 081 administratively splits the two cohorts into two regionally distinct protocols, providing for sovereign regulatory oversight in SSA, contributing local and regional expertise. Data is shared across the trials and trial design remains the same.

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>Women in sub-Saharan Africa</th>
<th>10 infusions total &amp; Infusions every 8 weeks</th>
<th>Study duration: ~22 months</th>
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</thead>
<tbody>
<tr>
<td>VRC01 10 mg/kg</td>
<td>500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VRC01 30 mg/kg</td>
<td>500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>500</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1500</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The AMP Study in SSA: Selected Eligibility Criteria

- 18-50 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
What Will an AMP Participant Need to Do?

- **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 & cervicovaginal swabs) at enrolment and thereafter as indicated
- **Questionnaires**: complete questionnaires about sexual behavior & general health every 4-8 weeks

**STUDY DURATION**: about 22 months
And Why Do We Ask This of Our Participants?

Because we want to END HIV...

• Whether through an antibody delivered by an IV
• Or through an HIV vaccine developed more quickly because of The AMP Study

...and our participants want to END HIV, too.
Review: AMP Science

- HIV Prevention in sub-Saharan Africa
- The AMP Study: a brief introduction
- Antibodies: what they are & how they work
- Antibody Vocabulary: bnAbs, mAbs
- The AMP Study Antibody: VRC01
- And it all comes together: The AMP Study
  - What questions does the AMP Study help answer?
  - What does the AMP Study ask of a participant?
- Questions???
THANK YOU!

AMP STUDY
HVTN 703/HPTN 081 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-Morelwe
- 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
QUESTIONS?
SUPPLEMENTAL SLIDES
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 enrolment

- **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
## Phase I Dose Escalation, Safety, and PK Studies VRC 601 & VRC 602

### VRC 601:
IV or SC in HIV-Infected Adults

<table>
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<th>Group</th>
<th>N</th>
<th>Days 0 and 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>1 mg/kg IV</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>5 mg/kg IV</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>5 mg/kg SC</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>20 mg/kg IV</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>40 mg/kg IV</td>
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</table>

17 clinical visits and 28 PK blood draws per subject

### VRC 602:
IV or SC in Healthy, HIV-Uninfected Adults

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Days 0 and 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>5 mg/kg IV</td>
</tr>
<tr>
<td>2</td>
<td>5</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>9</td>
<td>5 mg/kg or Placebo SC</td>
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</tbody>
</table>

16 clinical visits and 28 PK blood draws per subject
## Phase I Safety and PK Study: HVTN 104

<table>
<thead>
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<th>Group</th>
<th>Day</th>
<th>Dose/Route</th>
<th>Dose/Route</th>
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<th>Dose/Route</th>
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<td>VRC01 40mg/kg IV</td>
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<td>VRC01 20mg/kg IV</td>
<td>VRC01 20mg/kg IV</td>
<td>VRC01 20mg/kg IV</td>
<td>VRC01 20mg/kg IV</td>
<td>VRC01 20mg/kg IV</td>
<td>VRC01 20mg/kg IV</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>VRC01 40mg/kg IV</td>
<td>VRC01 5mg/kg SC</td>
<td>VRC01 5mg/kg SC</td>
<td>VRC01 5mg/kg SC</td>
<td>VRC01 5mg/kg SC</td>
<td>VRC01 5mg/kg SC</td>
<td>VRC01 5mg/kg SC</td>
<td>VRC01 5mg/kg SC</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>SC pl for VRC01</td>
<td>SC pl for VRC01</td>
<td>SC pl for VRC01</td>
<td>SC pl for VRC01</td>
<td>SC pl for VRC01</td>
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</tr>
<tr>
<td>4</td>
<td>2.5</td>
<td>VRC01 10mg/kg IV</td>
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<td>VRC01 10mg/kg IV</td>
<td>VRC01 10mg/kg IV</td>
<td>VRC01 10mg/kg IV</td>
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<td>5</td>
<td>3.5</td>
<td>VRC01 30mg/kg IV</td>
<td>VRC01 30mg/kg IV</td>
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<td>VRC01 30mg/kg IV</td>
<td>VRC01 30mg/kg IV</td>
<td>VRC01 30mg/kg IV</td>
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</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>Intravenous (IV) doses administered in 100 mL of normal saline over 1 hr</td>
<td>Subcutaneous (SC) doses administered by needle and syringe injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Two Dose Groups: Overlapping Serum Concentrations

<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