"Plan B"- bNAbs for HIV prevention

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We are at a pivotal point in the HIV epidemic with 2 efficacy trials currently being conducted in southern Africa. *Both concepts rely on HIV-specific antibodies.*
Active Immunization

Vaccination to stimulate binding antibodies previously shown to correlate with reduced risk of HIV infection. This is being tested in HVTN 702

Passive Immunization

Pre-formed broadly neutralizing antibody VRC01 is infused to provide instant protection against HIV infection. This is being tested in the HVTN 703 (AMP trial)
Most licensed vaccines work by inducing neutralizing antibodies that fight virus infections
Some HIV infected people make good neutralizing antibodies after many years of infection

- Co-evolution studies providing insights for vaccine design
- Source of biological drugs for passive immunization
Broadly neutralizing antibody targets on the HIV envelope trimer

- V1V2 Apex (eg CAP256-VRC26)
- CD4 Binding Site (eg VRC01)
- N332 Glycan Supersite
- gp120-gp41 Interface
- gp41 MPER
- Viral Membrane

Constantinos Kurt Wibmer
Broadly neutralizing antibody vary in potency and breadth against 200 Clade C isolates.
Desirable properties of monoclonal antibodies for HIV prevention

• Safe and effective at low doses
• Broad coverage of global HIV isolates (may require combinations of 2-3 bNAbS or bispecific antibodies)
• Long half-life (up to 4-6 months)
• Subcutaneous injection
• Cost comparable to ARV for PrEP
HVTN 703/HPTN 081, The AMP Study:
Filling the gap

AMP = Antibody Mediated Prevention

A phase 2b study to evaluate the efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection
What the AMP trial aims to show

• Administration of a bNAb will reduce HIV infection rates in high-risk groups
• The amount of antibody in the blood will directly correlate with the rate of protection
• Breakthrough viruses will show greater resistance to neutralization (and molecular signatures of escape)
• 28 healthy adults
• Dose escalation (5, 20, 40 mg/kg)
• 2 infusions (iv and sc)
• Safe and well tolerated
• Potentially protective VRC01 levels for up to 8 weeks after infusion
Variability in antibody levels between and within individuals, and by trial design

VRC01 levels in HVTN 104
Possible Scenario of Breakthrough Infections in AMP

PE >60%

David Montefiori and Peter Gilbert
Neutralization as Mechanistic Correlate of Prevention

Higher proportion of VRC01-resistant viruses in treatment group
AMP Trial

Important proof of concept that CD4bs bNAb can protect against the acquisition of HIV infection in humans.

If significant protection is seen:

- Strengthens the rationale for bNAb-based vaccines
- Adds validity to neutralization assays (e.g., TZM-bl)
- Adds validity to the NHP model
- Establishes a platform for passive immunization for HIV prevention
Study Sites

CAPRISA Vulindlela Clinical Research Site, KwaZulu-Natal

CAPRISA eThekwini Clinical Research Site, Durban
Broadly neutralizing antibodies take a long time and only develop in some infected people.

Neutralization breadth at 3 years p.i.

Elin Gray et al., JV 2011
Broadly cross-neutralizing antibodies have no impact on HIV disease progression: CAPRISA 002 cohort

Elin Gray et al., JVI 2011
CAP256-VRC26 bNAbIs isolated from a South African woman
Can the CAP256-VRC26.25 bNAb protect monkeys from infection?

Broadly neutralizing antibodies targeting the HIV-1 envelope V2 apex confer robust protection against a clade C SHIV challenge

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CAP256.25-LS injection

SHIV 325c (300 MID) intra-rectal challenge
2 days later

4 monkeys /group:
2 mg/kg
0.4 mg/kg
0.08 mg/kg
Viral loads in rhesus macaques pre-treated with V2-specific bNAb

Boris Julg...Dan Barouch, under review
Preventing HIV in women by passive immunization

bNAbs as long-acting PrEP - potential to impact on HIV in young women from 16 - 24 years with 3 - 4 subcutaneous doses / year
HIV in pregnant women in rural South Africa (2001-2013)

<table>
<thead>
<tr>
<th>Age Group (Years)</th>
<th>HIV Prevalence (N=4818)</th>
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<tbody>
<tr>
<td>≤16</td>
<td>11.5%</td>
</tr>
<tr>
<td>17-18</td>
<td>21.3%</td>
</tr>
<tr>
<td>19-20</td>
<td>30.4%</td>
</tr>
<tr>
<td>21-22</td>
<td>39.4%</td>
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<tr>
<td>23-24</td>
<td>49.5%</td>
</tr>
<tr>
<td>&gt;25</td>
<td>51.9%</td>
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</tbody>
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Source: Abdool Karim Q, 2014

Urgent need for feasible & effective prevention tools for young women in Africa
Great progress on increasing HIV treatment but we are lagging in prevention

Number of people receiving antiretroviral therapy, by WHO region, 2003–2016

Why CAP256-VRC26.25 is a candidate for passive immunization

1. Good coverage of clade C
2. Among the most potent bNAbs currently available
3. Part of best current combination of bNAbs
4. No identified cross-reactivity
5. Efficacious for prophylaxis in macaque model
6. Future translation to a HIV vaccine: this antibody can acquire breadth within months, not years
Development plan for CAP256-VRC26.25 for passive immunization

- Manufacture GLP lot ✔
- Monkey challenge study ✔
- GMP lot manufacture and formulation for human trials and stability studies
- Sub-cutaneous formulation
- Pre-clinical studies
- Regulatory filing of IND
- Phase I/II safety & proof-of-concept trial (CAPRISA 012)
Outline of the clinical trial pathway  
(Salim Abdool Karim, CAPRISA)

**Study Population:**
- HIV negative participants aged 18 - 40 years
- ART naïve HIV positive participants aged 18 - 40 years (VL >1000)

**Study Sites:**
- CAPRISA Vulindlela & eThekwini Clinics and VRC Research Clinic

**Study design (CAPRISA 012):**
- Phase I - Establish safety and dose
- Phase II - Extended safety & indication of potential efficacy of combinations
  - CAP256-VRC26.25.LS + PGT121
  - CAP256-VRC26.25.LS + VRC07-523.LS
- Phase III – Large network trial, if the Phase II data justify proceeding
CAP256-VRC26.25 combinations show higher breadth and potency against clade C viruses.
Summary

• Animal studies provide proof-of-concept for bNAbs but we need efficacy data in humans
• bNAbs targeting the CD4bs (VRC01/3BNC117) and V3 glycan (10-10-74/PGT121) are currently being tested in humans
• Trials of V2 glycan bNAbs (CAP256-VRC26.25 and PGDM1400) are planned
• Broader and more potent antibodies are being engineered including extending half-life of bNAbs
• Antibodies may be more useful for prevention than treatment and will provide a benchmark for vaccines
**Passive immunization**
- Short-lived protection
- Multiple injections
- Instant protection following injection
- Protective titer of VRC01

**Vaccination**
- Long-lasting
- 3-5 vaccinations
- Response develops over months
- Elicits polyclonal antibodies and other immune responses
Thanks to all the women who participate in the CAPRISA study