HIV Vaccines and monoclonal Antibodies - Preparation for success.
Policy & access considerations

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FROM PROOF OF EFFICACY TO POLICY DECISION, ACCESS AND USE of HIV Vaccines and Monoclonal antibodies
PREPARE FOR SUCCESS

Meeting objectives:

• Discuss the downstream considerations and requirements to achieve timely, effective use in populations with greatest need

• Contribute toward definition of Preferred Product Characteristics for the immunization tools.

• Review gaps in the current public health policy framework and prepare recommendations that would expedite access to effective products in the pipeline.

• Provide WHO with priority activities to advance preparedness supporting accelerated use upon primary licensure

• **Participants:** Funders, product developers, manufacturers, regulators and end-users (government representatives, civil society).
Key Questions

• How do projections of the HIV pandemic, current interventions and innovations in the pipeline support the future use of vaccines and monoclonal antibodies for HIV prevention?

• How can product development be coordinated with implementation planning?

• What can be learnt from implementation experience from the introduction of other biomedical prevention interventions? (HIV, Dengue, Malaria etc.)

• How can the needs of key and general populations best be met, taking into account resources required for supply and distribution?
### State of HIV/AIDS Epidemic

<table>
<thead>
<tr>
<th><strong>76.1 million infected</strong> since discovery in early 1980s</th>
<th><strong>30% of people living with HIV don’t know they have it</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>35 million deaths</strong> since discovery in early 1980s</td>
<td><strong>47% don’t have access to treatment</strong></td>
</tr>
<tr>
<td>Leading killer of women in reproductive age</td>
<td><strong>Many of those who do, don’t adhere well</strong></td>
</tr>
<tr>
<td><strong>36.7 million living with HIV</strong></td>
<td><strong>1.8 million new annual HIV infections</strong></td>
</tr>
</tbody>
</table>

UNAIDS, 2018
Evolving Landscape and Other Prevention Tools

• **Increasing treatment** of HIV infected people reducing onward transmission (90-90-90)

• Increasing PrEP availability

• Multiple proven HIV prevention tools (condoms, VMMC, VCT etc.)

• Other HIV Prevention Technologies
  
  o ASPIRE and the Ring dapivirine studies with modest efficacy results – ongoing licensure

  o Long-acting injectable ARV’s (Cabotegravir LA - HPTN 083, HPTN 084) – Results ≈ 2022

• Falling global HIV infection rates - most new infections occurring in pockets of large populations with relatively low overall incidence or general population (Southern Africa)
Current Phase 2b/3 HIV efficacy approaches

**HIV vaccine trials**
- **Uhambo** (Phase 2B/3) 
  - HIVTEN 702
- **Imbokodo** (Phase 2B/3) 
  - HIVTEN 705

**Broadly neutralizing antibody trials**
- **AMP (POC)** 
  - HIVTEN 703/704

- Duration of immune responses is currently unknown.
- Aim for years/decades of protection.
- BnAbs delivered passively, for prevention, treatment and as part of a functional cure strategy
- Periodic delivery.
## Current Efficacy Studies and Timelines

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Trial</th>
<th>Population</th>
<th>Location</th>
<th>N</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALVAC and bi-gp120/MF59</td>
<td>HVTN 702</td>
<td>Men &amp; women</td>
<td>South Africa</td>
<td>5400</td>
<td>Jan 2021</td>
</tr>
<tr>
<td>Ad26 and 4 mosaic + gp140/Alum</td>
<td>HVTN 705</td>
<td>Women</td>
<td>Southern Africa</td>
<td>2600</td>
<td>Mar 2021</td>
</tr>
<tr>
<td>VRC01 10mg/kg, 30mg/kg I.V.</td>
<td>HVTN 703</td>
<td>Women</td>
<td>Sub-Saharan Africa</td>
<td>1500</td>
<td>Jan 2021</td>
</tr>
<tr>
<td></td>
<td>HVTN 704</td>
<td>Men (MSM, transgender)</td>
<td>Americas, Lausanne</td>
<td>1800</td>
<td>Oct 2020</td>
</tr>
</tbody>
</table>
### HVTN 702: PHASE 2B/3 STUDY SCHEMA

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Primary Vaccine Regimen</th>
<th>Booster</th>
<th>Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Month 0</td>
<td>Month 1</td>
<td>Month 3</td>
</tr>
<tr>
<td>1</td>
<td>2700</td>
<td>ALVAC-HIV (vCP2438)</td>
<td>ALVAC-HIV (vCP2438)</td>
<td>ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59</td>
</tr>
<tr>
<td>2</td>
<td>2700</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo + Placebo</td>
</tr>
<tr>
<td>Total</td>
<td>5400</td>
<td></td>
<td></td>
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</tbody>
</table>

- Challenges of multi-pharma (component) HIV vaccine, varying manufacturing commitment
- Potential licensure in South Africa in 2029
- Pox-protein Public Private Partnership (P5) Roadmap working group planning for potential efficacy and futility scenarios
- P5 Global Access Committee set up to develop a vaccine access plan if vaccine regimen proves to be effective.

Sources: Nina Russell, Glenda Gray

© Bill & Melinda Gates Foundation
HVTN 705/HPX2008: Vaccine Aiming at Protection Against all Clades of HIV-1

1. Potent Priming Vectors
   Low seroprevalent Ad26

2. Mosaic inserts for global coverage
   (Gag-Pol-Env)

3. Trimeric env proteins for improved humoral immunity
   gp140 Clade C

Group | N  | Month 0 | Month 3 | Month 6 | Month 12 |
------|----|---------|---------|---------|----------|
2     | 1300| Placebo | Placebo | Placebo + Placebo | Placebo + Placebo |

Phase 2b Proof of Concept - Not a licensure trial

- **Protective Efficacy hypothesis:** 50% (lower bound >0%) reduction in HIV-1 acquisition,
- Preparatory work ongoing to move to Phase 3
- Ongoing planning around licensure and implementation (discussions with RA, pricing strategy, WHO prequalification)

Source: Maria Grazia Pau, © Janssen (Infectious diseases and Vaccines)
AMP - Phase 2b: Passive Antibody Prevention

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

AMP = Antibody Mediated Prevention Study

VRC01 administered at 30 mg/kg, or 10 mg/kg, vs placebo

• Administered once every 8 weeks by IV infusion
• High risk men in North and South America
• High risk women in South and East Africa
• Powered for 60% efficacy overall,
• No plan to develop this single monoclonal antibody

Determine serum level or neutralization titer of antibody required for protection.

Adapted from Richard A. Koup
# VRC HIV-1 mAb Portfolio

<table>
<thead>
<tr>
<th></th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>2021</th>
<th>2022</th>
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</thead>
<tbody>
<tr>
<td><strong>VRC01</strong></td>
<td></td>
<td></td>
<td>Phase II: AMP Study</td>
<td>Serum mAb level</td>
<td>Serum neutralization level</td>
<td>(bridge to other mAbs)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(Proof-of-concept)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>VRC07-523-LS</strong></td>
<td></td>
<td></td>
<td></td>
<td>Expanded Phase I: HVTN 127</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>/ HPTN 087</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Z258-N6-LS</strong></td>
<td>Dev. and Manufacturing</td>
<td></td>
<td>Phase I: Z258-N6LS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>10E8v5R-LS</strong></td>
<td>Development and Manufacturing</td>
<td></td>
<td>Phase I: 10E8v5R-LS</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>CAP256-LS</strong></td>
<td>Development and Manufacturing</td>
<td></td>
<td>Phase I: CAP256-LS</td>
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<td></td>
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<tr>
<td><strong>Tri-specific-LS</strong></td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td><strong>combo</strong></td>
<td>Down-select Optimal Mabs</td>
<td></td>
<td>Phase IIb: Proof of Product</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>99% coverage</td>
<td></td>
<td>(Two mAbs, or Tri-specific)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10x more potent</td>
<td></td>
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</table>

Source: Richard A. Koup
Industry Partner Highlights

- Strong business case for products with clear demand forecasting required for industry involvement, role of western markets important to recoup costs.
- High pharmacovigilance costs need to be factored in.
- No single industry partner, government or NGO alone can carry the burden of rollout and access – new public-private models needed to address funding, planning & coordination etc.
- Comprehensive funding landscape analysis is critical – not just ongoing prevention vs treatment research but also manufacturing, Ph. 4, rollout etc.
- Preferred Product Characteristics (PPC) debate – if WHO develops a PPC - will this stifle innovative R&D or iterative vaccine design?
Regulatory Considerations

• How to approach regulatory submissions, licensure, manufacturing in several countries, naming and packaging for an heterologous prime-boost vaccine regimen:
  • Harmonization of regulatory requirements would help accelerating licensure(s)
  • Could WHO drive harmonization discussion?
• There is a need to engage and build capacity for regulatory review of NRAs in LMICs early
• Licensure considerations of complex regimens (maybe of necessity).
  • When components owned by different groups, multiple vaccines – FDA: one sponsor is preferable for licensure applications
• Applications should have pharmacovigilance considerations included for post-licensure phase – Malaria vaccine example - how to do this and not hamper licensure process?
Country considerations

- Country specific roadmaps are necessary to include target populations, stakeholder definition.
- Early stakeholder engagement is required to facilitate more efficient rollout – e.g. MoH, regulators, advocates, civil society, NGOs, HCWs.
- Cost effectiveness and risk benefit, including cost of product and programmes, is needed to support decision-making process for governments.
- A need for better understanding of end user perspectives and potential barriers to uptake.
- Managing Vaccine Induced Seropositive tests: requirements for new testing products.
- Communication strategies needed in country for partially effective vaccine and for failure.
Recommendations from meeting

• WHO should dialogue between all relevant departments to integrate their roles in developing roadmaps with key partners, and with regulatory partners to align expectations.

• Separate roadmaps are needed for vaccines and bNAbs to allow proper timing of WHO and other stakeholder efforts in response to possible licensure.

• A global product public health value proposition evaluation (FPHVP) is needed, one that takes into account existing control measures and new interventions.

• It is important to plan for inclusion of diverse populations, thereby diminishing any delay for adolescents, for heterosexual men and boys, for populations in East Africa, West Africa and other regions with different circulating strains, and for infants, pregnant and nursing mothers.
Recommendations from meeting

• WHO can assist research teams to engage AVAREF and sub-regional structures to facilitate review of novel, complex products including joint reviews to expedite decision-making.

• Due to changing donor landscape and future needs for research and program support, new models needed to support HIV vaccines and bNAbs.

• Companies want a degree of confidence in several respects to participate, particularly regarding licensure and post-licensure requirements.

• Country considerations must be understood and addressed jointly and early.
Way Forward......

• Timely meeting - field appreciated renewed engagement by WHO
• Potential areas for WHO guidance and coordination identified,
• Field to make a coordinated strong case for sustained funding for R&D and Access
• Potential roles for PDPs, funders, governments, industry

“You need to have a good idea about where you want to end up and all of the steps you need to make to get there.” Mark Feinberg

Strategic coordination of the field to address long-term questions critical – a lot of work lies ahead......
Acknowledgements

• All presenters and attendees of the “WHO/UNAIDS Consultation: From Proof of Efficacy to Policy Decision, Access and Use of Products for Passive and Active Immunization to Prevent HIV Infection: Prepare for Success” Meeting held on February 28 – 1 March, 2018. Their input and presentations provided basis of this presentation including slides

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Thank You