GATES FOUNDATION HIV VACCINES STRATEGY

HIV VACCINE AWARENESS DAY: PLATFORMS & PIPELINES

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Bill & Melinda Gates Foundation
GATES FOUNDATION HIV PROGRAM STRATEGY

Strategic vision: Accelerate the reduction in the incidence of HIV infection in high-burden geographies and populations with the goal of achieving sustained epidemic control

Understand epidemic burden, programmatic progress and performance

Reduce onward transmission by maintaining viral suppression in HIV infected individuals

Prevent new HIV infections in uninfected individuals through primary prevention

Testing and linkage: Urgently and efficiently find people living with HIV, particularly hard-to-reach groups, and link them to treatment

Develop long-acting, high-efficacy PrEP interventions (incl. bNAbs)

Develop efficacious vaccines that provide durable protection to the general population

Promote evidence-based treatment and prevention programs with global partners and country governments

Promote scaling and sustained coverage of existing durable prevention intervention: VMMC

Develop innovative prevention service delivery approaches to support the effective use of new PrEP interventions

Develop innovative tools and methods to enable targeted service delivery

R&D

Delivery
Vaccine Discovery Consortia (VDC) brought together:

- To form communities of interest centered around scientific ideas
- To share pre-publication data
- To exchange knowledge and ideas

Central Service Facilities (CSF) provide:
- Best-in-class services to VDCs
- Enable comparative analysis of standardized data
- Enable translational efficiency

Alliance Management facilitates via:
- Scientific & logistical coordination and collaboration
- Incentives for sharing: legal agreements, contingent funding
- Mechanisms for sharing: web portal, meetings
HIV PROPHYLACTIC VACCINE

Vision

Broad coverage with a **durable high efficacy vaccine** will transform the HIV epidemic by reducing incidence

Goal

Develop a prophylactic HIV vaccine regimen that is safe and elicits a **coordinated and comprehensive** immune response

Focus

Elicitation of potent and sustained humoral and cellular immunity capable of overcoming HIV-sequence diversity by **preventing &/or rapidly aborting primary infection**
TARGET PRODUCT PROFILE

**Indication:** Prevention of HIV infection and/or containment of virus replication to rapidly abort primary infection

**Populations:** Healthy adults ≥18 years of age and prepubescent adolescents

**Efficacy:** ≥ 50%, preferable ≥ 70%

**Safety:** Safety and reactogenicity profile comparable to other licensed vaccines

**Duration of protection:** 3-5 years, preferable ≥ 10 years

**Onset of Immunity:** ≤28 days after full immunization, prefer ≤ 28 days after 1st dose

**Dosing Schedule & Route:** Full schedule within 6 mos.; IM/SC

**Stability/Shelf Life:** Stored at 2-8°C using EPI-compatible cold chain systems

**Access and Cost:** Deployed to LMICs with high disease burden within 6 months of vaccine approval by SRA/WHO; cost per dose comparable to GAVI negotiated pricing
VIRTUOUS (AND VICEIOUS) CYCLES OF LEARNING

**Virtuous cycle – a good result that enables more good results; Vicious cycle – a resolution of one problem which leads to new problems**

AMP TRIALS

HIV antibody trial results offer 'proof of concept'

Outcome of AMP shows feasibility of developing potent antibody combinations to block HIV

HVTN 702 - UHAMBO

Experimental HIV Vaccine Regimen Ineffective in Preventing HIV

No Safety Concerns Found; NIH and Partners Discontinue Vaccinations

February 3, 2020

HVTN 705 - IMBOKODO

HIV Vaccine Candidate Does Not Sufficiently Protect Women Against HIV Infection

Tuesday, August 31, 2021
WHAT HAVE WE LEARNED?

AMP
Level of sustained serum neutralizing titers (ID80>1:200) required for protection is higher than reasonably expected to be achieved currently via vaccination.

HVTN 702 & HVTN 705
The vaccine-elicited binding antibodies with effector functions, in combination with Class 1-restricted memory CD8+ T cells, are inadequate to prevent heterosexual transmission.
KEY QUESTIONS

- Can CD8+ T cell responses reduce the levels of neutralizing antibody required for protection?

- Can we develop a simple, translatable, regimen of immunogen(s) using nucleic acid platforms +/- viral vector(s) to elicit sustained levels of potent bnAbs and durable CD8 CTLs, including mucosal responses?

- Can we dramatically reduce the learning cycle time via faster, smaller, iterative human studies focused on specific critical hypotheses?
QUANTIFY CELLULAR & HUMORAL IMMUNITY NEEDED FOR AN EFFICACIOUS VACCINE

- Ongoing studies in Rh-SIV model (S. Hansen, L. Picker, D. Burton)

- Test hypothesis that a combination of cellular and humoral anti-SIV immune responses with partial efficacy will synergize to yield high efficacy

- Evaluate RhCMV-SIV vaccine (MHC-E-restricted CD8+ T cells) combined with SIV trimer immunogen and/or SIV mAb (bnAbs)
PORTFOLIO OF APPROACHES REQUIRING ITERATION

1. Immunogen/antigen design
   - Structure guided B cell immunogens
   - SHIV model to guide design (Shaw)
   - CD8+ T-cell epitopes
     • Mosaic/epigraph
     • Network-based

2. Immunogen delivery (platforms)

3. Adjuvants for dose sparing and/or innate/adaptive programming and continuing education of B cells

4. Sustained/Pulsatile Release Technologies

Select optimal components
FAST, ITERATIVE CLINICAL TRIALS WITH RAPID DATA ANALYSIS

- Iterative Vaccine Design and Testing in Experimental Human clinical studies

**Healthy Volunteers**
- Characterize Immune responses
- *Laboratory* assessment of functional activity of vaccine-induced responses

**PLWH + ATI**
- Characterize Immune responses
- *In vivo* assessment of functional activity of vaccine induced responses
mRNA VACCINE PLATFORM

RNA

Formulation/Delivery

Manufacturing
mRNA COMES IN DIFFERENT FLAVORS

**Unmodified**
Enhanced stability and translation by adding structural motifs at 3’ and 5’ locations

**Base-Modified mRNA**
Drives RNA translation, base modification leading to reduced innate immune response

**Self-Amplifying mRNA (saRNA)**
Contains genes of alphavirus that encode the non-structural proteins that replicate RNA and act as “adjuvant”
MRNA VACCINE PLATFORM CAN BE FURTHER LEVERAGED FOR GLOBAL HEALTH

1. BMGF has supported the mRNA vaccine platform for a while.
2. Opportunities: Other mRNA vaccines
   - HIV, TB, Malaria
   - T cell vaccines
   - Pandemic response
   - Immunogen design

Where we were and are now

- Early investments in mRNA platform and de-risking of mRNA/LNP vaccines by COVID; tap into even more value for Global Health

We can do more

- Access to mRNA/LNP vaccines for all
- Global mRNA/LNP vaccine footprint

RNA can be modified to make more efficacious products, broaden disease application and improve deliverability

- RNA optimization
- Reduced dose, improved T cell
- Manufacturing innovations (e.g., small-footprint processes)
- Develop platform further and pursue options for other GH-relevant antigens and other targets (combination vaccines)
- Delivery of biologics

RNA design

- Improved LNPs
- Derivitized LNPs with targeting receptors
- Non-LNP
- Manufacturing innovations
- Supply chain

Delivery

We can reach new frontiers

- Other RNA-based therapies
VACCINE DEVELOPMENT CAN BE MUCH FASTER

### TRADITIONAL VACCINES — 10 YEARS

<table>
<thead>
<tr>
<th>18 months</th>
<th>36 months</th>
<th>42 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Example</strong></td>
<td>Preclinical testing usually takes 1 to 2 years, but testing in humans may wait until an outbreak.</td>
<td><strong>Example</strong></td>
<td>The phase 1–2 study of GSK’s herpes zoster vaccine took nearly 1 year, and there was a 4-month gap between study completion and the start of phase 3.</td>
</tr>
<tr>
<td><strong>Accelerators</strong></td>
<td>Previous SARS-CoV-1, MERS, and RSV research</td>
<td><strong>Accelerators</strong></td>
<td>Merged phase 1–2 trial design</td>
</tr>
<tr>
<td></td>
<td>Parallel preclinical research</td>
<td></td>
<td>Continuous developer–regulator communication</td>
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<td></td>
<td>Multiple candidates manufactured at risk</td>
<td></td>
<td>Real-time clinical trial monitoring</td>
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### COVID-19 VACCINES — 1 YEAR

<table>
<thead>
<tr>
<th>1–2 weeks</th>
<th>1.5–1.9 months</th>
<th>15–16 weeks</th>
<th>5 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Example</strong></td>
<td>Cambridge University’s CAV20 platform optimization allowed the first vaccines to be ready within 60 days after sequence availability.</td>
<td><strong>Example</strong></td>
<td>Moderna tested its vaccine in separate phase 1 and 2 trials, taking a combined 19 weeks until phase 3 start, whereas Pfizer moved within 13 weeks into phase 3–1 testing.</td>
</tr>
<tr>
<td><strong>Accelerators</strong></td>
<td>Previous manufacturing-process development</td>
<td><strong>Accelerators</strong></td>
<td>Reduced time between interim data and phase 3 start</td>
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<td></td>
<td>Earlier technology transfer to production sites</td>
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<td>Platform readiness for commercial-scale manufacturing</td>
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Years Ahead in HIV Prevention Research

Time to Market

<table>
<thead>
<tr>
<th>Prevention Product</th>
<th>2020</th>
<th>2021</th>
<th>2022</th>
<th>2023</th>
<th>2024</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal Ring</td>
<td>Dapivirine Vaginal Ring</td>
<td>Positive EMA Opinion; WHO Prequalification and Recommendation</td>
<td>Zimbabwe Regulatory Approval</td>
<td>Additional regulatory approval &amp; early introduction</td>
<td></td>
</tr>
<tr>
<td>Long-Acting Injectables</td>
<td>CAB-LA</td>
<td>Early MPTN 083 and 084 results</td>
<td>US FDA approval; additional submissions to other regulators ongoing</td>
<td>Additional regulatory approvals, WHO recommendation, and early introduction</td>
<td>Efficacy trials of six monthly injectables (trials paused)</td>
</tr>
<tr>
<td>Dual Prevention Pill</td>
<td>TDF/FTC/ Combined oral contraceptives</td>
<td></td>
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<td></td>
<td>Possible regulatory approval &amp; early introduction</td>
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<tr>
<td>Oral PrEP</td>
<td>FTC/TAF</td>
<td></td>
<td></td>
<td></td>
<td>Daily oral FTC/TAF efficacy trials in cisgender women (trial paused)</td>
</tr>
<tr>
<td>Preventive Vaccine</td>
<td>Ad26</td>
<td></td>
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<td>Efficacy trial among MSM and trans people (trials paused)</td>
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January 2022