Biomedical Prevention & Cure Research Pipeline

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Treatment Action Group

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Biomedical prevention pipeline

- Pre-exposure prophylaxis (PrEP) with Truvada represents the first FDA-approved biomedical prevention intervention

- In the pipeline:
  - Alternative forms of antiretroviral PrEP
  - Microbicides
  - Passive immunization with broadly neutralizing antibodies (bNAbs)
  - bNAb gene transfer
  - HIV vaccines
## Alternative forms of antiretroviral PrEP

<table>
<thead>
<tr>
<th>Compound</th>
<th>Class/Type</th>
<th>Company/Sponsor</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORAL FORMULATIONS</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Descovy (TAF + FTC)</td>
<td>NtRTI/NRTI</td>
<td>Gilead</td>
<td>Phase III</td>
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<tr>
<td>Descovy (TAF + FTC)</td>
<td>NtRTI/NRTI</td>
<td>CONRAD</td>
<td>Phase I (in cisgender women)</td>
</tr>
<tr>
<td>Genvoya (EVG + COBI + FTC + TAF)</td>
<td>INSTI/NtRTI/NRTI</td>
<td>Emory University</td>
<td>Phase I</td>
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<tr>
<td><strong>LONG-ACTING FORMULATIONS</strong></td>
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<tr>
<td>Cabotegravir</td>
<td>INSTI</td>
<td>ViiV Healthcare</td>
<td>Phase IIb/III</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>NNRTI</td>
<td>PATH</td>
<td>Phase II</td>
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Microbicides

- MTN-020–ASPIRE Study:
  - Dapivirine vaginal ring self-inserted and removed once per month associated with 27% reduction in risk of HIV acquisition in phase III trial involving 2,629 women in Malawi, South Africa, Uganda, and Zimbabwe.
  - Higher efficacy in women >21 yrs (56% reduction in risk), no efficacy <21yrs - associated with differences in adherence
  - Highest adherence associated with 65% reduction in risk (72% >21 yrs, 50% <21 yrs)

- IPM 027 Study:
  - Dapivirine vaginal ring associated with 30% reduction in risk of HIV acquisition in phase III trial involving 1,959 women in South Africa and Uganda
  - Slightly higher efficacy of 37.5% in women >21 yrs

- Open label follow up studies are planned for both trials

- International Partnership for Microbicides plans to submit the dossier of dapivirine vaginal ring evidence required for licensure to regulatory agencies
## Multipurpose technologies

<table>
<thead>
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<th>Compound</th>
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<tbody>
<tr>
<td>Tenofovir + levonorgestrel vaginal ring</td>
<td>NtRTI/HC</td>
<td>CONRAD</td>
<td>Phase I</td>
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<tr>
<td>Dapivirine + levonorgestrel vaginal ring</td>
<td>NNRTI/HC</td>
<td>IPM + MTN</td>
<td>Phase I</td>
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<tr>
<td>MB66</td>
<td>Anti-HIV + anti-HSV antibodies in vaginal film</td>
<td>LeafBio, Inc.</td>
<td>Phase I</td>
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# Microbicide combinations

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<th>Compound</th>
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<tbody>
<tr>
<td>Maraviroc + dapivirine</td>
<td>CCR5 inhibitor/NNRTI</td>
<td>IPM</td>
<td>Phase I</td>
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<tr>
<td>vaginal ring</td>
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<tr>
<td>MK-2048 + vicriviroc</td>
<td>INSTI/CCR5 inhibitor</td>
<td>MTN</td>
<td>Phase I</td>
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<tr>
<td>vaginal ring</td>
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<tr>
<td>Dapivirine + darunavir</td>
<td>NNRTI/PI</td>
<td>CHAARM</td>
<td>Phase I</td>
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<tr>
<td>vaginal gel</td>
<td></td>
<td></td>
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<tr>
<td>Dapivirine + DS003</td>
<td>NNRTI/EI</td>
<td>IPM</td>
<td>Preclinical</td>
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## Rectal microbicides

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<th>Compound</th>
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<tbody>
<tr>
<td>Dapivirine rectal gel</td>
<td>NNRTI</td>
<td>IPM</td>
<td>Phase I (planned)</td>
</tr>
<tr>
<td>MIV150 rectal gel</td>
<td>NNRTI</td>
<td>MTN</td>
<td>Phase I (planned)</td>
</tr>
<tr>
<td>Elvitegravir rectal insert</td>
<td>INSTI</td>
<td>MTN</td>
<td>Phase I (planned)</td>
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<tr>
<td>IQP-0528 rectal gel</td>
<td>NNRTI</td>
<td>ImQuest</td>
<td>Phase I</td>
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<td>Griffithsin rectal gel</td>
<td>Cell-viral fusion–blocking agent</td>
<td>University of Louisville</td>
<td>Phase I</td>
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<tr>
<td>PC-1005 vaginal and rectal gel</td>
<td>NNRTI, ZA, CGN</td>
<td>Population Council</td>
<td>Phase I</td>
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<tr>
<td>Maraviroc vaginal and rectal gel</td>
<td>CCR5 inhibitor</td>
<td>IPM</td>
<td>Phase I</td>
</tr>
<tr>
<td>Tenofovir enema</td>
<td>NtRTI</td>
<td>Johns Hopkins University</td>
<td>Phase I</td>
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**Broadly neutralizing antibodies (bNAbs)**

- Explosion of bNAb discovery over the last decade or so
- Technological breakthroughs allow the identification of the exact individual B cell producing antibodies of interest
- The technology makes it possible to identify individual bNAbs from HIV+ individuals whose serum samples display ability to inhibit HIV replication in laboratory tests
- Some individuals develop bNAbs after several years of HIV infection
- Growing library of bNAbs with increasing potency (ability to strongly inhibit HIV at low concentrations) and breadth (inhibition of many different HIV isolates from all global clades)
- E.g. VRC01, VRC07, PG9, 3BNC117, 10-1074, PGT121, CAP256, PGDM1400, N6 (capable of neutralizing up to 98% of global isolates)
## Passive immunization with bNAbs

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<th>Compound</th>
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<tbody>
<tr>
<td>VRC01</td>
<td>Monoclonal bNAb administered i.v.</td>
<td>NIAID/HVTN/HPTN</td>
<td>Phase Iib</td>
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<tr>
<td>10-1074</td>
<td>“</td>
<td>Rockefeller University</td>
<td>Phase I</td>
</tr>
<tr>
<td>3BNC117 + 10-1074</td>
<td>“</td>
<td>Rockefeller University</td>
<td>Phase I</td>
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<tr>
<td>P2G12</td>
<td>“</td>
<td>St George’s, University of London</td>
<td>Phase I</td>
</tr>
<tr>
<td>PGT121</td>
<td>“</td>
<td>IAVI</td>
<td>Phase I</td>
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<tr>
<td>VRC01LS</td>
<td>Long-acting bNAb i.v. or s.c. delivery</td>
<td>NIAID</td>
<td>Phase I</td>
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<tr>
<td>VRC07-523LS</td>
<td>Long-acting bNAb i.v. or s.c. delivery</td>
<td>NIAID</td>
<td>Phase I</td>
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The Antibody Mediated Prevention (AMP) trials

- HVTN 704/HPTN 085 will enroll approximately 2,700 men and transgender people who have sex with men at sites in Brazil, Peru, and the U.S.

- HVTN 703/HPTN 081 will enroll approximately 1,500 women at sites in Botswana, Kenya, Malawi, Mozambique, South Africa, Tanzania, and Zimbabwe

- Participants will be randomly assigned to receive either placebo or VRC01 at one of two doses: 30 mg/kg or 10 mg/kg

- Intravenous infusions are scheduled every eight weeks

- The primary endpoints are safety and efficacy

- Secondary analyses including assessments of VRC01 levels, markers of protection, and antibody effector functions

- If the trials proceed as expected, results are likely to become available around 2022
Antibody gene transfer

- As an alternative to intravenous or subcutaneous delivery, researchers are exploring the use of viral vectors to transfer the genetic code for bNAbs into muscle tissue.
- The idea is for the vector to act as a mini-factory producing enough bNAbs to attain protective levels in the body (akin to gene therapy).
- Idea pioneered by Phil Johnson, who is collaborating with the International AIDS Vaccine Initiative (IAVI) on a phase I trial of an adeno-associated virus (AAV) vector encoding the bNAb PG9.
- Trial is ongoing in the UK.
- Some concern that immune responses will be induced against the bNAb, potentially limiting efficacy (problem has been observed in macaque studies).
HIV vaccines

- To date the only reported evidence of significant vaccine-induced protection against HIV acquisition comes from the RV144 trial in Thailand
- Results were published in 2009, describing a 31.2% reduction in risk associated with receipt of a “prime-boost” vaccine regimen comprising an ALVAC canarypox vector prime and a gp120 protein boost
- Protection appeared higher at 12 months of follow up (~60%) in a post hoc analysis
- Result was borderline statistically significant and there remains some controversy as to whether it reflects vaccine efficacy
- No induction of bNAbs
- Some evidence protection associated with non-neutralizing antibody responses to a particular region of the HIV envelope (V2) and CD4 T cell responses to HIV
HIV vaccines

- After many delays, a similar vaccine regimen has now been tailored for South Africa and a large efficacy trial—HVTN 702—began last fall.
- The ALVAC and gp120 protein components are derived from HIV-1 clade C, the most common strain in South Africa.
- The trial is sponsored by a large collaborative effort known as the Pox-Protein Public-Private Partnership (P5), involving NIAID, the Bill & Melinda Gates Foundation, the South African Medical Research Council, HVTN, Sanofi Pasteur, GSK and the U.S. Military HIV Research Program.
- Results are expected by 2020.
HIV vaccines

- Next efficacy trials likely to be launched by a partnership led by Janssen/Johnson & Johnson
- Significant because there has been limited pharmaceutical industry involvement in HIV vaccine research
- Partnership is studying prime-boost vaccine regimens involving adenovirus serotype 26 (Ad26) and Modified Vaccinia Ankara strain (MVA) viral vectors and trimeric gp140 protein boosts
- Employing novel “mosaic” antigens that incorporate elements from multiple different global HIV strains
- Regimens have shown promise in SIV/macaque model
- Plan is to launch first placebo-controlled efficacy trial (HPX2008/HVTN 705) in late 2017 or early 2018, enrolling 2,600 women aged between 18 and 35 at sites in South Africa, Zambia, Zimbabwe, Malawi, and Mozambique
HIV vaccines

- Many other candidates in earlier phase studies
- Results from efficacy trials should help shed light on which other candidates may have promise
- The holy grail of HIV vaccine research is induction of bNAbs, but this is a difficult challenge
- B cells undergo prolonged, complex process (somatic hypermutation) to generate bNAbs
- Researchers still figuring out how to coax B cells through this process with vaccines, but some signs of progress
- Trials of vaccine candidates that may be capable of *starting* the process may begin next year
HIV cure research pipeline

- Timothy Ray Brown – a one man proof of concept
- HIV+ and on ART
- Diagnosed with acute myeloid leukemia (AML)
- Received stem cell transplants from a CCR5Δ32 homozygous bone marrow donor circa 2007
- Chemotherapy and radiotherapy conditioning
- Stopped ART without HIV rebound
- 10 years later: considered cured
- Dangerous procedure (20-30% mortality risk) only appropriate for people needing stem cell transplants to treat serious cancers
HIV cure research goals

- Reduce or eliminate the reservoir of HIV-infected cells that persists despite ART
- Prevent or control the rebound of HIV replication that occurs when ART is interrupted
- Eliminate need for ongoing medication
- No symptoms
- No disease progression/immune damage
- No risk of transmission
Current approaches

- **Latency-reversing**: approaches that aim to awaken the dormant “latent” HIV that persists after viral replication is suppressed by ART

- **Immune-enhancing**: interventions intended to strengthen the immune response to HIV in hopes of enabling the body to control or even gradually eliminate HIV reservoirs

- **Kick & kill**: combinations of latency-reversing and immune-enhancing approaches that aim to 1) awaken latent HIV so that infected cells become visible to the immune system 2) induce immune responses capable of targeting the infected cells for elimination

- **Cell-protecting**: gene therapies designed to protect potential target cells from HIV infection

- **HIV-eliminating**: gene therapies designed to specifically excise the HIV genome from latently infected cells
Kick & kill
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<tr>
<td>ROADMAP: romidepsin + 3BNC117</td>
<td>HDAC inhibitor + bNAb</td>
<td>Rockefeller University</td>
<td>Phase Iia</td>
</tr>
<tr>
<td>eCLEAR: romidepsin + 3BNC117</td>
<td>HDAC inhibitor + bNAb</td>
<td>Aarhus University Hospital</td>
<td>Phase II</td>
</tr>
<tr>
<td>Panobinostat + pegylated interferon- alpha2a</td>
<td>HDAC inhibitor + cytokine</td>
<td>Massachusetts General Hospital</td>
<td>Phase II</td>
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<tr>
<td>ChAdV63 + MVA. HIVconsv vaccines + vorinostat</td>
<td>Therapeutic vaccines + HDAC inhibitor</td>
<td>Imperial College London</td>
<td>Phase II</td>
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<tr>
<td>AGS-004 + vorinostat</td>
<td>Therapeutic vaccine + HDAC inhibitor</td>
<td>NIAID</td>
<td>Phase I</td>
</tr>
<tr>
<td>MVA.HIVconsv + romidepsin</td>
<td>Therapeutic vaccine + HDAC inhibitor</td>
<td>IrsiCaixa</td>
<td>Phase I</td>
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<tr>
<td>vorinostat + HXTC (HIV-specific T cell therapy)</td>
<td>HDAC inhibitor + adoptive immunotherapy</td>
<td>University of North Carolina, Chapel Hill</td>
<td>Phase I</td>
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Monitored Antiretroviral Pause (MAP)

- 13 participants have interrupted cART to date.

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Diverse approaches in trials

- Adoptive immunotherapy – 2
- Antibodies – 11
- Anti-fibrotic – 2
- Anti-inflammatory – 2
- Antiretroviral therapy – 2
- Combinations – 16
- Gene therapies – 6
- Gene therapies for HIV+ people with cancers – 7
- Hormones – 1
- Imaging studies – 1
- Immune checkpoint inhibitors -3
- Janus kinase inhibitors – 1
- Latency-reversing agents – 7
- mTOR inhibitors -2
- Proteasome inhibitors – 1
- Stem cell transplantation – 4
- Therapeutic vaccines – 11
- Traditional Chinese medicine – 1
- Treatment intensification/early treatment – 14

http://www.treatmentactiongroup.org/cure/trials
Evidence prolonged remission is possible

- The Mississippi baby
  - Immediate ART at birth, maintained for ~18 months, ART then interrupted with no viral load rebound for 2 years 3 months

- The Boston patients
  - Two HIV+ individuals with cancers who received stem cell transplants, ART was maintained throughout, HIV reservoirs not detectable after procedures. ART ultimately interrupted with no viral load rebound for 3 and 8 months, respectively

- Mayo clinic patient
  - HIV+ individual with cancer who received stem cell transplant, ART ultimately interrupted with no viral load rebound for 288 days

- UCSF patient diagnosed entering PrEP project
  - Initiated on ART within days of HIV infection, maintained for >1 yr. After eventual ART interruption, no viral load rebound for 220 days
Many challenges remain

- Best HIV reservoir reductions reported to date in studies of chronic HIV infection <0.5 log, mathematical models indicate reduction of 4-6 logs required for lifelong cure
- The HIV reservoir is difficult to comprehensively measure, majority resides in tissues
- Evidence of population-specific differences in the HIV reservoir (e.g. men vs. women)
- Therapeutic candidates can have serious toxicities e.g. HDAC inhibitors, immune checkpoint inhibitors
- Ethical questions relating to studying potentially toxic interventions and/or conducting ART interruptions in healthy HIV+ individuals with life expectancy increasingly comparable to HIV- counterparts