European RAVE
HIV Prevention Science and Advocacy Training

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European RAVE
June 12–13, 2014
The 3 D’s

- Develop
- Demonstrate
- Deliver
The “research-to-rollout” continuum encompasses the many steps between an initial scientific concept and a new tool offered in an effective public health program. Today, HIV prevention research advocacy is needed at every stage. It is critical to sustain support for research to develop game-changing tools such as microbicides or an AIDS vaccine; pilot projects that demonstrate the impact of emerging tools like pre-exposure prophylaxis (PrEP); and public health programs that deliver combination prevention including treatment as prevention and voluntary medical male circumcision (VMMC) for maximum impact. To learn more visit www.avac.org.
Biomedical HIV Prevention Efficacy Trials, 2014–2016

- **FACTS 001**: 2,900 women in South Africa, BAT-24 dosing regimen
  - **FACTS 002** and other adolescent studies
- **The Ring Study/IPM 027**: 1,650 women in Rwanda and South Africa, testing 4-week vaginal dapivirine ring
- **ASPIRE/MTN 020**: 3,476 women in Malawi, South Africa, Uganda, Zimbabwe testing 4-week vaginal dapivirine ring

**Rectal TFV gel efficacy trial**

**Earliest regulatory submission**

**Possible Long-acting ARV injectable efficacy trial**

**South Africa licensure trial (HVTN 702)**

**Southern African correlates trial (701)**

**Thai licensure trial**

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* Trial end dates are estimates; due to the nature of clinical trials, the actual dates may change. For full trial details, see www.avac.org/pxrd.

* This table only includes efficacy evaluations of biomedical strategies in HIV-negative people. There are ongoing pilot and demonstration projects of oral PrEP, an open-label evaluation of 1% tenofovir gel in the community where CAPRISA 008 took place, and numerous Phase I and II trials of other options.

AVAC Report 2013: Research & Reality
www.avac.org/report2013
Treatment as Prevention
What is treatment as prevention?

- Use of ARVs in HIV-positive people to reduce the risk passing HIV to others
- The strategy is a **secondary** benefit of ARV treatment
- The **primary benefit** is the individual’s health
- The rational is that ARV's reduce viral load, which decreases infectiousness
- Recently proven to work in HPTN 052 study—reduces risk of transmission by 96%
WHO 2013 guidelines recommend initiating ART in HIV positive people with CD4 cell counts of 500 or below. Implementing these guidelines will reduce infections and save lives.

### Annual HIV Infections in 2015
- **2010 Guidelines**
- **2013 Guidelines**
- **36%**

### Annual HIV-related deaths in 2015
- **2010 Guidelines**
- **2013 Guidelines**
- **39%**

**3.5 million additional new HIV infections averted**

**3 million additional lives saved**

The Global HIV Treatment Gap: Existing people on ART versus people eligible under past and current WHO guidelines

- Total people on ART in 2012: 9.7 M
- People in need of ART based on WHO 2010 Guidelines: +7 M
- Additional people in need of ART based on WHO 2013 Guidelines: +9.2 M
- People eligible for HIV treatment based on WHO 2013 Guidelines: ≈ 26 M
- Treatment Gap based on 2013 WHO Guidelines: 16.2 M
How do we know Tx as Px Works?

- **HPTN 052 (2011 Top Scientific Breakthrough! *Science Magazine*)**
  - Randomized clinical trial (RCT) in heterosexual, serodiscordant couples in Africa, Asia and the Americas
  - Showed that **immediate treatment** for healthy HIV-positive sexual partners with high CD4 counts (between 350-550) **reduced risk** of transmission to their HIV-negative sexual partner **by 96% [possibly 100%?]** and lowered TB rates and improved health in the HIV positive partner.
  - There is a movement to get people tested, into care and on treatment with antiretroviral therapy at 350 CD4s and above, in an effort to prevent HIV.
Evolving Treatment (and Px) Guidelines

• March 2012: US HHS recommends treating all HIV positive individuals regardless of CD4 count
  – Strongly recommended for those with AIDS-defining illness, TB, and serodiscordant couples

• June 2013: WHO updates its guidelines to start treatment at 500 CD4 count

• Community Consensus Statement on TasP 2014
Tx as Px Benefits

- **Individual survival rates increase**
  - Reduce disease and death
  - Control of TB and other HIV/AIDS-related illnesses
- **Population levels of HIV decrease**
  - 2004-2011 Kwazulul Natal (30-40% of HIV-infected on ART, decreased incidence by 38%)
  - 2002-2008 San Francisco: Increased tx, decreased community viral load and decreased HIV infections
  - But conflicting signals from incidence rates in London and other jurisdictions.
- **Simplified clinical management**
- **Reduce stigma with routine testing**
- **Cost-effective over time**
Tx as Px Challenges

- Current waiting lists
- Low rates of HIV testing
- Questions about HPTN 052’s durability, other sexual transmission routes, such as anal sex (but see Partners study)
- High viral load during acute phase of infection
  - Inconclusive data showing that starting early—above 500—is good for individual health. Ongoing clinical and observational evidence that early treatment is best for a person’s health. Being confirmed in START trial.
- Long-term toxicity
- Adherence in healthy people
Narrow the Gaps in the HIV Treatment Cascade

Test

HIV-Positive

HIV TESTING
- Improved HIV rapid tests (e.g., oral tests)
- Home- and community-based counseling and testing
- HIV testing by community and lay health workers
- Provider-initiated HIV testing and counseling and integration with primary care
- Targeted mobile testing for hard-to-reach groups at schools, taxi ranks, farms, workplaces

Engage, counsel, monitor, support

HIV Care (Pre-ART)

PRE-ART REGULAR CLINIC CARE
- Strong referral and linkage to care
- Free HIV care and treatment
- Point-of-care CD4 count testing
- Rapid diagnosis and treatment of TB
- Regular visits, TB and PCP prophylaxis
- Support tools (mobile messages, patient-held appointment cards)

Retain, counsel, monitor, support

ART Eligible

ART

EARLY ART RETENTION IN CARE
- Timely and/or earlier ART initiation
- Adapted adherence support
- Decentralization, primary care integration
- Task-shifting
- Non-toxic robust drugs; once-daily fixed-dose combinations
- Viral load monitoring
- Out-of-clinic care

Adherence and viral suppression

UNDETECTABLE

LONG-TERM ART AND UNDETECTABLE VIRAL LOAD
- Simplified clinical and refill schedules
- Community-based, peer-supported ART
- Viral load–triggered adherence support
- Reliable drug supply, multiple month refills
- Defaulter tracing

Sources:
Engagement in HIV Care in France in 2010

Trends in HIV incidence among MSM

Delpech, V. Health System Concerns Related to TasP and Most At Risk Populations. IAPAC Treatment as Prevention and PrEP. London, UK: June 2012.
Number of new HIV diagnoses by prevention group, UK: 2000-2009

Health Protection Report, Weekly Report, 4 (47), 26 November 2010
Partners Study

- Study in gay and heterosexual couples on ART in Europe has no cases where someone with a viral load under 200 copies/ml transmitted HIV, either by anal or vaginal sex.
- Likely chance of transmission via anal sex from someone on successful HIV treatment was 1% a year for any anal sex and 4% for anal sex with ejaculation where the HIV-negative partner was receptive.
- There were no transmissions despite high levels of STIs. If the HIV-positive partners had not been on treatment in this group, 50-100 (median: 86) transmissions would have been expected in the gay couples, and 15 transmissions in heterosexual couples.
- PARTNERS still recruiting gay male couples and, as noted above, its full results will not be out till 2017.
**Potential Challenge: Uninformed Treatment**

### Assessing HIV-positive Persons’ Readiness to Start and Maintain ART

<table>
<thead>
<tr>
<th>Stage of readiness to start ART</th>
<th>Support Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>Preparation:</strong> I want to start, I think the drugs will allow me to live a normal life.</td>
<td>Support: Reassure the person that the physician considers the regimen to be the most convenient regimen. Educate the person on adherence, resistance, side effects. Discuss integration into daily life. Respect the person’s self-assessment. Help: Are you sure you can take your medication as we discussed (specify) since you have started? Use ARVs (p. 121).</td>
</tr>
<tr>
<td>2. <strong>Action:</strong> I will start today.</td>
<td>Formalize the decision, possibly MOAD. Directly observed Therapy with educational support. Use aids: mobile phone alarm, pillboxes. Provide support information where appropriate.</td>
</tr>
</tbody>
</table>

### Stages of readiness to start ART

1. **Preparation:** I want to start, I think the drugs will allow me to live a normal life.
2. **Action:** I will start today.
3. **Maintenance:** I will continue or I have difficulty continuing over the long run.
4. **Crisis:** A person can relapse in an earlier stage, even from maintenance by ‘resistance-collapser’

### Identify the person in each stage of readiness using AMI/SP/techniques.

- The person’s response to the stage question/balancing on ART can be divided into five stages. Knowing the person’s stage, healthcare providers can apply appropriate techniques to assist them to start and maintain ART.

### EACS Treatment Guidelines 2013

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**EACS Treatment Guidelines 2013**
Ongoing Research: Timeline on randomized clinical control trial projects with early antiretroviral therapy (CD4 count ≥ 350 cells/mm3)
<table>
<thead>
<tr>
<th>Focus of studies</th>
<th>No. of studies</th>
<th>Countries / Regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early (≥500) or immediate ART initiation</td>
<td>9</td>
<td>Argentina, Australia, <strong>Austria</strong>, Belgium, Brazil, Chile, Cote d'Ivoire, <strong>Czech Republic</strong>, Denmark, Estonia, Finland, <strong>France</strong>, Germany, Greece, India, <strong>Ireland</strong>, Israel, Italy, Kenya, Luxembourg, Malaysia, Mali, Mexico, Morocco, Nigeria, Norway, Peru, Poland, <strong>Portugal</strong>, Puerto Rico, South Africa, Spain, Swaziland, <strong>Sweden</strong>, Switzerland, Thailand, Uganda, <strong>United Kingdom</strong>, United States, Zambia</td>
</tr>
<tr>
<td>ART for HIV+ partner in serodiscordant couples</td>
<td>3</td>
<td>Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, United States, Viet Nam, Zimbabwe, <strong>Europe</strong></td>
</tr>
<tr>
<td>TasP for key populations (MSM, PWID, transgender women)</td>
<td>16</td>
<td>Australia, Canada (BC), China, India, Kenya, Peru, Puerto Rico, Thailand, United States, Viet Nam</td>
</tr>
<tr>
<td>Combination HIV prevention (ART at &lt; 350)</td>
<td>7</td>
<td>Botswana, Lesotho, South Africa, Tanzania, Uganda, Zambia</td>
</tr>
<tr>
<td>Community-based HIV testing</td>
<td>1</td>
<td>Uganda</td>
</tr>
<tr>
<td>Seek, test, treat and retain strategies</td>
<td>24</td>
<td>China, British Columbia, India, Kenya, Peru, Swaziland, Uganda, United States, Viet Nam</td>
</tr>
</tbody>
</table>
• Need to implement while researching to improve
• Of WHO’s 90 priority countries, 80% intend to adopt policies to treat CD4 <500.
• Less than 10% of the cost of care is in commodities (drugs/diagnostics)
• A costing study of the new guidelines in Rwanda found by investing US $12.7 million over next 5 years, an estimated 12,800 patients put on treatment, 7,586 infections would be averted and it would save the government US$27.3 million.
• Early estimates from Temprano TasP show the protective effect to be about 90%, about the same as HPTN 052.
Treatment as Prevention: Next Steps

- Influence countries to adopt new WHO guidelines and influence WHO to move to treatment on demand (at any CD 4 count)
- Utilize PEPFAR blueprint to influence Country Operating Plans
- Influence countries to adopt TasP guidelines for gay and other MSM.
- Advocate for easier regimens with few side effects – longer acting drugs/formulations – pipeline monitoring
- Build community AND provider understanding of and demand for TasP – and also amplify concerns
- Advocate for implementation – the development of service delivery and training systems.
- Monitor for impact – what’s working?
- Invest in country and community specific “cascade” research
Pre-exposure Prophylaxis (PrEP)
Pre-exposure Prophylaxis

Pre-exposure prophylaxis, or PrEP, is a strategy that involves use of antiretroviral medications (ARVs) to reduce the risk of HIV infection via sexual and drug-injecting exposure. All of the current *effectiveness* and *follow-on* trials are testing tenofovir-based regimens—using either TDF/FTC (Truvada) or TDF (Viread).
Clinical Trial Evidence for Oral and Topical Tenofovir-Based Prevention (December 2013)

Prevention of sexual transmission

- **Partners PrEP** – daily oral TDF/FTC
  (Serodiscordant couples – Kenya, Uganda)
- **Partners PrEP** – daily oral TDF
  (Serodiscordant couples – Kenya, Uganda)
- **TDF2** – daily TDF/FTC
  (Heterosexual men and women – Botswana)
- **iPrEx** – daily oral TDF/FTC
  (MSM – North and South America, South Africa, Thailand)
- **CAPRISA 004 – BAT-24 dosing vaginal tenofovir gel**
  (Women – South Africa)
- **MTN 003/VOICE** – daily dosing vaginal tenofovir gel
  (Women – South Africa, Zimbabwe)
- **FEM-PrEP** – daily oral TDF/FTC
  (Women – Kenya, South Africa, Tanzania)
- **MTN-003/VOICE** – daily oral TDF/FTC
  (Women – South Africa, Uganda, Zimbabwe)
- **MTN-003/VOICE** – daily oral TDF
  (Women – South Africa, Uganda, Zimbabwe)

Prevention in people who inject drugs

- **Bangkok Tenofovir Study – Daily oral TDF**
  (IDUs – Thailand)

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect size (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partners PrEP</td>
<td>75% (55; 87)</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>67% (44; 81)</td>
</tr>
<tr>
<td>TDF2</td>
<td>62% (22; 84)</td>
</tr>
<tr>
<td>iPrEx</td>
<td>44% (15; 63)</td>
</tr>
<tr>
<td>CAPRISA 004</td>
<td>39% (6; 60)</td>
</tr>
<tr>
<td>MTN 003/VOICE</td>
<td>15% (-21; 40)</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>6% (-52; 41)</td>
</tr>
<tr>
<td>MTN-003/VOICE</td>
<td>-4% (-49; 27)</td>
</tr>
<tr>
<td>MTN-003/VOICE</td>
<td>-49% (-129; 3)</td>
</tr>
<tr>
<td>Bangkok Tenofovir</td>
<td>49% (10; 72)</td>
</tr>
</tbody>
</table>

Source: Salim S. Abdool Karim, CAPRISA

AVAC Report 2013: Research & Reality
www.avac.org/report2013
Effectiveness & Adherence

Effectiveness and Adherence in Trials of Oral and Topical Tenofovir-Based Prevention

Trials of oral and topical tenofovir-based PrEP show that these strategies reduce risk of HIV infection if they are used correctly and consistently. Higher adherence is directly linked to greater levels of protection.

Source: Salim S. Abdool Karim, CAPRISA

AVAC Report 2013: Research & Reality
www.avac.org/report2013
Ongoing PrEP research

Alternative dosing, drugs, delivery

- IPERGAY (Truvada on-demand)
- NEXT (maraviroc)
- Long-acting injectables
  - Phase II: GSK744, Éclair & HPTN 077, 12 wks, 2016
  - Phase II: Rilpivirine (TMC278), HPTN 076, 8 wks,
- ARV-containing rings
  - Phase III: Ring and Aspire
Implementation

- Jan 2011 CDC Interim Guidance for gay men and other MSM
- Dec 2011 BHVA Position Statement on PrEP
- June 2012 South Africa and Quebec develop provider guidelines
- July 2012 US FDA approves Truvada as PrEP
- July 2012 WHO issues guidance on PrEP demonstration projects (sero-discordant couples and MSM & TG)
- July 2012 CDC Interim Guidance for prevention of HIV infection in heterosexually active adults
- May 2014 US CDC release New Clinical Guidelines for PrEP
- 2015 WHO expected PrEP guidelines??
- Rest of Europe??
Unanswered questions

- Will people seek out PrEP?
- Will they adhere to and sustain PrEP?
- How to integrate with other services?
- Optimal dosing?
- Condom migration?
- HIV resistance?
- Side effects?
- Who pays?

http://www.avac.org/resource/ongoing-and-planned-prep-evaluation-studies
Evaluation studies

How to deliver PrEP

Over two dozen evaluation projects:

- PROUD
- iPrEx OLE
- Partners Demonstration Project

Looking at:

- MSM, trans, sex workers, IDUs, sero-discord couples

In:

- Australia, Botswana, Brazil, Ecuador, India, Kenya, Nigeria, Peru, Uganda, South Africa, Thailand, Uganda, US

### Planned PrEP Demonstration Projects in Resource-Poor Settings as of December 2013

There are a range of planned or ongoing demonstration projects or open-label extension studies happening in the United States and Europe. This table includes those few projects in resource-poor settings that are not linked to one of the efficacy trials. A complete list is available at www.avac.org/prep.

<table>
<thead>
<tr>
<th>Trial/project</th>
<th>Sponsor/Funder</th>
<th>Location</th>
<th>Population</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partners Demonstration Project</td>
<td>Led by a team of scientists from Kenya, Uganda and the US; funded by NIMH/NIH, USAID and BMGF</td>
<td>Kenya, Uganda</td>
<td>Serodiscordant couples</td>
<td>All four sites open and enrolling as of August 2013; results expected in 2016.</td>
</tr>
<tr>
<td>LVCT and SWOP</td>
<td></td>
<td>Kenya</td>
<td>Young women, female sex workers and MSM</td>
<td>Formative research in planning phase.</td>
</tr>
<tr>
<td>Nigerian National Agency for the Control of AIDS</td>
<td>Implemented by national partners in collaboration with WHO, UNAIDS, O’Neill Institute of Georgetown University, London School of Hygiene and Tropical Medicine, Imperial College London; funded by Bill &amp; Melinda Gates Foundation</td>
<td>Nigeria</td>
<td>Serodiscordant couples</td>
<td>Formative discussions underway.</td>
</tr>
<tr>
<td>Wits Reproductive Health and HIV Institute</td>
<td></td>
<td>South Africa</td>
<td>Female sex workers</td>
<td>Expected start date of February 2014, with expected completion September 2016.</td>
</tr>
<tr>
<td>Durbar (DMSC) and Ashodaya Samiithi</td>
<td></td>
<td>India</td>
<td>Female and transgender sex workers</td>
<td>Feasibility study underway.</td>
</tr>
<tr>
<td>Implementation of PrEP</td>
<td>Oswaldo Cruz Foundation</td>
<td>Brazil</td>
<td>MSM and transgender women</td>
<td>Starting January 2014.</td>
</tr>
</tbody>
</table>

AVAC Report 2013: Research & Reality  
www.avac.org/report2013
Highlighted in darker blue are the areas where biomedical HIV prevention research has the most experience to date. The “gap” between positive effectiveness data and access for trial participants and their communities is less familiar territory – as are the steps in lighter blue.

From Research to Rollout

- **Post-trial access**
  - Intervention provided to trial participants and, sometimes, their communities, after trial & before product is available for widespread use

- **Open label extensions**
  - Intervention made available in follow-on protocol in which participants from previous RCT know they are receiving active intervention
  - Gather information about how product use in people who are now aware of potential benefit

- **Open label/Implementation studies**
  - Research protocols similar to above but enrolling new participants

- **Demonstration projects**
  - “Road test” use of new option in real-world settings – not in trial site
  - Can address both infrastructure needs to deliver intervention and ways individuals integrate it into daily activities and decision making.
  - Can help answer core questions about for whom and how

- **Product introduction**
  - Complex process of formally making new options widely available. Can include meeting regulatory requirements, WHO prequal, various country-specific requirement, logistical challenges

- **Scale-up**
  - Ramping up access to new options for all who need them – mobilization of resources for procurement, distribution, delivery, worker training and other costs associated with rollout; quick ID and resolution of bottlenecks
## Long-Acting Injectable PrEP

### Selected Trials of Long-Acting Injectables for Prevention and/or Treatment of HIV (April 2014)

<table>
<thead>
<tr>
<th>Active LA Drug</th>
<th>Other Name</th>
<th>Developer</th>
<th>Phase of Research</th>
<th>Trial Name</th>
<th>Population</th>
<th>Class of Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-acting TMC278</td>
<td>Rilpivirine (RPV), Edurant</td>
<td>Janssen</td>
<td>Phase II</td>
<td>HPTN 076 (planned)</td>
<td>HIV-negative at risk women</td>
<td>Nonnucleoside reverse transcriptase inhibitor</td>
</tr>
<tr>
<td>Long-acting GSK744</td>
<td>GSK1265744</td>
<td>GlaxoSmithKline (GSK)</td>
<td>Phase IIA</td>
<td>ÉCLAIR (ongoing); HPTN 077 (planned)</td>
<td>HIV-negative at-risk men, MSM; HIV-negative at risk women and men</td>
<td>Integrase strand transfer inhibitor</td>
</tr>
<tr>
<td>Ibalizumab</td>
<td>TMB-355, monoclonal antibodies</td>
<td>Aaron Diamond AIDS Research Center</td>
<td>Phase I</td>
<td>TMB-108 (completed)</td>
<td>HIV-negative women and men</td>
<td>Entry inhibitor</td>
</tr>
<tr>
<td>Oral TMC278 and GSK744</td>
<td>Rilpivirine (RPV), Edurant and Trivicay</td>
<td>Janssen and GlaxoSmithKline (GSK)</td>
<td>Phase II</td>
<td>LATTE (ongoing)</td>
<td>HIV-positive men (96%) and women</td>
<td>Nonnucleoside reverse transcriptase inhibitor plus integrase strand transfer inhibitor</td>
</tr>
</tbody>
</table>

For a complete list of long-acting injectable trials, visit [www.avac.org/long-acting-injectables](http://www.avac.org/long-acting-injectables).
A full list of HIV prevention clinical trials is available at [www.avac.org/pxrd](http://www.avac.org/pxrd).
PrEP Advocacy

- Big picture PrEP implementation strategy
- Advocate for TDF/FTC access for participants at the end of open-label extension studies (ppts rolling off iPrEx OLE and Partners PrEP open-label)
- Advocate for national and clinician guidelines development on PrEP
- Use PrEP demo project information to guide national policy and programs
- Create demand – from users
- PrEP as standard of prevention in future trials
- Keep PrEP pipeline flush: long-acting injectables, etc.
Microbicides

Rebekah Webb
PxROAR Europe Meeting, Paris
12th June, 2014
What is a microbicide?

- An effective microbicide could be used in the vagina or rectum to reduce the risk of HIV transmission during sex.

- Microbicides are being tested in various forms – creams, foams, gels, slow release vaginal rings, films, injectables, enemas and suppositories/pessaries.

- Microbicides being explored include: single ARVs, combination ARVs, non-ARVs and dual-purpose products (with contraception).
Why do we need microbicides?

- To put something in women’s (and men’s) hands
- Increase options from which to choose
- Easier to negotiate than condoms
- Increased pleasure (like lube)
- Not systemic like a drug or vaccine
- Giving drug **topically** delivers drug:
  - *where it is needed* in genital tissue
  - closer to *when it is needed* as absorption is local
  - at a much *higher level* (10-100x) than a tablet

*Source: Prof Sheena McCormack, MRC UK*
How might a microbicide work?

- Active ingredient (e.g. ARV) might block HIV activity directly – OR –
- Physical barrier at the site of exposure might block infection
Where are they?

• Proof of concept in July 2010; CAPRISA 004 trial of 1% tenofovir gel (“BAT-24” dosing) safe and reduce HIV risk by 39% in heterosexual women

• Confirmatory study of same product and dose—FACTS 001—is ongoing; results early 2015 (daily dosing VOICE did not show efficacy)

• Two efficacy trials of monthly vaginal dapivirine ring – ASPIRE and The Ring Study – ongoing; results later in 2015
Proof of Concept: CAPRISA 004

39% effectiveness (95% CI: 6-60%)(p=0.017)

- Tenofovir 1% vaginal gel
- Heterosexual women (Mostly general population in rural Kwa Zulu Natal with smaller urban KZN population which included sex workers early on in enrolment)
- HIV incidence in the control group was 10%; reported condom use 80%
- Dosing was BAT24: up to 12hrs Before sex, After sex up to 12 hrs and no more than Two in 24 hrs
CAPRISA 008

- Phase III trial of 1% tenofovir gel
- Confirmatory trial for Caprisa 004
- 700 women in South Africa
- Results expected February 2015

- The Centre for the AIDS Programme of Research in South Africa undertakes research that contributes to understanding HIV pathogenesis, prevention and epidemiology
FACTS 001

- Phase III trial of 1% tenofovir gel (BAT24 dosing)
- 2900 women in South Africa
- Results expected December 2014

- The ‘Follow-on African Consortium for Tenofovir Studies’ was set up to provide critical follow-on research after the results of Caprisa 004
- FACTS 002 is a planned adolescent safety study designed to test the safety and acceptability of tenofovir gel in 16 and 17-year-old South African young women.
The Ring Study (IPM 027)

- Phase III trial of a 4-week vaginal dapivirine ring (NNRTI)
- 1650 women
- Rwanda and South Africa
- Results expected August 2015

IPM’s mission is to develop new HIV prevention technologies and make them available to women in developing countries.

- Results expected soon for Phase I trial comparing the dapivirine ring with a combined ARV ring.
ASPIRE (MTN 020)

- Phase III trial of a 4-week vaginal dapivirine ring (NNRTI)
- 3476 women
- 5 countries in sub-Saharan Africa
- Results expected mid-2015

MTN is a U.S. National Institutes of Health-funded network focused on preventing the sexual transmission of HIV

MTN has five other studies of rings and gels underway in the US and India
CHAAARM

- EU-funded (5 years)
- 31 participating research institutions
- Ends December 2014

Aims:

1. To develop new microbicides
   - Biologics: peptides, small proteins
   - Drugs: new reverse transcriptase inhibitors
2. To develop combination anti-retroviral drug-based microbicides to include protease inhibitors: Dapivirine + Darunavir - pre-clinical, phase I clinical trial
Rectal microbicides

- In earlier research stages than vaginal microbicides
- Barriers: Stigma, denial, homophobia, anal sex Scientific and biological challenges
- First Phase II study – MTN 017
  - Reformulated tenofovir gel for anal use
  - Safety and acceptability
  - 186 MSM and transgender women in Peru, South Africa, Thailand and the United States; Start 2013
  - Watch *Rectal Revolution is here* at [http://www.youtube.com/watch?v=ulqFQ87dlf0](http://www.youtube.com/watch?v=ulqFQ87dlf0)
Multi Purpose Technologies

A single product, configured for at least two SRH prevention indications:
Pregnancy, STI, and/or HIV
Could be different combinations:
Drug:Drug       Drug:Device       Vaccine

- Greater efficiency in terms of cost, access and delivery of SRH prevention products
- Capitalize on the demand in populations using one product type to achieve uptake and use of a second “product”

http://www.cami-health.org
New approaches

• New delivery mechanisms
  – Film
  – Fast dissolve vaginal tablets

• Non-ARV-based
  – Griffithsin in early phase
  – Zinc?

• Other ARV-based options
  – Vaginal ring with maraviroc alone and maraviroc with dapivirine in early phase
Advocacy agenda

1. Prepare communities and policy makers for FACTS study results this year
2. Prepare communities and policy makers for DSMB ring study reviews this year
3. Ensure gels don't get rejected from the pipeline
4. Ensure non-ARV-based microbicide research
Tough questions (general)

• A number of HIV prevention research trials have stopped due to “futility findings” – what does that mean and how can we communicate that to our community?

• Adherence in clinical trials; what’s the ideal timing and/or delivery mechanism? Will ring studies overcome adherence issues?

• Concern about focusing on condoms as the main prevention intervention.
HIV Vaccines
How vaccines are crucial to ending AIDS

A Three-Part Agenda for Ending AIDS

Deliver proven tools for immediate impact
- Align programs, models and funding to stay on track to end AIDS.
- Expanded testing and viral lead monitoring
- Treatment
- Voluntary medical male circumcision
- Female and male condoms
- Prevention of pediatric infection
- Syringe exchange programs

Demonstrate and roll out new HIV prevention tools
- Plan for immediate follow-up on current gel and ring trials, regardless of results.
- Map the pathway beyond pilot projects.
- Daily oral TDF/FTC as PrEP
- Non-surgical devices for voluntary medical male circumcision
- 1% tenofovir gel

Develop long-term solutions to end the epidemic
- Safeguard HIV prevention research funding.
- Launch complex trials to answer complex questions.
- Don’t abandon user-dependent methods.
- AIDS vaccines
- Cure
- Multipurpose prevention technologies
- Next-generation ARV-based prevention
- Non-ARV-based microbicides
- Rectal microbicides

GOAL: A sustained decline in HIV infections (currently at 2.3 million/year)

Years to impact
- Zero to 5
- 5 to 10
- 10 to End

AVAC Report 2013: Research & Reality
www.avac.org/report2013
Types of AIDS vaccines

- **Preventive vaccines**
  - Designed for people who are not infected with HIV
  - If effective, would reduce risk of infection
  - May also reduce viral load set point after infection

- **Therapeutic vaccines**
  - Designed for people who are living with HIV
  - If effective, would use the body’s immune system to help control or clear HIV in the body
Preventing vs. controlling infection

HIV

PREVENT ESTABLISHED INFECTION?

*****

A. Lower Initial Peak of Viremia
B. Lower Set Point
C. Delay Progression

Vaccine Administered

HAART

Courtesy of HIV Vaccine Trials Network
Preventive HIV vaccines are meant to elicit two arms of the immune system – **humoral** and cellular

(1) **Humoral immunity**
- Primary action of humoral arm is creating antibodies
- Antibodies are Y-shaped proteins developed in response to a pathogen to prevent infection
How are AIDS vaccines made?

Recombinant vaccines
- DNA vaccines
- Vector vaccines
- Subunit vaccines

Do not contain HIV – only synthetic copies or fragments of HIV that will create an immune response but do not cause HIV infection.
AIDS Vaccine Research: An overview

This graphic shows the big picture of AIDS vaccine concepts and clinical trials in process and on the horizon. It is an intentionally simplified representation of a complex field. Some approaches are not listed, and related arenas like therapeutics vaccines and cure research are omitted.

Vaccine Strategies in Development

There are over 20 ongoing AIDS vaccine trials and approximately 10 different vaccine strategies in various stages of development. The summaries below highlight some of the concepts in preclinical and early clinical trials. For more information visit www.avac.org/vaccines.

### Preclinical Trials

- **Replicating vectors**
  - Promising results from attenuated CMV, HHV-8 and varicella virus in non-human primate studies.

- **Neutralizing antibodies**
  - Basic research is ongoing to identify vaccine antigens that would trigger the body to create bNAbs. Passive immunization trials are underway that would lead to testing the concept that bNAbs reduce the risk of infection.

- **DNA**
  - There are currently eight ongoing DNA vaccine trials in Phase I and II.

- **Adenovirus**
  - Ad26, Ad35 and Chimp Ads are currently in Phase I and II trials.

### Clinical Trials

- **Phase IIIb/III (Safety and efficacy)**
- **Phase II (Safety, adherence, acceptability, feasibility)**
- **Phase I/II (Safety, adherence, acceptability, feasibility)**

A meta-analysis of the combined data from Step and Phambili trials showed that there was a 33 percent greater risk of HIV infection among vaccine recipients compared to placebo recipients. HVTN 505 did not show significant increased risk among vaccine recipients; it tested a different Ad5 based strategy. While HVTN is planning future trials, including efficacy trials, some of the upcoming studies use the Ad5 vaccines.

Visit www.avac.org for more information.
In 2009, the RV144 trial in Thailand was the first to show that an AIDS vaccine could reduce the risk of HIV infection in people.

The Pox-Protein Public Private Partnership was formed to coordinate the follow-up research agenda, including selection and development of a new protein boost for the regimen.

The P5 timelines have shifted, with delays that have challenged the sense of momentum and optimism. However, follow-on trials are still expected to begin in South Africa in 2015—and it is critical to support this effort, even while urging the P5 to remain transparent, efficient and accountable.

Thailand is continuing research with participants in RV144 and preparing for its own efficacy trial, although these timelines remain uncertain.

Advocate’s Checklist

Track Timelines
Delays are part of the reality of clinical trials and product development. Advocates should look to the current P5 timelines to hold and/or for clear explanations of why they are being revised.

Follow Pharma
Industry involvement in AIDS vaccine research is essential. With GSK taking over Novartis’ vaccine portfolio, it must show leadership and commitment of human and financial resources.

Get Engaged
Stakeholder engagement in the RV144 follow-on trials is already happening in South Africa and Thailand—civil society needs to be informed, engaged and active in these discussions.
The Thai prime boost trial: RV144

- Sept 2009: First glimpse of evidence a vaccine has a protective effect
- 31.2 % (modest effect)
- Not for licensure
- Sept 2011: Announcement of two immune responses potentially linked to risk of infection
- Research ongoing with possibility of additional efficacy trials starting in 2016

Adenoviruses are cold-causing viruses. There are many different types, including Ad5, which has been used in two different AIDS vaccine candidates.

One of those candidates, which was tested in the Step and Phambili trials, increased risk of HIV infection. The other, evaluated in HiTN 505, did not.

The scientific community has worked together to map unanswered questions and best practices for continuing to work with "alternative" Ad-vectored vaccines (other than Ad5).

These candidates are potent and warrant further study. With innovation and caution, these trials can be conducted safely and advance the search for an AIDS vaccine.

Dr. Anthony Fauci and colleagues publish recommendations on moving forward with research on adenovirus - vectored vaccines—and analyze approaches to working with other types of candidates that increase immune activation.
**Replicating vectors**

Promising results from attenuated CMV, HHV-8 and varicella virus in non-human primate studies.

Sendai virus vaccine is currently in Phase I study and replicating Tian Tan is in Phase II study.

**STATE OF THE FIELD**

- Replicating vectors use disabled viruses that retain some of their ability to copy themselves in the body. Such vectors provide ongoing stimulation to the immune system. They may also migrate to the key sites of exposure during sexual transmission.

- Animal trials of replicating vectors have hit the headlines in the past year. In these trials, some animals were completely protected, others controlled the virus. Controversially, others had no protection at all.

- There are a lot of questions about if and how the replicating vectors that have shown such promise in animals (CMV, HHV-8 and varicella) can be safely tested in humans. Expect plenty of consultation and discussion—including input from the US Food and Drug Administration—in the coming years.

- In the next one to two years, the early-phase trials of replicating vectors in humans will have data that can inform decisions on further trials.

**PHASE I SeV-G TRIAL**

IAI and partners expanded enrollment in a Phase I safety and tolerability trial in Kenya, Rwanda and the UK in September 2013 of a vaccine known as SeV-G that uses a replicating vector based on the Sendai virus (related to measles but altered so that it does not cause disease in humans).

**PHASE II TIAN TAN TRIAL**

Expected completion in May 2014 of a Phase IIa trial in China of a vaccine combination that includes a DNA prime and a replicating vector known as Tian Tan (a type of vaccinia virus).

**ADVOCATE’S CHECKLIST**

- **HELP MANAGE THE HYPE**
  
  There are many steps between positive animal data and trials to test efficacy in humans. Headlines that tout efficacy before it’s been proven can over-inflate expectations. We need to pursue replicating vectors with caution, realism and speed.
  
- **GET REAL ABOUT REGULATORY ISSUES**
  
  Funders, researchers and regulators are already in deep discussions about human trials and possible licensure of replicating vectors. Civil society advocates should be informed and involved.
**PRECLINICAL and EARLY CLINICAL TRIALS**

**Neutralizing antibodies**

Basic research is ongoing to identify vaccine antigens that would trigger the body to create bNAbs. Passive immunization trials are underway that would lead to testing the concept that bNAbs reduce risk of infection.

---

**STATE OF THE FIELD**

- bNAbs are potent immune responses that block HIV activity. This is an active area of AIDS vaccine research, and progress is being made.
- The past 12 months have seen “firsts” in bNAbs clinical trials—see timeline for details.
- Researchers continue to isolate new bNAbs from HIV-positive individuals and learn about how these responses attach to the virus to block its activity.

---

**ADVOCATE’S CHECKLIST**

- **DEMAND A PLAN**
  
  Scientists still don’t know how to turn a bNAb isolated from an HIV-positive person into a potent treatment or vaccine concept. The current trials will provide more information, but the field has to be vigilant and selective, so that concepts advance or are set aside swiftly, with clarity about next steps.

- **SUSTAIN FUNDING**
  
  bNAbs research is still basic science—it is exploratory, open-ended and expensive. It is also necessary. Funding for the bNAb pipeline needs to be robust and sustained.

- **INFORM THE ETHICS**
  
  Civil society input is needed to be sure that trials in HIV-positive and HIV-negative adults and infants are acceptable, and address the concerns of the communities who might be asked to participate—and who might benefit from the research in the future.
**Neutralizing Antibodies: Research pathways**

**HIV-infected individual**

**Broadly neutralizing antibodies**

**Reverse Engineering Vaccines**
- A protein from HIV surface (envelope) interacting with an antibody.
- Molecular characterization of the interaction between HIV envelope and BNAbs
- Development of immunogens to mimic the portion of HIV envelope that connects with BNAbs
  - Modified env
  - Combination of several immunogens = vaccine

**Passive Immunization Trials**
- Development of clinical grade purified form of BNAbs
  - Phase I: Safety and pharmacokinetic evaluation
  - Phase II/III: Efficacy trials

Clinical Trials in Europe

- European Commission - Cuthivax GTU-DNA and EuroNeut41
- France - Inserm - ANRS DNA and LIPO-5 vaccines (Dec. 2014)
- Italy – ISS – Tat
- Janssen Pharmaceutical (Crucell) – Ad26/gp140/MVA
- Sweden/EDCTP - TAMOVAC-02 DNA-MVA (Jan 2015)
- UK HIV Vaccine Consortium DNA-MVA-adjuvanted protein
- Env DNA + ZM96 ; ChAdV63.HIVconsv
Therapeutic Vaccines

- First generation of clinical trials
  - Delay ART
  - Alternative to ART
  - Allowing ART holidays

- Next scientific and clinical goals
  - Functional cure (i.e transform to LTNP or elite controllers)
  - Eradication (HIV reservoir)
  - Physiopathogenesis: reducing non-AIDS morbidity
  - Identifying patients who may benefit
Therapeutic vaccine clinical trials performed in the last 15 years:

- **Clinical efficacy:** effect on viral load (HIV RNA copies/ml in plasma)
  - 9 clinical trials: no therapeutic efficacy
  - 6 clinical trials: therapeutic efficacy not measured
  - 1 clinical trial (ongoing)
  - 15 clinical trials: modest therapeutic efficacy measured (delayed viral load rebound in 5 trials, prolongation ART free time in 4 trials, 0.5-1 log reduction in plasma viremia in 5 trials and 0.26 reduction in plasma viremia in 1 trial)

- Some trials have shown a correlation between vaccine-elicited immune responses and the magnitude of viral load after HAART cessation.

*G. Pantaleo & Lévy IAS HIV cure, 2012*
### Annual Investments in HIV Vaccine R&D 2006 – 2012 (US$ millions)

<table>
<thead>
<tr>
<th>Year</th>
<th>Public Sector</th>
<th>Philanthropic Sector</th>
<th>Non-Commercial Sector</th>
<th>Commercial Sector</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>US</td>
<td>Europe</td>
<td>Other</td>
<td>Multilaterals</td>
</tr>
<tr>
<td>2006</td>
<td>654</td>
<td>82</td>
<td>38</td>
<td>2</td>
</tr>
<tr>
<td>2007</td>
<td>659</td>
<td>79</td>
<td>49</td>
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<tr>
<td>2008</td>
<td>620</td>
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<td>2009</td>
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<td>1</td>
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<tr>
<td>2010</td>
<td>632</td>
<td>61</td>
<td>32</td>
<td>1</td>
</tr>
<tr>
<td>2011</td>
<td>615</td>
<td>48.5</td>
<td>30</td>
<td>0.5</td>
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<tr>
<td>2012</td>
<td>623</td>
<td>52</td>
<td>31</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td><strong>Total public</strong></td>
<td></td>
<td></td>
<td><strong>Total global investment</strong></td>
</tr>
<tr>
<td></td>
<td>776</td>
<td></td>
<td></td>
<td><strong>933</strong></td>
</tr>
<tr>
<td></td>
<td>789</td>
<td></td>
<td></td>
<td>961</td>
</tr>
<tr>
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<td></td>
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<td>702</td>
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<td></td>
<td>645</td>
</tr>
<tr>
<td></td>
<td>707</td>
<td></td>
<td></td>
<td>847</td>
</tr>
</tbody>
</table>

* Numbers may be rounded.

* Data submitted in currency other than US$ is converted using a 1 July 2012 conversion rate; otherwise, inflation is not taken into account.
What is needed now?

- Vaccination to protect against infection, mitigate infection and prevent transmission to others
- Focus investigation to better understand the RV144 trial result
- Ensure diversity of approaches beyond RV144, exploring novel directions for vaccine design such as UK HIV Vaccine Consortium; Vaccine Research Institute, EDCTP, EU
- More stakeholder involvement, e.g. on trial design, standard of prevention/care
Voluntary Medical Male Circumcision
Voluntary medical male circumcision

VMMC is one of the most powerful and cost-effective HIV prevention tools at hand. Studies from 2005/6 showed that it reduces a man’s risk of acquiring HIV from a female partner by up to 60 percent, increasing to around 75 percent over time.
VMMC Efficacy studies

- VMMC reduces risk by up to 60% in Kenya, South Africa, Uganda (2005/2006)
- VMMC is cost-effective HIV prevention method
  - One-off intervention with no adherence challenges
- In 2007, WHO/UNAIDS recommended scale-up of national VMMC programs in East and Southern Africa (13 countries)
- Phase 2 is scale-up of early infant MC
• 20 million circumcisions - would cost US$1.5 billion and would result in net savings of US$16.5 billion by 2025 due to averted treatment and care costs. Achieving, and maintaining, 80% coverage through 2025 would avert 3.4 million new HIV infections.

• More than 5 mn adult male circumcisions since 2007
  – One quarter of the 20 mn goal
  – A substantial number of circumcisions were in past 12 months
Non-Surgical Devices for VMMC

The PrePex device (bottom) and Shang Ring (top) are two of the non-surgical devices in development.
There is a range of evaluation studies underway to learn more about how non-surgical devices can be used for adult male circumcision. These evaluations, also called implementation pilots, address questions about safety, efficacy, etc. The World Health Organization has already determined that one device, known as PrePex, meets required standards of quality, safety and efficacy for international use. Evaluations of PrePex and other devices will provide information on how to use these strategies in the real world. Most evaluations are enrolling, ongoing or recently completed. Results can be expected within a year.

AVAC Report 2013: Research & Reality
www.avac.org/report2013
Women and VMMC

- VMMC works for women
- VMMC reduces the number of men living with HIV, resulting in benefits for women (Orange Farm, new data)
- VMMC lowers men’s risk of transmitting other STIs, including HPV, the cause of cervical cancer
- By 2025, VMMC scale-up would avert as many infections in women as in men
Other populations

Other populations

- **MSM**
  - No conclusive evidence that VMMC protects MSM
  - Some data that insertive-only partners could benefit

- **Africa diaspora**
  - VMMC could be beneficial as an HIV prevention if there is high HIV prevalence in sexual networks
VMMC Advocacy

- Use evaluation studies to inform device introduction in countries
- Amplify demand – for VMMC whether surgical OR non-surgical (use media; consider cultural context) – involve women!
- Link with implementers to ensure training/capacity building of civil society and providers
- Explore device introduction in context – e.g. South Africa and concern with Tara Klamp
- Safe (traditional) male circumcision—integrate VMMC
- Revisit country target numbers
- Advocate for WHO’s timely monitoring of VMMC numbers
- Roll-out early-infant circumcision
Hormonal Contraception and HIV
## Common methods of hormonal contraception

<table>
<thead>
<tr>
<th>Type of contraceptive</th>
<th>Provision frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral Contraceptive Pills</strong></td>
<td></td>
</tr>
<tr>
<td><em>Combined oral pill “the Pill”</em></td>
<td>Taken daily</td>
</tr>
<tr>
<td><em>Progestin-only (POPs)</em></td>
<td>Taken daily</td>
</tr>
<tr>
<td><em>Progesteron-only injectables</em></td>
<td></td>
</tr>
<tr>
<td><em>DMPA</em></td>
<td>Injected every 3 months</td>
</tr>
<tr>
<td><em>NET-EN</em></td>
<td>Injected every 2 months</td>
</tr>
<tr>
<td><strong>Long-acting methods</strong></td>
<td></td>
</tr>
<tr>
<td><em>Implant</em></td>
<td>Can last up to 5 years</td>
</tr>
<tr>
<td><em>Hormonal IUD</em></td>
<td>Can last up to 5 years</td>
</tr>
</tbody>
</table>

Note: Progestin is a type of progesteron

Source: USAID PEPFAR Technical Brief on Hormonal Contraception
Where are we coming from?

HC/HIV Acquisition Research Timeline:

- 1987 – Plummer presentation - IAS Meeting, Wash DC
- 1988-on – Multiple secondary analyses
- 1996 – NIH/OPA review
- 2007 – 1st WHO HC/HIV Consultation
- 2011 – Univ Washington HC/HIV analysis
- 2012 – 2nd WHO HC/HIV Consultation
WHO Consultation, Feb'12

- Group reviewed available published data
- Used GRADE criteria to determine if there should be any restrictions on use of Depo and HC for women

<table>
<thead>
<tr>
<th>Quality of the evidence</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Randomized trial</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Very low</td>
<td>Observational study</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Downgrade the quality of the evidence if...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study limitations</td>
</tr>
<tr>
<td>Inconsistency</td>
</tr>
<tr>
<td>Indirectness</td>
</tr>
<tr>
<td>Imprecision</td>
</tr>
<tr>
<td>Publication bias</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Upgrade the quality of the evidence if...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large magnitude of effect</td>
</tr>
<tr>
<td>Evidence of dose-response</td>
</tr>
<tr>
<td>All plausible confounding factors accounted for</td>
</tr>
</tbody>
</table>
After detailed, prolonged deliberation...

...the group agreed that the data were not sufficiently conclusive to change current guidance.

However, because of the inconclusive nature of the evidence, women using progestogen-only injectable contraception should be strongly advised to *also always use condoms*...

The group further wished to draw the attention of policy-makers and programme managers to the potential seriousness of the issue and the complex balance of risks and benefits.

Expansion of contraceptive method mix and further research on the relationship between hormonal contraception and HIV infection is essential.
What then happened?
What has happened since?

- A consultation on how to communicate and operationalize the guidance – what does it mean to counsel women at high risk of HIV to use a condom? … but no guidance or communications strategy issued by a normative agency, though one may be forthcoming
- Much discussion and debate about the need for and feasibility of a randomized controlled trial to directly evaluate the impact of various methods
- South Africa has moved to “method mix” with a new contraceptive policy
- The global FP2020 initiative was launched as a coordinating entity to achieve ambitious targets for family planning by 2020 – hasn’t directly engaged the HC-HIV issue
- More data
Epidemiology: Distribution of injectable progestin contraceptive use

Injectable hormonal contraceptive use among 15-49 year-old women

From: AR Butler, JA Smith, D Stanton, TB Hallett. The global impact of an interaction between injectable hormonal contraception and HIV risk
European advocacy agenda

- Move towards method mix
- Get clear communication at country level about uncertainty
- Move ahead with a clinical trial:
  - “ECHO” trial would evaluate various methods directly.
  - EDCTP is considering funding
## Advantages of Specific Contraceptive Arms

<table>
<thead>
<tr>
<th>DMPA</th>
<th>NET-EN</th>
<th>IMPLANT</th>
<th>Copper IUD</th>
</tr>
</thead>
</table>
| • Most widely used in areas of high HIV incidence  
• Most strongly implicated with HIV risk  
• Consensus that additional data necessary | • Injectable= potentially easier method transition  
• Different progestin than DMPA  
• Widely used in South Africa – esp. in young women | • Low dose hormonal method  
• Different progestin than DMPA  
• Long-acting  
• Better continuation rates  
• Highly effective  
• Use is rapidly increasing in Africa | • Non-hormonal  
• Long-acting  
• Highly effective  
• Low-cost |
ECHO HC/HIV RCT - Current 3-Arm Design

8,600 Women Wanting Not to Conceive Willing to be randomized

Randomize

DMPA
NET-EN
Jadelle
Cu IUD

3 Month Visits

1° Endpoint: HIV Infection

Other Endpoints: Method Continuation, Pregnancy
Where is ECHO going to happen?

Current plans are to have 14 sites across:

- Kenya
- South Africa
- Swaziland
- Zambia
- Zimbabwe
## (Tentative) Timeline

<table>
<thead>
<tr>
<th>Month</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 2014</td>
<td>- Receive final comments on protocol</td>
</tr>
<tr>
<td></td>
<td>- Protocol completed</td>
</tr>
<tr>
<td>July 2014</td>
<td>- DSMB finalized</td>
</tr>
<tr>
<td></td>
<td>- DSMB plan, including stopping rules</td>
</tr>
<tr>
<td>August 2014</td>
<td>- Central IRB approval</td>
</tr>
<tr>
<td></td>
<td>- Protocol to sites’ IRBs / Ethics Committees</td>
</tr>
<tr>
<td>Aug – Dec 2014</td>
<td>Site preparedness activities, including hiring and training staff &amp; stakeholder and community engagement (ongoing)</td>
</tr>
<tr>
<td>January 2015</td>
<td>- Start enrolment of ECHO Study!</td>
</tr>
</tbody>
</table>
## ECHO Cost Compared to Other Trials with HIV Endpoints

<table>
<thead>
<tr>
<th>Trial</th>
<th>Estimated Cost</th>
<th>No. of Participants</th>
<th>Cost per Participant</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPTN 052</td>
<td>$100 M</td>
<td>~3800</td>
<td>$26,300</td>
</tr>
<tr>
<td>VOICE</td>
<td>$100 M</td>
<td>~5000</td>
<td>$20,000</td>
</tr>
<tr>
<td>FACTS</td>
<td>$55 M</td>
<td>2900</td>
<td>$19,000</td>
</tr>
<tr>
<td>ECHO</td>
<td>$59 M</td>
<td>8600</td>
<td>$6,900</td>
</tr>
</tbody>
</table>
Other advocacy issues

- Working with east and southern African advocates to expand method mix/adapt South African policy approach – in the absence of data, it is a “win-win”
- Work with European members of FP2020 working groups, funding entities and so on and push for greater engagement of this important initiative with the HC-HIV questions