Pre-Exposure Prophylaxis: state-of-the-art and roll-out

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8th Interest Workshop on HIV treatment, pathogenesis, and prevention research in resource-poor settings
Lusaka, Zambia
May 5-9, 2014
Pre-Exposure Prophylaxis: state-of-the-art and roll-out

- HIV prevention: position of pre-exposure prophylaxis
- State-of-the-art:
  - Results of randomised controlled trials (RCT)
  - Additional analyses
- Roll-out:
  - Phase IV studies and demonstration projects
  - Implementation challenges and issues
- Trials underway and pipeline
- Standard of prevention in RCT
HIV prevention with antiretroviral drugs (since 2010)

- Topical pre-exposure prophylaxis (microbicides) for women
  - Abdool Karim Q, Science 2010

- Oral pre-exposure prophylaxis
  - Grant R, NEJM 2010 (MSM)
  - Baeten J, NEJM 2012 (Couples)
  - Thigpen M, NEJM 2012 (Heterosexuals)
  - Choopanya K. Lancet 2013 (PWID)

- Treatment for prevention
  - Cohen M, NEJM 2011

- Male circumcision
  - Gray R, Lancet 2007

- Treatment of STIs
  - Grosskurth H, Lancet 2000

- Female Condoms

- Male Condoms

- HIV Counselling & Testing
  - Coates T, Lancet 2000

HIV prevention (before 2010)

- Behavioural Interventions
  - Abstinence
  - Be Faithful

Note: preventing mother-to-child transmission, screening transfusions, harm reduction, structural interventions, etc. have not been included
Antiretroviral Prevention Train
Antiretroviral Drugs to Prevent HIV Transmission and Acquisition

Antiretroviral therapy for HIV-positive persons

Reduces risk of onward HIV transmission

- **TasP:** treatment as prevention:
  population-level benefits of lower community viral load as ART is scaled up according to national eligibility criteria [e.g. Hlabisa]

- **T4P:** early treatment for prevention:
  before CD4+ cell count falls to eligibility criteria [current WHO: less than or equal to 500 cells/uL]

- **test and treat:**
  offering ART to all those who test HIV-positive regardless of CD4 count

Antiretroviral prophylaxis for HIV-negative persons

Reduces risk of HIV acquisition

- **pre-exposure prophylaxis** preventing transmission from men to women, men to men, women to men
Clinical Trial Evidence: Prevention of Sexual HIV Transmission

**Study**
- Treatment for prevention (Africa, Asia, America’s)
- PrEP for discordant couples (Partners PrEP)
- PrEP for heterosexuals (Botswana TDF2)
- Medical male circumcision (Orange Farm, Rakai, Kisumu)
- PrEP for MSMs (America’s, Thailand, South Africa)
- STD treatment (Mwanza)
- Microbicide (CAPRISA 004 tenofovir gel)
- HIV Vaccine (Thai RV144)

**Effect size (CI)**
- 96% (73; 99)
- 75% (55; 87)
- 62% (22; 83)
- 54% (38; 66)
- 44% (15; 63)
- 42% (21; 58)
- 39% (6; 60)
- 31% (1; 51)

PrEP for PWID (Bangkok): 49% (10-72)
HPTN 052: HIV-1 Transmission
(Cohen et al NEJM 2011)

39 partners became infected with HIV

28 acquired HIV from their partner

11 acquired HIV from a partner outside the couple

1763 stable, healthy, serodiscordant, sexually active couples in 9 countries
CD4 count: 350 to 550 cells/mm³
randomised for the HIV+ partner to:

- start ART immediately or
- delay until CD4 250

96% reduction

Immediate ART: 1

Delayed ART: 27

p < 0.001

28%
Serodiscordant couples and PrEP

- HPTN 052 trial: 72% from within the couple  
  [Cohen et al. NEJM 2011]

- Zambia DNA sequencing: 87% of new infections in discordant couples were acquired from HIV-positive partner  
  [Allen et al. AIDS 2003]

- 14-site study in Eastern and Southern Africa: 64% of seroconversions in couples were linked through viral sequencing  
  [Celum et al. NEJM 2010]

- PrEP could be used by the HIV-negative partner:
  - during the first 6 months of ART until HIV-positive partner’s viral loads are undetectable
  - to prevent HIV acquisition with outside partners
Sexual and reproductive health needs of serodiscordant couples

Risk-reduction options for conception:

- Timed unprotected intercourse limited to fertile period
- Antiretroviral treatment (ART) for HIV-positive partner to achieve undetectable viral load before conception
- Periconception pre-exposure prophylaxis (PrEP) for HIV-negative male partner and/or VMMC >6 weeks before
- Periconception pre-exposure prophylaxis (PrEP) for HIV-negative female partner

Having achieved HIV-free conception, how to:

- Remain serodiscordant (non-penetration, consistent condom use, ART, PrEP)
- prevent mother-to-child transmission (ART, PrEP)
PrEP in pregnancy for primary prevention in women

- Women participating in clinical trials committed at enrolment to contraception and stopped product if they became pregnant
- Side effects: good track record TDF and FTC in non-pregnant HIV-negative women and in pregnant HIV-positive women as part of combination ART
- Challenge to identify women at high ongoing risk of HIV infection
- Need for provider training/tools to assess risk profiles and motivation and to explore adherence support needs
- Importance of ruling out acute infection to prevent development of drug resistance that could:
  - reduce eventual antiretroviral treatment options
  - be transmitted to the foetus
Pre-exposure prophylaxis strategies

Tenofovir (TDF)
Tenofovir/emtricitabine TDF/FTC

- iPrEx
- Partners PrEP
- TDF2

Topical PrEP: 1% tenofovir gel

- Partners
- CAPRI SA 004

Injectable PrEP: subcutaneous or intramuscular (Phase 2 trials)

ASPIRE and IPM trials
Why does PrEP work for some people but not for others?

Possible explanations for diverse PrEP effectiveness results:

• **Pharmacokinetics**: anal, vaginal tissue concentrations by route of administration

• **Adherence** to daily regimens

• Differences in **risk of increased exposure**, including exposure to people with acute HIV infections
Systemic Versus Topical Administration

- Tenofovir and emtricitabine are phosphorylated intracellularly to form active agents that inhibit HIV replication.

- Tenofovir diphosphate concentrations are:
  - 100-fold higher in rectal tissue than in cervicovaginal tissue with oral TDF/FTC (Patterson 2011)
  - 1000-fold higher in vaginal tissues with tenofovir gel than with oral TDF/FTC (Dumond 2007, Gengiah 2012)
## Pre-Exposure Prophylaxis for Women as of May 2014

<table>
<thead>
<tr>
<th>Trial</th>
<th>Country</th>
<th>1% Tenofovir vaginal gel</th>
<th>Oral TDF (tenofovir) daily tablets</th>
<th>Oral TDF/FTC (emtricitabine) daily tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPRISA 004</td>
<td>South Africa</td>
<td>✓</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>VOICE gel [daily]</td>
<td>Uganda, South Africa, Zimbabwe</td>
<td>X</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>FACTS 001</td>
<td>South Africa</td>
<td>?</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fem PrEP</td>
<td>Ken, SA, Tanz</td>
<td>-</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>VOICE oral</td>
<td>Uga, SA, Zim</td>
<td>-</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>Kenya, Uganda</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>TDF-2</td>
<td>Botswana</td>
<td>-</td>
<td>-</td>
<td>✓</td>
</tr>
</tbody>
</table>
### Fem-PrEP: Adherence measurements

<table>
<thead>
<tr>
<th></th>
<th>Drug</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reported</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usually/always took study pill</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td><strong>Reported</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Easy/very easy to take pills</td>
<td>97%</td>
<td>96%</td>
</tr>
<tr>
<td><strong>Measured</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pills taken</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(based on number returned)</td>
<td>86%</td>
<td>89%</td>
</tr>
<tr>
<td><strong>Measured</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effective drug levels in blood near time of infection</td>
<td>&lt;26%</td>
<td>NA</td>
</tr>
</tbody>
</table>

70% of women reported feeling at little risk for acquiring HIV despite a nearly 5% annualized HIV incidence in Fem-PrEP.
Adherence drives trial results: Consistent adherence to daily drug gives high levels of protection

<table>
<thead>
<tr>
<th></th>
<th>% of blood samples with tenofovir detected</th>
<th>HIV protection efficacy in randomized comparison</th>
<th>HIV protection estimate with high adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Partners PrEP</strong></td>
<td>81%</td>
<td>75%</td>
<td>90% (tenofovir in blood)</td>
</tr>
<tr>
<td><strong>FTC/TDF arm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TDF2</strong></td>
<td>79%</td>
<td>62%</td>
<td>78% (prescription refill)</td>
</tr>
<tr>
<td><strong>BTS</strong></td>
<td>67%</td>
<td>49%</td>
<td>70% - 84% (tenofovir in blood / pill count)</td>
</tr>
<tr>
<td><strong>iPrEx</strong></td>
<td>51%</td>
<td>44%</td>
<td>92% (tenofovir in blood)</td>
</tr>
<tr>
<td><strong>FEM-PrEP &amp; VOICE</strong></td>
<td>&lt;30%</td>
<td>No HIV protection</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Baeten et al 2013

Less than 50% of participants assigned to active product in the VOICE C substudy (similar to VOICE overall), had drug on board despite 97% study retention.

[Van Straten, AIDS Impact 2013]
Risk of increased exposure and effectiveness of PrEP - 1

Is PrEP’s protective effect reduced when challenged with greater or more frequent HIV exposure?

- HIV incidence in the placebo arms of trials demonstrating PrEP effectiveness was 2-4 per 100 person-years compared to 4-5 per 100 person-years in those that did not.

- Analysis undertaken within the Partners PrEP trial to test this hypothesis.
  - Composite risk score defined, e.g. partner viral load >50,000 copies/ml.
  - Higher risk sub-groups confirmed by comparing HIV incidence with full study placebo arm incidence.

Murnane et al AIDS 2013
## Risk of increased exposure and effectiveness of PrEP - 2

<table>
<thead>
<tr>
<th></th>
<th>Placebo arm incidence</th>
<th>PrEP efficacy</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall study</td>
<td>2.0 per 100 PY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF</td>
<td>67%</td>
<td>44-81%</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>TDF/FTC</td>
<td>75%</td>
<td>55-87%</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Partner VL&gt;50,000</td>
<td>3.9 per 100 PY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF</td>
<td>76%</td>
<td>30-92%</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>TDF/FTC</td>
<td>78%</td>
<td>35-93%</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Women with partner VL&gt;50,000</td>
<td>5.4 per 100 PY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF</td>
<td>84%</td>
<td>29-96%</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>TDF/FTC</td>
<td>72%</td>
<td>13-91%</td>
<td>0.03</td>
<td></td>
</tr>
</tbody>
</table>

Murnane et al *AIDS* 2013
Why does PrEP work for some people but not for others?

Possible explanations for diverse PrEP effectiveness results:

✓ **Pharmacokinetics**: anal, vaginal tissue concentrations by route of administration

✓ **Adherence** to daily regimens

✗ **Differences in risk of increased exposure**
Behavioural risk compensation

- Increased sexual risk taking by people using known effective HIV prevention interventions
- Transition from a placebo-controlled blinded trial (TDF, TDF/FTC, placebo) to one in which participants knew they were on either TDF or TDF/FTC: natural experiment
- 56,132 person months (33,198 before unmasking, 22,934 after); 98% retention both periods
- Modelled trends before and after unmasking
- No significant differences in frequency of:
  - Sex, unprotected sex with HIV-positive study partner
  - Pregnancy, sexually transmitted infections
- Modest increase in unprotected sex with outside partners 6.2 vs 6.8 in 12 months (p=0.04)
Modelling PrEP cost and impact

The Cost and Impact of Scaling Up Pre-exposure Prophylaxis for HIV Prevention: A Systematic Review of Cost-Effectiveness Modelling Studies

Gabriela B. Gomez, Annick Borquez, Kelsey K. Case, Ana Wheelock, Anna Vassall, Catherine Hanks

1 Department of Global Health, Academic Medical Centre, University of Amsterdam and Amsterdam Institute for Global Health and Development, The Netherlands, 2 School of Public Health, Imperial College London, United Kingdom, 3 Centre for Patient Safety and Service Quality, Imperial College London, United Kingdom, 4 London School of Hygiene and Tropical Medicine, United Kingdom

- 13 studies of cost and impact among heterosexual couples, men who have sex with men (MSM), people who inject drugs (PWID) in generalised and concentrated epidemics in southern Africa, Ukraine, USA, and Peru
- Cost-effectiveness depends on cost, epidemic context, PrEP programme coverage, prioritisation strategies, and adherence
- Most cost-effective strategy: delivery of PrEP to key populations at highest risk of HIV exposure

Pre-Exposure Prophylaxis: state-of-the-art and roll-out

- HIV prevention: position of pre-exposure prophylaxis
- State-of-the-art:
  - Results of randomised controlled trials (RCT)
  - Additional analyses
- Roll-out:
  - Phase IV studies and demonstration projects
  - Implementation challenges and issues
  - Trials underway and pipeline
- Standard of prevention in RCT
FDA NEWS RELEASE
For Immediate Release: July 16, 2012
Media Inquiries: Erica Jefferson, 301-796-4988, erica.jefferson@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA
FDA approves first drug for reducing the risk of sexually acquired HIV infection
Evidence-based approach enhances existing prevention strategies
Today, the U.S. Food and Drug Administration approved Truvada (emtricitabine/tenofovir disoproxil fumarate), the first drug approved to reduce the risk of HIV infection in uninfected individuals who are at high risk of HIV infection and who may engage in sexual activity with HIV-infected partners.
<table>
<thead>
<tr>
<th>Project</th>
<th>Funder/Sponsor</th>
<th>Location</th>
<th>Population</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partners Demonstration Project</td>
<td>USAID, NIH, BMGF Univ Wash</td>
<td>Kenya, Uganda</td>
<td>Serodiscordant couples</td>
<td>Enrolling</td>
</tr>
<tr>
<td>Benin FSW project</td>
<td>BMGF/Univ Quebec</td>
<td>Benin</td>
<td>FSW</td>
<td>Approved</td>
</tr>
<tr>
<td>Senegal FSW project</td>
<td>BMGF</td>
<td>Senegal</td>
<td>FSW</td>
<td>Feasibility studies</td>
</tr>
<tr>
<td>LVCT and SWOP project</td>
<td>BMGF, USAID, WHO, LSHTM, Georgetown Univ</td>
<td>Kenya</td>
<td>Young women, MSM, FSW</td>
<td>Feasibility studies</td>
</tr>
<tr>
<td>Nigeria National AIDS Agency</td>
<td>BMGF, USAID, WHO, LSHTM, Georgetown Univ</td>
<td>Nigeria</td>
<td>Serodiscordant couples</td>
<td>Feasibility studies</td>
</tr>
<tr>
<td>Wits RH Institute</td>
<td>BMGF</td>
<td>South Africa</td>
<td>FSW</td>
<td>Poised to start</td>
</tr>
<tr>
<td>Durbar (DMSC)</td>
<td>BMGF</td>
<td>India</td>
<td>FSW, transgender women</td>
<td>Feasibility studies</td>
</tr>
<tr>
<td>Implementation of PrEP</td>
<td>Oswaldo Cruz Foundation</td>
<td>Brazil</td>
<td>MSM, transgender women</td>
<td>Approved</td>
</tr>
<tr>
<td>SAPPHIRE</td>
<td>DfID-D-Zimbabwe</td>
<td>Zimbabwe</td>
<td>FSW</td>
<td>Feasibility studies</td>
</tr>
</tbody>
</table>
## Priority questions for implementation

<table>
<thead>
<tr>
<th>Topic</th>
<th>Key questions</th>
</tr>
</thead>
</table>
| Priority populations | Who should be prioritized for PrEP?  
Who are key PrEP messages, and how best to disseminate? |
| Uptake               | What is level of interest in PrEP? Who will want PrEP?  
How to increase uptake in those who need it most? |
| Adherence            | How will PrEP be used? (adherence, persistence)  
How to start/stop PrEP safely?  
What are effective strategies to increase PrEP adherence? |
| Sexual behavior      | How will sexual practices change while taking PrEP?  
What are best approaches to minimize risk compensation? |
| Safety               | What is long term safety of PrEP? (renal, bone)  
What is optimal HIV testing strategy and frequency? |
| Delivery             | Where are PrEP delivery systems best located?  
How best to support PrEP providers? |
| Impact               | How can cost-effectiveness of PrEP be maximized?  
How should PrEP be prioritized with other prevention strategies? |

Baeton, Haberer, Liu, Sista. *JAIDS* 2013
Lessons for PrEP from oral contraceptives: A pill for HIV prevention: Déjà vu all over again

- Minimal tolerance for toxicity
- Aim is to make sex safer
  - Criticism about sexual freedom
- Concerns about feasibility and resources (prioritisation)
- Listen to prescribers and patients
- PrEP is not for 100% of people, 100% of the time
- First generation products are a first step:
  - We should not wait for a perfect product or let the perfect be the enemy of the good
- Oral PrEP will remain part of choice options for HIV prevention
Research and Development Pipeline: Trials underway

MSM populations:

- Intermittent PrEP (IPERGAY, France): TDF/FTC vs placebo
  [controversy post FDA announcement]
- PROUD: UK immediate vs deferred TDF/FTC
  [controversy post FDA announcement]
- ADAPT (HPTN 067): daily versus intermittent TDF/FTC
  [testing to see if intermittent provides coverage]
- NEXT-PREP (HPTN 069): TDF/FTC +/- maraviroc
  [CCR5 blocker not used much in treatment]

Women:

- FACTS 001 1% Tenofovir gel (pericoital)
- Ring study (IPM) & ASPIRE (MTN) phase III dapivirine ring

Safety, acceptability, PK

- Phase II trials of long-acting injectables starting May 2014
  [NNRTI rilpivirine (TMC 278) and integrase inhibitor S/GSK1265744]
Long-acting Rilpivirine (TMC278 LA)

- Licensed for oral use in combination antiretroviral therapy
- Licensing agreement Janssen R&D Ireland to PATH to develop long-acting injectable formulation with royalty-free rights
- TMC278 LA is an injectable nanosuspension 300 mg/ml
- Partners: BMGF (grant to PATH) and NIH (through HPTN)
- HPTN 076 Phase 2 trial:
  - 132 HIV-uninfected women aged 18-45 years randomised to TMC278 or placebo
  - USA (New York, New Jersey), South Africa (Cape Town), Zimbabwe (Harare)
  - Intramuscular (buttock) dosing of 1200 mg every 8 weeks (2 injections)
  - Duration: 44 weeks with a 6-month follow-up period
GSK744 LA

• analog of dolutegravir; inhibits integrase-mediated strand transfer

CROI 2014
• low dose intrarectal challenges in rhesus macaques provide rationale for efficacy studies in high risk MSM (Chastity Andrews)
• intravaginal challenges in rhesus macaques (high dose) and pigtail macaques with lunar menstrual cycles (low dose) provide rational for efficacy studies in high risk women (Gerardo Garcia Lerma)

GSK744 LA nanosuspension: nanocrystals suspended in liquid
• 800 mg in 4 ml [2 injections every 3 months]
• Phase II clinical trials evaluating safety and acceptability with 4 week oral run-in:
  • ÉCLAIR: 120 MSM [5:1] in USA
  • HPTN 077: 160 at risk women (60%) and men [3:1] in USA, sub-Saharan Africa, South America
• Phase III trials evaluating efficacy planned with 2400+ subjects [minimum of 2 trials with 1200 at risk MSM and women]
Research and Development Pipeline

- **Vaginal and rectal gels**
- **Silicon rings**
- **Oral**
- **Injectable**
- **Rings with other polymers**
- **Pod Rings**
- **Other gels**
  - pH transition
  - Subliming Solid matrix
- **Devices +/- Gels**
- **Vaginal Films**
- **Quick Dissolve Tablets**
- **Drug in nanoparticles for films & rings**
Evolving standard of prevention issues

When does PrEP become part of the standard of prevention offered to all arms of an HIV prevention trial?

Not offering PrEP may be appropriate [UNAIDS/WHO guidance]:
- in populations where FTC/TDF was not found effective
- in settings in which FTC/TDF is not approved by national authorities

**Note:**
- VMMC was offered in the Phambili Trial
- PrEP referral was offered in HVTN 505

**Guidance Point 13:**
**Standard of Prevention**

Researchers, research staff, and trial sponsors should ensure, as an integral component of the research protocol, that appropriate counselling and access to all state of the art HIV risk reduction methods are provided to participants throughout the duration of the biomedical HIV prevention trial. New HIV-risk-reduction methods should be added, based on consultation among all research stakeholders including the community, as they are scientifically validated or as they are approved by relevant authorities.
With thanks for ideas, photos, and slides to:

- Myron Cohen
- Jared Beaton
- Salim Abdool Karim
- Mitchell Warren
- Lut Van Damme
- John Mellors
- Quarraisha Abdool Karim
- Nelly Mugo
- Connie Celum
- Ariane Van Straten
- Zeda Rosenberg
- Sheena McCormack
- Martin Markowitz
- Ponni Subbiah
Registration is Open for HIV R4P 2014

The world’s first global conference dedicated exclusively to HIV prevention research

Abstract, Scholarship and Satellite Application Deadline is Friday, 2 May 2014

April Newsletter

Arrive early, satellites begin 27 October
Thank you for your attention!