Use of Pre-exposure Prophylaxis (PrEP) in pregnancy for primary prevention of HIV infection in women

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Use of PrEP in pregnancy for primary prevention of HIV infection in women

- Conflicting evidence about HIV acquisition risk during pregnancy
- Risk of vertical transmission when HIV acquired in pregnancy or post-partum
- Sexual and reproductive health needs of serodiscordant couples
- Evidence on pre-exposure prophylaxis (PrEP) in women
- PrEP for pregnant HIV-negative women at higher risk of HIV exposure
Conflicting evidence about risk of HIV acquisition during pregnancy

- **Increased risk in pregnancy**

- **Non-significant increased risk**
  - Multi-site study of serodiscordant couples in Eastern and Southern Africa, adjusted for age, unprotected sex in previous month, and contraceptive use
    - [Mugo et al. *AIDS* 2011]
  - Similar findings from Uganda study

- **No increased risk** in large southern Africa study
  - [Reid et al. *J Acq Imm Def Syn* 2011]

- Uganda and Zimbabwe study: no increased risk and evidence of a **protective effect** of pregnancy at one site
  - [Morrison et al. *AIDS* 2007]
Recent evidence about risk of HIV acquisition during pregnancy

**Systematic review and meta-analysis** based on 19 cohorts (22,908 person-years):

- Incidence 4.7/100 PY in pregnancy and 2.9/100 PY postpartum
- 3.8/100 person-years pregnancy/postpartum (95%CI 3.0-4.6)
- Pooled cumulative HIV incidence higher in African than non-African countries 3.6% vs 0.3% p<0.001
- HIV risk was *not significantly higher* in pregnant (HR 1.3, 95%CI 0.5-2.1) or postpartum women (HR 1.1, 95%CI 0.6-1.6) than among non-pregnant, non-postpartum women in 5 studies
- **Conclusion:** pregnancy and postpartum are times of persistent high HIV risk

  [Drake et al *PLoS Medicine* 2014]

**Secondary analysis of pooled data** from 6 community cohorts (178,000 person-years):

- Pregnant women have a lower risk of acquiring HIV (both in the periods before and after widespread PMTCT scale-up) than women not pregnant (HRR 0.79, 95%CI 0.70-0.89).

  [Marston et al *PLoS One* December 2013]
Discordant couples in sub-Saharan Africa

- In sub-Saharan Africa, at least half of people living with HIV (PLHIV) in stable relationships have a seronegative partner
  
  [Chemaitelly et al *Sex Trans Inf* 2012]

- Population-based estimates of serodiscordance range from 2% (Rwanda) to 13% (Zimbabwe, Lesotho)
  
  [DHS surveys cited in Dunkle et al *Lancet* 2008]

- Men and women equally likely to be the index (HIV-positive) partner in a serodiscordant couple
  
  [Ewayo et al *Lancet Infect Dis* 2012]

- Couples HIV testing and counselling (CHTC) - *risk assessment with sensitivity to foster facilitated disclosure, avoid blame, counsel, and refer to HIV care and prevention services* - reduces HIV incidence
  
Serodiscordant couples: where does HIV come from?

- Estimated proportion of all HIV transmission that arises within serodiscordant couples ranges from 10% in Kenya to 56% in Rwanda
  
  [Bishop and Foreit. Health Policy Initiative 2010]

- Zambia DNA sequencing: 87% of new infections in discordant couples were acquired from the 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]

- HPTN 052 trial provides recent data
  
  [Cohen et al. NEJM 2011]
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

96% reduction

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

p < 0.001
Risk of vertical transmission when HIV acquired in pregnancy or post-partum

- Increased viral load associated with acute infection exposes the foetus to a high risk of *in utero* mother-to-child transmission
  
  [Garcia et al NEJM 1999; Birkhead et al Obstet Gynecol 2010]

- Acute infection in the post-partum period is associated with higher risk of mother-to-child transmission
  
  [Moodley et al. J Infect Dis 2011]

- In African cohorts, risk significantly higher among women with incident versus chronic infection in postpartum (OR 2.9, 95% CI 2.2-3.9) or in postpartum/pregnancy periods combined (OR 2.3, 95%CI 1.2-2.4)
  
  [Drake et al PLoS Medicine 2014]

- The challenge is to identify those women most at risk of acquiring HIV during conception, pregnancy, and breast feeding
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Sexual and reproductive health needs of serodiscordant couples

- Preconception care and counselling for those wishing to conceive; infertility treatment tailored to specific needs

- Safer conception options:
  - Risk-free for HIV-negative male partner:
    - artificial insemination (AI) \([low\ technology\ method:\ timed,\ self-administered,\ vaginal\ insemination]\)
    - assisted reproductive techniques \([in-vitro\ fertilisation\ (IVF),\ intracytoplasmic\ sperm\ injection\ (ICSI)]\) for bilateral tube blockage or male factor infertility
  - Risk-free for HIV-negative female partner:
    - Donor sperm (HIV-negative donor)
    - Sperm wash/preparation followed by AI or IVF/ICSI
Sexual and reproductive health needs of serodiscordant couples

Risk-reduction options:

- Timed unprotected intercourse limited to fertile period
- ART for 6 months for HIV-positive partner to achieve undetectable viral load before conception
- Periconception 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 discordant (non-penetration, consistent condom use, ART, PrEP)
- prevent mother-to-child transmission (ART, PrEP)
Antiretroviral drugs to prevent HIV transmission to pregnant women

Antiretroviral therapy for HIV-positive male partners to reduce 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, reduces the probability of encountering an infectious HIV+ male partner.

- **T4P**: early treatment for prevention:
  Individual-level benefit of reduced transmission before CD4+ cell count falls to eligibility, e.g. 500 cells/μL.

- **test and treat**: offering ART to all men who test HIV-positive regardless of CD4 count who have pregnant partners.

Antiretroviral prophylaxis for HIV-negative pregnant women to reduce risk of HIV acquisition

- **PrEP** to prevent transmission from men to women (during the first 6 months of ART until partner’s viral load is undetectable).
Antiretroviral therapy policy:
CD4 count threshold for initiation
Challenges in reaping the prevention benefits of ART: suboptimal viral suppression

**US treatment cascade - 28% virally suppressed**

- HIV infected: 1,178,350 (100%)
- HIV diagnosed: 941,950 (79%)
- Linked to HIV care: 725,302 (62%)
- Retained in HIV care: 480,395 (41%)
- On ART: 426,590 (36%)
- Suppressed viral load (equal or less than 200): 328,475 (28%)

**West Africa treatment cascade - 10% virally suppressed**

- PLWHA: 100%
- Access to screening: 75%
- Actually do the test: 70%
- Fetch their results: 65%
- Are supported: 60%
- Benefit from ARV treatment: 55%
- Remain on ARV (death, loss of sight): 40%
- Have access to a second line treatment: 10%

Adapted from Wilson and Fraser 2013
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Pre-exposure prophylaxis strategies for women

- **Tenofovir (TDF)**
- **Tenofovir/emtricitabine (TDF/FTC)**

**Topical PrEP:** 1% tenofovir gel

**Injectable PrEP:** Phase 2 trials of intramuscular rilpivirine (q8 weeks) or GSK744 (q12 weeks)

**Partners PrEP**

- **CAPRISA 004**

- **ASPIRE and IPM trials**

- **Partners**

- **TDF2**
Pre-Exposure Prophylaxis for Women as of February 2015

<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>
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<tr>
<td>VOICE oral</td>
<td>Uga, SA, Zim</td>
<td>-</td>
<td>X</td>
<td>X</td>
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<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>
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<td>✔</td>
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Hankins
Results of placebo-controlled randomised controlled trials assessing ARV PrEP effectiveness

<table>
<thead>
<tr>
<th>Prevention in injecting drug users</th>
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<tbody>
<tr>
<td>Bangkok tenofovir study: daily oral tenofovir (injecting drug users in Thailand)</td>
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<table>
<thead>
<tr>
<th>Prevention of mother-to-child transmission</th>
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<tbody>
<tr>
<td>PACTG076: zidovudine to mother during pregnancy and labour and infant (HIV-positive pregnant women in USA and France)</td>
</tr>
<tr>
<td>Thai AZT trial: zidovudine to mother during pregnancy and labour (HIV-positive pregnant women in Thailand)</td>
</tr>
<tr>
<td>HIVNET012: single dose nevirapine to mothers and infants (HIV-positive pregnant women in Uganda)</td>
</tr>
<tr>
<td>DITRAME: zidovudine to mother during pregnancy, labour, and post partum (HIV-positive pregnant women in Côte d’Ivoire and Burkina Faso)</td>
</tr>
<tr>
<td>Africa AZT: zidovudine to mother during pregnancy and labour (HIV-positive pregnant women in Côte d’Ivoire)</td>
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<thead>
<tr>
<th>Sexual transmission prevention</th>
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<tbody>
<tr>
<td>Partners PrEP: daily emtricitabine and tenofovir (serodiscordant couples in Kenya and Uganda)</td>
</tr>
<tr>
<td>Partners PrEP: daily oral tenofovir (serodiscordant couples in Kenya and Uganda)</td>
</tr>
<tr>
<td>TDF2: daily emtricitabine and tenofovir (heterosexual men and women in Botswana)</td>
</tr>
<tr>
<td>iPrEx: daily emtricitabine and tenofovir (men who have sex with men in the Americas, Thailand, and South Africa)</td>
</tr>
<tr>
<td>CAPRISA 004: coital tenofovir gel (women in South Africa)</td>
</tr>
<tr>
<td>MTN003/VOICE: daily tenofovir gel (women in South Africa, Uganda, and Zimbabwe)</td>
</tr>
<tr>
<td>FEMPrEP: daily emtricitabine and tenofovir (women in Kenya, South Africa, and Tanzania)</td>
</tr>
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</table>
Explaining diverse trial findings

- Actual strength of the intervention
- Host factors
- Trial population behavioural characteristics (risk, likely adherence, retention)
- Level of HIV exposure:
  - assumed equivalence across study arms
  - challenge of measurement (self-report, proxy measures of unprotected sex – STI, pregnancy, semen biomarkers)
- Intervention dose: [triangulated data]
  - Prospective objective measures: electronic devices, unannounced product counts
  - Biological measures: drug levels in plasma, CVL, vaginal tissue
  - Participant self-report

Koblin, Andrasik, and Austin. *JAIDS* 2013
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]

Figure 3. Boxplots of TFV and TFV-DP concentrations by anatomic site.

Hendrix et al. *PLoS ONE* 2013
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>Partners PrEP FTC/TDF arm</td>
<td>81%</td>
<td>75%</td>
<td>90% (tenofovir in blood)</td>
</tr>
<tr>
<td>TDF2</td>
<td>79%</td>
<td>62%</td>
<td>78% (prescription refill)</td>
</tr>
<tr>
<td>BTS</td>
<td>67%</td>
<td>49%</td>
<td>70% - 84% (tenofovir in blood / pill count)</td>
</tr>
<tr>
<td>iPrEx</td>
<td>51%</td>
<td>44%</td>
<td>92% (tenofovir in blood)</td>
</tr>
<tr>
<td>FEM-PrEP &amp; VOICE</td>
<td>&lt;30%</td>
<td>No HIV protection</td>
<td>N/A</td>
</tr>
</tbody>
</table>

70% of women in the Fem-PrEP trial reported feeling at little risk for acquiring HIV despite a nearly 5% annualized HIV incidence

Baeten et al 2013

Van Damme CROI 2012, LB32 More info NEJM
Socio-ecological framework of factors affecting perceptions about ARV for PrEP, by levels of influence (VOICE-C study)

<table>
<thead>
<tr>
<th>Social-Structural</th>
<th>HIV stigma</th>
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<tbody>
<tr>
<td></td>
<td>HIV/AIDS trivialisation</td>
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<table>
<thead>
<tr>
<th>Community</th>
<th>ARV for treatment versus PrEP</th>
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<tbody>
<tr>
<td></td>
<td>Rumors around research</td>
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<tr>
<td></td>
<td>Potency and monetary value of ARVs</td>
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<table>
<thead>
<tr>
<th>Organisational</th>
<th>Researchers’ motivations/mistrust</th>
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<tbody>
<tr>
<td></td>
<td>Investigational products (active vs. placebo)</td>
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<tr>
<td></td>
<td>Product ingredients; mechanism of action</td>
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<table>
<thead>
<tr>
<th>Household</th>
<th>Misattribution of seropositivity</th>
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<tbody>
<tr>
<td></td>
<td>Suspicion; discrimination</td>
</tr>
<tr>
<td></td>
<td>Privacy needs for storage and usage</td>
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<td></td>
<td>Disclosure and (lack of) support</td>
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<table>
<thead>
<tr>
<th>Individual</th>
<th>ARV potency, protection, safety, side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dosage form preference</td>
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</tbody>
</table>

Van der Straten et al. JAIS 2014
Risk of increased exposure and effectiveness of PrEP - 1

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

- 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><strong>Overall study</strong></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>
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<tr>
<td><strong>Partner VL&gt;50,000</strong></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><strong>Women with partner VL&gt;50,000</strong></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>
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Murnane et al *AIDS* 2013
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PrEP in pregnancy for women - 1

**Issues:**

- Women participating in clinical trials were HIV-negative, 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, in pregnant and breastfeeding HIV+ women, as part of combination antiretroviral therapy.

- Few safety data on tenofovir gel, dapivirine ring, or injectables (rilpivirine and GSK 744) in pregnancy.

- Integration of HIV, PrEP, family planning and other reproductive health services are needed for quality programming.
PrEP in pregnancy for women - 2

Challenges:

- Identifying women at high on-going risk of HIV infection
- Training providers and providing risk profile assessment tools
- Assessing motivation and adherence capacity
- Ruling out acute infection in order to prevent development of drug resistance that could:
  - reduce eventual antiretroviral treatment options
  - be transmitted to the foetus
Baseline:

• Document HIV-negative status
• Measure serum creatinine (Cr), calculate estimated Cr clearance (Cl) to assess renal function. [Do not use if CrCl is less than 60ml/min]
• Conduct STI screen, check hepatitis B infection and vaccination status
• Assess motivation and explore adherence support needs

If attempting pregnancy:

• Recommend monthly visits for HIV testing, adherence support. Come for unscheduled visit if menses missed.
• Daily oral TDF/FTC beginning one month before attempting conception
Baseline and follow up monitoring - 2

At least every 3 months:

• Repeat HIV testing, assess for signs and symptoms of acute infection
• Repeat pregnancy test (and STI screen if indicated)
• Assess side effects, HIV risk behaviours, adherence challenges
• Explore women-driven solutions supporting adherence and risk reduction strategies, including condom use

At least every 6 months:

• Monitor CrCl

[In the USA, report to Antiretroviral Pregnancy Registry when pregnancy confirmed, if on PrEP:

http://apregistry.com/ Phone: 1 800 258 4263]
Pregnancy and post-partum

• Continue PrEP:
  • for at least one month after a conception is achieved
  • through pregnancy if at risk of seroconversion during pregnancy

• Postpartum options:
  • discuss risks and benefits of breastfeeding
  • determine if partner’s viral load is undetectable, if condoms can be used correctly and consistently
  • discuss continuing on PrEP to prevent seroconversion during breastfeeding and beyond
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With thanks for ideas, photos, and slides to:

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- Ariane van Straten

- Connie Celum
- Myron Cohen
- Quarraisha Abdool Karim
- Zeda Rosenberg
- Erika Aaron

Thank you for your attention!