PrEP:
Easier than falling off a log....

Linda-Gail Bekker
Desmond Tutu HIV Centre, UCT
Southern Africa HIV Clinicians Society
Effective use = When drug levels in blood are high, HIV protection is consistent and high. The converse is true......

PrEP is protective for HIV across populations. It has few significant safety risks and no evidence of behavioural risk compensation.

Fonner et al., AIDS, 2016
PrEP Works – What we already know

- Drug resistance does occur when PrEP is initiated when already acutely HIV infected – but the risk of acquiring drug-resistant HIV when on PrEP is low.

PrEP is safe
- Rates of death, serious adverse events, and lab’ abnormalities (+ renal dysfunction) were low and not different between those taking PrEP vs placebo

PrEP is well tolerated
- Side effects were minimal and occurred in minority of people
Where it all started.....

Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women

Quarraisha Abdool Karim, Salim S. Abdool Karim, Janet A. Frohlich, Anneke C. Grobler, Cheryl Baxter, Leila E. M...

From Proof-of-Concept to Prevention Phenomenon

- **iPrEx results**
- **Partners PrEP, TDF2 results**
- **US FDA approval, WHO guidance**
- **Open-label extension results**
- **PreP discussion surges in US**
- **WHO recommends PrEP as option for all at substantial risk**
- **Truvada as PrEP approved in over 15 countries**

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<tbody>
<tr>
<td></td>
<td>Research</td>
<td>Regulatory</td>
<td>Cultural shifts</td>
<td>Country programming</td>
<td></td>
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</tbody>
</table>

- **PrEP**
  - **iPrEx (TDF/FTC)**
    - 42%
    - Cl: 16-88
  - **TDF2 (TDF/FTC)**
    - 49%
    - Cl: -22-81 Cl: 25-97
  - **sPrEP (TDF/FTC)**
    - 66%
    - Cl: 28-84 Cl: 54-94

Has the global action on daily oral PrEP been as fast as possible? No. But there has been tremendous activity over the past five years. This timeline can be used to anticipate and speed action on the next generation of ARV-based prevention options. For the latest, visit [www.avac.org/infographics](http://www.avac.org/infographics).
Effectiveness

• Based on 12 randomized trials (placebo/no PrEP)
  • Overall RR 0.5
  • Better adherence: RR 0.3
  • male/rectal: RR 0.3
  • Female/Vaginal: RR 0.5
  • >25 yrs: RR 0.4
  • <25 yrs: RR 0.7

Recommendation

Oral PrEP containing TDF should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches (strong recommendation, high-quality evidence).
New 2020 GL is myth busting....

- PrEP is for anyone who is at risk
- PrEP can be used by pregnant people
- PrEP has few issues
- PrEP can be tailored to lifestyle needs
- PrEP is easy to use
- There are exciting developments on the horizon
PrEP doesn’t work in women-
- Viral clade
- Tissue penetration/PK
- Viral load/Risk
- Vaginal Dysbiosis
- STIs
For the first time in my life – I own my sexuality

Its like a pregnancy pill- if you take a pill you don’t get pregnant......if you take PrEP you won’t get HIV.

Personal Control Part of a movement
- Approximately half of the women never had TFV detection in plasma.
- Fewer than a quarter of the women had TFV detected in all samples.
- The remaining women had some evidence of using product, albeit intermittently.

Source slide: Lynne M. Mofenson, M.D.
Meta-Analysis of Adherence and Efficacy of Oral TDF-Based PrEP in Women

**Hanscom B et al.  JAIDS 2016;73:606-8**

- Adherence-based meta-analysis model included 5 studies.
- Wide variation adherence and efficacy between studies.
- Oral PrEP effective with moderate/high adherence:
  - 32% efficacy with 50% and 61% efficacy with 75% adherence.

<table>
<thead>
<tr>
<th>Study (Drug)</th>
<th>Region</th>
<th>Enrollees</th>
<th>Exposure</th>
<th>Clade</th>
<th>Adhere</th>
<th>PrEP events</th>
<th>Control events</th>
<th>Oral PrEP vs Placebo Relative Risk [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. FEM-PrEP (TDF/FTC)</td>
<td>S.Africa</td>
<td>Individuals</td>
<td>Mucosal</td>
<td>C</td>
<td>24%</td>
<td>33</td>
<td>35</td>
<td>0.95 [0.60, 1.52]</td>
</tr>
<tr>
<td>2. VOICE (TDF/FTC)</td>
<td>S.Africa</td>
<td>Individuals</td>
<td>Mucosal</td>
<td>C</td>
<td>29%</td>
<td>61</td>
<td>60</td>
<td>1.03 [0.73, 1.46]</td>
</tr>
<tr>
<td>3. VOICE (TDF)</td>
<td>S.Africa</td>
<td>Individuals</td>
<td>Mucosal</td>
<td>C</td>
<td>30%</td>
<td>52</td>
<td>35</td>
<td>1.49 [0.98, 2.27]</td>
</tr>
<tr>
<td>4. TDF2-Botswana (TDF/FTC)</td>
<td>S.Africa</td>
<td>Individuals</td>
<td>Mucosal</td>
<td>C</td>
<td>81%</td>
<td>7</td>
<td>14</td>
<td>0.49 [0.20, 1.21]</td>
</tr>
<tr>
<td>5. Partners PrEP (TDF/FTC)</td>
<td>E.Africa</td>
<td>Couples</td>
<td>Mucosal</td>
<td>A/C/D</td>
<td>77%</td>
<td>9</td>
<td>28</td>
<td>0.35 [0.17, 0.74]</td>
</tr>
<tr>
<td>6. Partners PrEP (TDF)</td>
<td>E.Africa</td>
<td>Couples</td>
<td>Mucosal</td>
<td>A/C/D</td>
<td>30%</td>
<td>8</td>
<td>28</td>
<td>0.30 [0.14, 0.65]</td>
</tr>
<tr>
<td>7. Bangkok (TDF)</td>
<td>Thailand</td>
<td>Individuals</td>
<td>Parenteral</td>
<td>B/AE</td>
<td>66%</td>
<td>2</td>
<td>9</td>
<td>0.22 [0.05, 1.01]</td>
</tr>
</tbody>
</table>

**Meta-analyses Estimates, By Subgroup**

(a) Southern Africa Only, Studies 1-4, (Low Adherence) 1.05 [0.78, 1.41]
(b) All Mucosal Exposure, Studies 1-6 (Mixed Adherence) 0.70 [0.42, 1.18]
(c) All Available Data, Studies 1-7 (Mixed Adherence) 0.64 [0.38, 1.08]
(d) 50%+ Adherence, Studies 4-7 (Moderate/High Adherence) 0.35 [0.22, 0.54]

**Meta-analysis Regression Estimates, All Studies, By Adherence**

<table>
<thead>
<tr>
<th>Adherence</th>
<th>Regression Estimate, All Studies</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>25%</td>
<td>1.19 [0.89, 1.61]</td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td>0.66 [0.53, 0.88]</td>
<td></td>
</tr>
<tr>
<td>75%</td>
<td>0.39 [0.25, 0.60]</td>
<td></td>
</tr>
</tbody>
</table>
HIV in pregnancy

- HIV acquisition during pregnancy and immediately following pregnancy remains high.

- In South Africa, the maternal HIV incidence rate was 10.7 per 100 person years (PY), and 12.4 per 100 PY in urban health facilities in 2013.

- In a recent meta-analysis, MTCT risk was significantly higher among women with incident vs. chronic HIV infection in the postpartum period (OR 2.9) or in pregnancy/postpartum periods combined (OR 2.3)


PrEP’d while Conceiving? Protection for discordant couples who want to conceive.

High-risk for sero-discordant couples:

- **China**: 5-fold ↑ odds of seroconversion in those desiring to conceive a child (Tang, 2016, PLoS One)
- **Kenya**: 1.8-fold ↑ relative risk of seroconversion in couples in whom pregnancy occurred (Brubaker et al., 2011, HIV Med)

**PrEP is protective**: Swiss study of 46 discordant couples using timed intercourse with PrEP (Vernazza et al., 2011, AIDS)

- 75% of couples achieved natural conception
- None of the female partners seroconverted for HIV.

**Not conceiving?** PrEP was found to not reduce the effectiveness of hormonal contraceptives in preventing pregnancy in the Partners PrEP study. It was concluded that PrEP is safe to use in conjunction with hormonal birth control. Murnane et al., CROI Poster Abstract 2014
High Adherence to PrEP During Peri-Conception Period – Partners PrEP
Matthews L et al. JAIDS 2014;67:91-7

- 1785 HIV-uninfected women in Partner’s PrEP placebo-controlled trial; 267 women had 288 pregnancies
- Adherence to study drug (blinded PrEP or placebo) was high among 267 women experiencing pregnancy.
- 95-100% adherence to study drug in the 6 months prior to pregnancy
PrEP’d in Pregnancy?

Significant TDF exposure in utero occurs: no review has found any adverse effects on pregnancy outcome or infant growth.

• No difference in low birth weights between tenofovir and control regimens
• No increase in reported birth defects (for both HIV-infected and not infected women)
• No significant difference found in infant growth
• No significant impact on maternal health was found
  • Increased neonatal mortality risk with tenofovir exposure
  • Need to assess infant growth/bone effects

Challenge: considered SAFE, but limited studies (16) in HIV-uninfected women + low adherence in PrEP studies

WHO: “PrEP may be offered and continued during pregnancy in women at substantial risk of HIV acquisition”

Source: Nachega et al, 2017
PrEP’d while breastfeeding?

- Transfer of tenofovir from maternal plasma to breast milk is **limited**
- Infant exposure was found to be **>200 times lower** than the proposed infant therapeutic dose
- Tenofovir was **not** detected in 94% of infant plasma samples

It is predicted that oral PrEP is **safe** for breastfeeding, HIV-uninfected women.

Source: Mugwanya et al., 2016
WHO recommendations:

- [Link](https://www.who.int/hiv/pub/toolkits/prep-preventing-hiv-during-pregnancy/en/)

- **Continuation on PrEP during pregnancy and BF.** Woman taking PrEP who subsequently becomes pregnant and remain at substantial risk of HIV infection

- **PrEP as part of eMTCT.** Pregnant or breastfeeding HIV- woman living in a setting with high HIV incidence who are at substantial risk of HIV acquisition

- **PrEP for safer conception.** Women with HIV+ partners but not virally suppressed, or status unknown for safer conception

<table>
<thead>
<tr>
<th>Population</th>
<th>Risk group</th>
<th>Special considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescents</td>
<td>Any/all</td>
<td>Must weigh &gt;35 kg. Should be allowed to consent independently</td>
</tr>
<tr>
<td>Women</td>
<td>Mostly vaginal sex, but may also engage in oral* and anal sex</td>
<td>PrEP is highly efficacious when dosed daily in HIV uninfected women. It is a user-dependent, discreet addition to the prevention menu for women. When providing PrEP to women, it is important to provide it in the context of other health interventions.</td>
</tr>
<tr>
<td>Men</td>
<td>Penile and oral</td>
<td>PrEP works for men who are HIV negative and at risk of HIV acquisition.</td>
</tr>
<tr>
<td>Men who have sex with men (MSM)</td>
<td>Penile, anal, and oral</td>
<td>Tissue concentrations of TDF/FTC appear to be higher at the anal mucosa and are reached more rapidly in the anal mucosa than vaginal mucosa.4 doses per week may be sufficient to safely protect MSM. Recent trials have also confirmed that on-demand PrEP is efficacious.</td>
</tr>
<tr>
<td>Pregnant and breastfeeding women</td>
<td>Primarily vaginal sex but may also engage in anal and oral sex</td>
<td>PrEP is safe in pregnancy and during lactation. There are no contraindications to taking PrEP during pregnancy and breastfeeding. 19,25 HIV incidence is high during pregnancy and breastfeeding with HIV acquisition risk more than doubling during pregnancy and the postpartum period compared to when women are not pregnant 30.</td>
</tr>
<tr>
<td>Serodiscordant couples</td>
<td>A partner has unknown or HIV-positive status and is not virally suppressed</td>
<td>PrEP may be used as a &quot;bridge&quot; until the partner living with HIV has an undetectable viral load – at that point the PrEP may be discontinued depending on the preference of the couple. 31</td>
</tr>
<tr>
<td>Safer conception</td>
<td>Serodiscordant couples wishing to conceive</td>
<td>PrEP may be provided to the HIV-negative partner during condomless sex while trying to conceive, and whilst pregnant and breastfeeding. 32-35 PrEP should be continued until the partner living with HIV has initiated ART and achieved viral suppression (viral load &lt;200 copies/mL).</td>
</tr>
<tr>
<td>Drug using individuals</td>
<td>Needle sharing caries HIGH HIV risk</td>
<td>PrEP has been shown to be effective in one large RCT and some demonstration studies of intravenous drug using populations of both sexes.</td>
</tr>
<tr>
<td>Transgender people</td>
<td>Anal and oral sex</td>
<td>Transgender (TG) women have very high rates of HIV acquisition and PrEP is effective although specific evidence is limited.</td>
</tr>
</tbody>
</table>
When should PrEP NOT be offered?

• PrEP should not be offered to anyone who is suspected or confirmed to be HIV-positive.
• Individuals who refuse to HIV test should be counselled and PrEP should not be offered.
• PrEP should be delayed in anyone with an acute viral illness that could be due to HIV seroconversion.
• Tenofovir-based PrEP should not be offered to anyone with pre-existing renal dysfunction (eGFR < 50 mL/min). Clients can return in 1-3 weeks to re-test eGFR to re-assess eligibility.
• Individuals < 35 kg should not be given oral PrEP.
Modeling studies- complicating PrEP

Time to Protection? Cell type? Tissue?

Steady state concentration? Cell type? Tissue?

7 days MSM 21 days WSM

Time to protection

Anderson: PMID: 23226529, 25202923, 11000253

Penetration of oral antiretrovirals into mucosal surfaces.

<table>
<thead>
<tr>
<th>Equivalent</th>
<th>Rectal mucosa</th>
<th>Fold-change versus plasma</th>
<th>Female genital tract mucosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.75</td>
<td>NRTI</td>
<td>40</td>
<td>NRTI</td>
</tr>
<tr>
<td>0.5</td>
<td>NNRTI</td>
<td>30</td>
<td>NNRTI</td>
</tr>
<tr>
<td>0.25</td>
<td>PI</td>
<td>20</td>
<td>PI</td>
</tr>
<tr>
<td>0.25</td>
<td>EL</td>
<td>10</td>
<td>EL</td>
</tr>
<tr>
<td>0.25</td>
<td>I</td>
<td>40</td>
<td>I</td>
</tr>
<tr>
<td>0.25</td>
<td>FTC* (4.4)</td>
<td>30</td>
<td>FTC* (4.4)</td>
</tr>
<tr>
<td>0.25</td>
<td>TFV* (33)</td>
<td>20</td>
<td>TFV* (33)</td>
</tr>
<tr>
<td>0.25</td>
<td>RTV (13)</td>
<td>10</td>
<td>RTV (13)</td>
</tr>
<tr>
<td>0.25</td>
<td>MRV (27)</td>
<td>10</td>
<td>MRV (27)</td>
</tr>
<tr>
<td>0.25</td>
<td>MRV (4)</td>
<td>40</td>
<td>MRV (4)</td>
</tr>
<tr>
<td>0.25</td>
<td>BTC &amp; FTC</td>
<td>30</td>
<td>BTC &amp; FTC</td>
</tr>
<tr>
<td>0.25</td>
<td>ZDV (2.3)</td>
<td>20</td>
<td>ZDV (2.3)</td>
</tr>
<tr>
<td>0.25</td>
<td>TFV (1.1)</td>
<td>10</td>
<td>TFV (1.1)</td>
</tr>
<tr>
<td>0.25</td>
<td>ETR (1.3)</td>
<td>10</td>
<td>ETR (1.3)</td>
</tr>
<tr>
<td>0.25</td>
<td>IDV (2)</td>
<td>10</td>
<td>IDV (2)</td>
</tr>
<tr>
<td>0.25</td>
<td>DRV (1.5)</td>
<td>10</td>
<td>DRV (1.5)</td>
</tr>
<tr>
<td>0.25</td>
<td>RAL (2)</td>
<td>10</td>
<td>RAL (2)</td>
</tr>
<tr>
<td>0.25</td>
<td>NVP (0.8)</td>
<td>10</td>
<td>NVP (0.8)</td>
</tr>
<tr>
<td>0.25</td>
<td>APV (0.5)</td>
<td>10</td>
<td>APV (0.5)</td>
</tr>
<tr>
<td>0.25</td>
<td>ddl (0.2)</td>
<td>10</td>
<td>ddl (0.2)</td>
</tr>
<tr>
<td>0.25</td>
<td>DLV (0.2)</td>
<td>10</td>
<td>DLV (0.2)</td>
</tr>
<tr>
<td>0.25</td>
<td>ABC (0.08)</td>
<td>10</td>
<td>ABC (0.08)</td>
</tr>
<tr>
<td>0.25</td>
<td>d4T (0.05)</td>
<td>10</td>
<td>d4T (0.05)</td>
</tr>
<tr>
<td>0.25</td>
<td>EFV (0.04)</td>
<td>10</td>
<td>EFV (0.04)</td>
</tr>
<tr>
<td>0.25</td>
<td>LPV (0.08)</td>
<td>10</td>
<td>LPV (0.08)</td>
</tr>
<tr>
<td>0.25</td>
<td>SQV (0)</td>
<td>10</td>
<td>SQV (0)</td>
</tr>
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</table>

* Single dose

Walid Heneine, and Angela Kashuba Cold Spring Harb Perspect Med 2012;2:a007419

©2012 by Cold Spring Harbor Laboratory Press
The time to act is short!

Post exposure prophylaxis must be initiated within 24-36 hours of exposure, 48 hours may be too late.

Exposure: 30-60 mins

DC-T cell transfer 1-4 hours
(virological synapse)

Localized infection: 16-72 hours

Dissemination to draining LN: 24-72 hours
(virological synapse)

Induction of memory responses: 3-5 days

Pinto Al, 1997; Spira LA 1996
Steady state in Oral Truvada dosing

Time To Maximal Protection; Daily Dosing with Truvada®

Maximal Protection by dose 2 in RT

Maximal Protection by dose 3 in FGT

% Achieving EC95 Target Ratio

Dose

Cottrell et al J Infect Dis. 2016 Jul 1;214(1):55
Slide courtesy: Angela Kashuba
Anal Mucosa: Fewer doses still effective

100% HIV protection was seen with adherence consistent with ≥4 tablets per week

Grant et al. Lancet ID 2014
GL’s take on time to efficacy....

- 7 days for women, heterosexual men and MSM, based on PK and an expert meeting.
  - [https://www.who.int/hiv/pub/prep/appropriate-medicine-prep/en/](https://www.who.int/hiv/pub/prep/appropriate-medicine-prep/en/)

- Stopping ‘rules’: 28 days. This is based on PEP practice and there is no evidence for this 28 days – it is just a best guess.

- Better to advise daily dosing in people where vaginal mucosa is site of transmission.
Anal mucosa: On demand PrEP works

- 2 tabs 2-24 hours before sex (or 1 pill if most recent dose taken between 1-6 days prior)
- 1 tab 24 and 48 hours after the last pre-sex dose
Achieving steady state in Rectal vs FGT.

Slide courtesy: Angela Kashuba

iPrEx OLE = ↓ HIV incidence by 90% with 2 Truvada doses per week

Partners PrEP = ↓ HIV incidence by 90% with 7 Truvada doses per week


Intermittent or “On-Demand” PrEP for High-Risk MSM
IPERGAY: Results

Due to high effectiveness of PrEP, participants unrandomized and all offered PrEP

Source: Molina JM, et al. CROI. 2015; Abstract 23LB.
On demand PrEP....

Open-Label Prospective Cohort Study in the Paris Region

n ≥ 3,000
May 3rd 2017
May 31st 2020

- HIV-negative high risk adults
- Inconsistent Condom use
- eGFR ≥ 50 mL/mn
- HbS Ag negative if On Demand

- Participants opted for either Daily or On Demand PrEP and could switch regimen
- Follow-up every 3 months with 4th Gen ELISA HIV test and plasma creatinine
- STI screening at physician’s discretion (Guidelines recommend every 3 months in MSM)
- Condoms, gels, risk reduction and adherence counseling, Q on sexual behavior

Show 15% reduction in new HIV diagnoses among MSM in the Paris Region
Choice: 50:50
### Clinical Experience with On-Demand PrEP in MSM

<table>
<thead>
<tr>
<th></th>
<th>Number choosing On-Demand</th>
<th>Number of Infections on PrEP</th>
<th>Infection Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>France¹</strong></td>
<td>1581 (57%)</td>
<td>0</td>
<td>0 (0 to 0.0030)</td>
</tr>
<tr>
<td><strong>Montreal²</strong></td>
<td>225 (22%)</td>
<td>0</td>
<td>0 (0 to 0.020)</td>
</tr>
<tr>
<td><strong>Combined observed</strong></td>
<td>1806 (47%)</td>
<td>0</td>
<td>0 (0 to 0.0026)</td>
</tr>
<tr>
<td><strong>Expected if not effective³</strong></td>
<td>1806 (47%)</td>
<td>119</td>
<td>6.6 (0.05 to 0.08)</td>
</tr>
</tbody>
</table>

1. Molina IAS 2017 (WEPE0939) Paris, 35% had STIs in the past 12 months; Also new efficacy analysis stratified by sex frequency (Antoni IAS 2017 Tuesday 11:15).
2. Greenwald Adherence 2017 Miami;
3. Assumes incidence 6.6/100 PY as observed in Ipergay, and that patients were followed for an average of 12 months, CI by Wilson method with continuity corrections.
PEP to PrEP -

• One Fenway study – 21% of PEP patients reported condomless anal sex and 11% reported condomless anal sex during follow-up

• Recurrent PEP use has ranged from 9-28% in different studies

• HIV incidence in Australian PEP users: 1.3%; 2.9% in Brazilian MSM; 6.4% in Dutch PEP users

Jain, *Clinical Infectious Diseases*, 2015
From PEP to PrEP?

Looking for people who present for PEP might be an efficient means of identifying candidates that would benefit from PrEP.
1. Need to first determine reasons for risk and initial HIV exposure that lead to PEP; if risk is considered to be ongoing can refer to PrEP
2. PEP (TDF/FTC) users would be tolerant of PrEP as the same ARVs are commonly involved
3. The clinical visits required for PEP could provide opportunities to provide risk reduction counselling, monitor PEP uptake, and pre-emptively evaluate factors (s.a. mental health, substance use) that might be barriers to PrEP adherence.

Guidelines for transitioning from PEP to PrEP:
- CDC guidelines recommend waiting at least 4 weeks after PEP usage if HIV negative and no signs or symptoms of acute retroviral syndrome
- Earlier transition might be required for particularly high-risk participants, if a 4th gen antibody-antigen assay is used.
- Further research is needed to optimise this process.
PrEP and side effects.....

![Systematic Review Diagram](image)
PrEP adverse events

Significant Increase in Risk on PrEP?

<table>
<thead>
<tr>
<th>None</th>
<th>None</th>
<th>None</th>
<th>None</th>
<th>None</th>
<th>p=0.04</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>%Events/Total People</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.4</td>
</tr>
<tr>
<td>9.4</td>
</tr>
<tr>
<td>3.7</td>
</tr>
<tr>
<td>0.1</td>
</tr>
<tr>
<td>4.3</td>
</tr>
</tbody>
</table>

n = 15,678

Pilkington et al. Glasgow HIV 2018. Poster 0143
Glasgow HIV Treatment Conference 2018
Bone Mineral Density and TDF PrEP

TDF-2 Study: Kasonde M et al. PLoSOne 2014;9:e90111
VOICE study Mirembe BG et al. JAIDS 2016;71:287-94

• Abnormal baseline BMD (<-2 z-score) not infrequent in HIV-uninfected pts (5.8-6.8% in VOICE and TDF-2).

• Both studies showed small but statistically significant decreases (-0.8 to -1.6% difference) in BMD with TDF-based PrEP compared to placebo.

  • TDF-2: -0.8% (forearm) to -1.5 to -1.6% (hip, spine) difference in mean percent change in BMD at 6-30 months from baseline comparing TDF/FTC vs placebo.

  • VOICE: In subset of women with TFV detection in 75-100% of plasma samples, -0.9% (hip) to -1.4% (spine) difference in BMD compared to placebo at 48 weeks.
TAF/FTC: Works for Treatment—How about PrEP?

- TAF 25 mg results in >90% lower TFV plasma levels
- OAT, organic anion transporter; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir.

Lower plasma levels
Less toxicities
Smaller pill

Discover: oral PrEP with F/TAF (emtricitabine/tenofovir alafenamide) compared to F/TDF (emtricitabine/tenofovir disoproxil fumarate) in a randomised, double-blind, noninferiority trial.

Noninferiority was achieved:
- 22 HIV infections in 8756 PY of follow up
- Confirmed in a sensitivity analysis

Primary analysis:
- HIV incidence/100 PY when 100% complete Week 48 & 50% complete Week 96

Spinner et al., IAS 2019 Mexico, Oral Abstract
Discover: F/TAF found to have a more rapid onset and longer sustained duration of protection than F/TDF.

F/TAF achieved EC90 More Rapidly than F/TDF:
• median TFV-DP concentrations exceeded EC90 within 1-2 h.
In contrast, 3 daily doses of F/TDF are needed to achieve EC90.


F/TAF has a Longer Duration > EC\textsubscript{90} After Last Dose: At steady state, after the last dose, F/TAF would provide TFV-DP levels in PBMCs above EC90 for 16 days compared to 10 days with F/TDF.

TAF vs TDF?

Glasgow HIV Treatment Conference 2018

TDF vs TAF

Unboosted TDF/FTC vs TAF/FTC (n=3181)

Grade 3+4: No risk difference

Serious Adverse Events: No risk difference

Bone Fractures: No risk difference

Renal D/C: No risk difference

Hill et al. J Virus Erad 2018, 4:72-78

Pilkington et al. Glasgow HIV 2018 Poster 0143

Glasgow HIV Treatment Conference 2018
F/TAF for PrEP: F/TAF is a safer, potentially more efficacious option than F/TDF for prevention of HIV.

FDA approves Descovy for HIV PrEP, excluding cisgender women

October 3, 2019

But not women...

The FDA has approved Descovy as a second option for pre-exposure prophylaxis, or PrEP, in at-risk adults and adolescents. The drug will not be approved for this indication in women, who were excluded from the trial. The drug was associated with fewer side effects and a lower risk of kidney damage compared to the current standard of care, the agency said. 

Spinner et al., IAS 2019 Mexico, Oral Abstract
Resistance in PrEP:

Summary of HIV drug resistance prevalence among PrEP users who tested HIV positive in RCTS and Open Label studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Acute HIV infection at study enrolment</th>
<th>HIV infection occurred during the study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV cases</td>
<td>HIVDR to TDF and/or XTC</td>
</tr>
<tr>
<td>Bangkok Tenofovir Study [8]</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>FEM-PrEP [9]</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>iPrEx [10, 19]</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Partners PrEP [11, 20]</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>TDF2 [12]</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>VOICE [13]</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>IPERGAY [14]</td>
<td>3 (^a)</td>
<td>NR</td>
</tr>
<tr>
<td>PROUD [15]</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>iPrEx OLE [16]</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>USA DEMO [17]</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>HPTN-067 [18]</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>39</td>
<td>13</td>
</tr>
<tr>
<td><strong>%</strong></td>
<td>33.3</td>
<td>7.7</td>
</tr>
</tbody>
</table>

NR: Not reported

\(^a\) The three cases were excluded from the total number of HIV cases because HIVDR data were not reported

\(^b\) Two of the 17 cases were excluded from the total number of HIV cases because HIVDR testing was not successful
Theoretical Infection-Exposure-Resistance Relationships

- Zone of Resistance
  - No Drug
  - No Resistance
  - Infection

- Zone of Resistance Risk
  - HIV infection
  - Resistant infection

- No Infection
  - No Resistance

Drug Exposure

Fraction infected or resistant

J. Mellors FDA Hearing 2012
PrEP: STIs, Hep B
No New HIV Infections With Increasing Use of HIV PrEP in a Clinical Practice Setting
— Kaiser Permanente Volk J 2015

- **657 PrEP Initiators**
- **187 diagnoses with >1 STI during follow-up; 78 with multiple STIs (range 2-10). Total 344 diagnoses.**
- After 6 mo of PrEP use: **30%** (95% CI 36-35%) diagnosed with any STI
- After 12mo of PrEP use: **50%** (95% CI 43-56%) diagnosed with any STI
- **No HIV diagnoses**, over 388 py follow-up
MSM in CT and PE

- **Significant community engagement** activities led to 87% retention at 12 months.

- HIV incidence in this cohort was high, particularly among the youngest age groups, highlighting the need for targeted prevention efforts.

- **Interest in PrEP was high**, and delivering PrEP is feasible in public and research clinics in South Africa as part of a comprehensive prevention package.

- Interest in **non-standard condoms** was high.
Symptomatic STI diagnoses

- In addition to laboratory testing, symptomatic screening for STIs was completed.
- At baseline, of those with a biologically confirmed STI diagnoses, 8% (10/124) had a symptomatic STI diagnosis during the clinical assessment.
- At the 6 month visit, 6% (3/49) of STI diagnoses had a symptomatic diagnosis.
- At the 12 month visit, 15% (8/53) of STI diagnoses had a symptomatic diagnosis.

![Graph showing symptomatic STI diagnoses over time.](chart.png)
Asymptomatic STI in YW in RSA

In addition to laboratory testing, symptomatic screening for STIs was completed:

• At baseline, of those with a biologically confirmed STI diagnoses, 20% (8/41) had a symptomatic STI diagnosis

• At the 12 week visit, 5% (2/43) of STI diagnoses had a symptomatic diagnosis

• At the week 48 visit, 3% (1/34) of STI diagnoses had a symptomatic diagnosis

Need to move to laboratory based diagnostic screening

Gill K IAS2017
PrEP’d for STI’s?

STIs were with us before the HIV epidemic, before condoms and before PrEP.

While PrEP is a solution for HIV prevention it is not the solution for STI’s.

**On the one hand:**

PrEP shouldn’t exist outside of a package:

- Testing, Contraception, Condoms, STI screening and treatment

**ON THE OTHER:**

IT HAS THE POTENTIAL TO ENHANCE STI SCREENING AND HEALTHY SEXUAL/REPRODUCTIVE HEALTH PRACTICES.

PreP attracts individuals who are prone to risky behaviours.
GL take on this

- High incidence of STI- (especially CT and NG) at baseline. (MSM, AGYW, Pregnant women)
- Condoms challenging....likely to be so in future
- So high prevalence during taking prep.
- So PrEP service an opportunity for better STI services.
- NAAT testing and aetiologically tailored treatment preferred but expensive
- Not a reason NOT to PrEP.
- Syndromic management an alternative.
- TDF is treatment for Hepatitis B
- Therefore theoretical risk of flare on stopping treatment in person with Hep B infection
- Hep B screening preferred with vaccination recommended in those who are NON-immune
Prevention is a lifestyle

Taking the pain out of prevention

PrEP FOR YOUR WILD TIME WITH A BEAR, WITH 1 PILL A DAY.

NEW WAYS TO PREVENT HIV Daily PrEP & Emergency PEP
Getting PrEP right by eliminating strategies that promote failure.

Steps to reposition PrEP for Success.

“The Sell” : Focus on Safety, ease of use - not Risk: Frame PreP positively and as an empowerment tool to maximise SRH and wellness.

Amico & Bekker, Submitted 2018
Then who is "at risk"?

And if not now at risk......why not tomorrow?

Engage- Who?

If we direct prevention to those “at risk” within a specific pop...
People’s sex lives are often in transition.....

- May “transition” to a risky profile
- May move in and out of a risky profile
- May not fully identify as a risky individual

“At Risk” mantle may be desirable or deniable

Profiling (rationing) may alienate people or stigmatise PrEP and reduce PrEP impact?
PrEP is seasonal

If PrEP can be implemented at certain periods as a prevention intervention
May be reduced need for treatment & prevention during later stages of life:

PrEP for 3-4 Years while young and at risk

15-24 Years

Less need for PrEP here

PrEP for 3-4 Years while youngish

24-28 Years
The Lexicon

- Seasons of use
- Effective use
- Cycling on and off
- In use, off use
- Persistence
- Clients, users
- Non-PrEP users
- NOT: adherence, LTFU, Retention,

**PrEP is safe, well tolerated and easy to administer.**
Step 1: Check client desirability for PrEP.

The aims of initiation consultations for PrEP are:

- **Understanding and insight of potential PrEP user**: To ensure that the PrEP user understands what PrEP is and the protection it provides, and has a personal plan for its effective use.

- **HIV-negative status of User**: To ensure that the PrEP user is confirmed to be HIV-negative (rapid HIV testing acceptable).

- **Suitability and safety of PrEP for User**: To assess the suitability and safety of PrEP in those with renal and or other potential contraindications.
Step 2: Test for HIV status

HIV testing is required at initiation and at least-3-monthly whilst on PrEP to confirm HIV-negative status

- Follow HIV-testing guidelines
- Elicit a medical history and conduct a targeted examination to exclude acute exposure (symptoms suspicious of acute infection may be followed with repeat testing after two weeks to confirm HIV-negative status)
- HIV testing is advised 3-6 monthly whilst on PrEP to ensure breakthrough infection has not occurred
- HIV self-testing may be used as an alternative whilst on PrEP
- Inconclusive HIV test results should be referred for confirmatory testing
- PrEP should be stopped immediately in anyone with a positive or indeterminate HIV test result
- Should an interruption in PrEP occur, then initiation testing should be performed (as above) prior to restart
HIV self-testing kits for PrEP

WHO 2016 Guidelines recommended HIV self-testing as a means of increasing knowledge of HIV status in people who:
- Lack access to HIV testing healthcare services
- Fear stigmatisation & discrimination

A literature review on global attitudes and acceptability of HIV self-testing amongst key populations (Figueroa et al., 2015, AIDS Behav) indicate MSM:
- Like self-testing due to convenience and privacy
- Some worries about lack of counselling & fear of test errors

Other worries include lack of linkage to care in countries that have limited HIV services or barriers to accessing these services (WHO 2016)
Step 3: Check general wellbeing

Clinical assessment: A clinical assessment for STIs should be performed at initiation, 6-monthly or when indicated

• Appropriate STI screening is recommended and aetiologic testing and treatment should be provided when available. This should include nucleic acid antigen testing for Chlamydia Trachoma and Neisseria Gonococcus and serology for Treponema Pallidum.
• Syndromic STI screening and management is otherwise recommended
• Viral hepatitis B screening is recommended at PrEP initiation/screening if status unknown.
• Hepatitis B vaccination is recommended if available if screening serology test is negative.
Step 4: Check for contraindications

**Renal function:** A baseline assessment of renal function should be performed (creatinine and eGFR) in patients who are >40 yrs, have co-morbidities and/or are on concomitant meds.

PrEP should not be used in people with a baseline eGFR of < 50 mL/min.

Renal function may be checked annually and more frequently as dictated by an underlying renal problem or comorbidity.
### Renal monitoring

<table>
<thead>
<tr>
<th></th>
<th>At PrEP start</th>
<th>At PrEP follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Well individual, ≤ 40 years</strong></td>
<td>Recommended, not essential</td>
<td>Not required</td>
</tr>
<tr>
<td><strong>&gt; 40 years</strong></td>
<td>Recommended</td>
<td>6 and 12 months</td>
</tr>
<tr>
<td><strong>Pregnant</strong></td>
<td>Recommended</td>
<td>6 and 12 months; not required after pregnancy if ≤ 40 years</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td>Recommended</td>
<td>6 and 12 months</td>
</tr>
<tr>
<td><strong>Concomitant chronic medication</strong></td>
<td>Recommended and essential or contra-indicated if nephrotoxic concomitant medication</td>
<td>6 and 12 months/Contraindicated</td>
</tr>
</tbody>
</table>
Step 5: Plan follow up visits

- Assess how pill-taking is going for PrEP user.
- Interactions should be supportive and affirming.
- Identify a motivator to support effective pill-taking.
- Provide PrEP education regarding effective use and effectiveness of PrEP.
- Identify barriers to effective use.
- Provide realistic strategies to address barriers.
- Discuss use of other HIV prevention measures that are relevant to situation.
- Review need for PrEP and any change in sexual risk.
Provide PrEP on the same day as HCT

PrEP alone provides high levels of HIV prevention, however better in a package of combination prevention that may include:

- Counselling on effective use, starting and stopping PrEP
- HIV testing and counselling of sex partners (including HIV self-screening)
- Commodities such as condoms and sexual lubricants
- Sexual health screening, including STI symptom check, aetiological STI testing if available and treatment either syndromically or as per laboratory results
- Discussions on reproductive intent and provision of contraception as needed.
- Active safer conception counselling and guidance should be offered to women/couples who wish to conceive (see safer conception guidelines).
- Gender affirming counselling and treatment for transgender populations
- Immediate access to ART for potential PrEP users who screen HIV-positive and require treatment.
- Multi-month dosing recommended
- Adolescents and younger users or those who have identified pill taking difficulties may be invited to return after 1 month to trouble shoot adherence difficulties.
- Telephonic contact may help with mild side effect management and difficulties with establishing pill taking routines.
- A follow up visit for clinical monitoring, counselling on persistence at three months, and then every six months or as required. Again, younger users may benefit from more regular contact.
Tips to support PrEP pill-taking

• Schedule medication taking time to correspond with the client’s daily routine activities (e.g. brushing teeth, eating breakfast, going to bed).
  • Take pills at night if worried about side effects (e.g. in pregnant women).
• Use reminders e.g. cell phone, alarms, beepers, calendars.
• Use of pillboxes to ensure daily use.
• Review disclosure issues to identify those who can support the client’s intentions to take their pills or barriers to pill-taking due to lack of disclosure/privacy at home.
• Join an on-line support group e.g. Facebook: PrEP Rethinking HIV Prevention.
The prevention continuum and PrEP implementation

- Identification: Persons at risk for HIV
- Linkage: Persons who might benefit from PrEP
- Clinical Support: Evaluated for PrEP, Prescribed PrEP
Our model for PrEP use.....

Persistence → Cycle off → Restart

Pill Pick up
Pill Taking

HIV exposure
over time

↑ ↑

No HIV risk

↑ ↑

No HIV risk

EFFECTIVE USE

Jessica Haberer 2015
The PrEP cascade....

The PrEP Care Cascade

- Eligible: ...
  - is HIV Negative and at high risk for HIV infection

- Awareness: ...
  - knows about PrEP & whether they are eligible

- Willingness: ...
  - self-identifies as a good PrEP candidate and wants to take PrEP

- Access: ...
  - has a PrEP provider, and is able to afford PrEP

- Uptake: ...
  - receives a prescription and begins taking PrEP

- Effective use

- Persistence?

Cycling on/off:
- Need
- Convenience
A paradigm shift: **The Demedicalisation of PrEP**

- Seasons of use
- Effective use
- Cycling on and off
- In use, off use
- Persistence
- Clients, users
- Non-PrEP users

NOT: adherence, LTFU, Retention, failure,
The Contraceptive CHOICE Project Round Up: what we did and what we learned

McNicholas Et al Clin Obs Gynaecology 2014

Comparison of pregnancy, birth, and abortion rates among sexually active teens

>9200 women (>14yrs)

PrEP:
- Antiretroviral
- Dosing frequency
- Route of Administration
The Superheroes.....

Injectables

Infusables

Implantables

Injectables

Topicals
Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women


**Trial sites in South Africa, Uganda, Zambia, Zimbabwe, Malawi**

**Dapivirine Ring vs Placebo Ring**

- **2016**
- **27% reduction (CI 1, 46), p=0.046**

In both studies:
- **Open label extension**
- **Improved effectiveness RR 0.50**

**TOPICAL PrEP**

- **EMA reviewing data for approval for section 58**
- **WHO recommendations**
- **Women in LMIC ; Second line to PrEP.**

**2016**

- **Safety and Efficacy of a Dapivirine Vaginal Ring for HIV Prevention in Women**


**Trial sites in South Africa, Uganda**

- **31% reduction (CI 1, 52), p=0.04**
PrEP for the future.....considers intimacy, not just prevention:-

Formulations – fit to purpose & suited to varying personal choice

Active Ingredients – alone & in combination to provide depth

Thanks Craig H
PrEP Future

- TDF/FTC PrEP has set a high bar for preventive effectiveness
  - Daily and on-demand ("2-1-1") both work
- What will it take for a new agent to be "game changing"?
  - Long-acting preparations will solve some challenges, not all – and are in the pipeline
  - Future is ripe with possibility in injectables, infusables, implantables, topicals
  - Study designs will need to be adaptive, and negotiations with regulators likely complex
  - MPT may increase use for cisgender women
- More on-demand options, and better diagnostics are needed
- Demedicalisation of PrEP will help with scale up.
- Need a more sophisticated understanding and better partnership with most-affected communities.

More options are better !!
Guidelines 2020 team
