How to administer PrEP; A typical clinical consultation.

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SAHCS
Gallagher Estate 24 October 2018
'Nothing will ever be attempted if all possible objections must first be overcome’ – Samuel Johnson (1709-1784)
Disclosures

MSD

Mylan

aspen

AstraZeneca

Cipla

Gilead

Janssen
WHY PREP??
Ongoing HIV transmission despite expanding access to ART – SA

Source: HSRC, 2012

Treatment exposure has doubled from 16.6% in 2008 to 31.2% in 2012.
Will 90-90-90 do it?

- 90% Combination prevention
- 90% Diagnosed
- 90% On ART
- 90% Virally suppressed
- 90% Good health-related quality-of-life
HIV Prevention incorporates multiple interventions

**Behavioral interventions**
- Avoidance of injection use of safe injection habits
- Delayed sexual debut
- Sexual abstinence
- FTC/TDF for PrEP
- Post-Exposure Prophylaxis (PEP)
- Treatment as Prevention (TasP)

*Behavioral interventions: Aim: to lower the number of partners, alter risk-tasking behavior*

**Biomedical interventions**
- Patient and partner education
- Correct and consistent condom use
- Sexual monogamy
- Testing and treatment of STIs
- Prevention of mother-to-child transmission
- Circumcision

*Biomedical interventions: Aim: to reduce the efficiency of transmission or to shorten the duration of infectiousness*

PrEP in South Africa

- TDF/FTC combination pill approved for use as PrEP (Dec 2015) by the Medicine Control Council, in combination with safer sexual practices
- Current guidelines: Tenofovir/emtricitabine (TDF/FTC) in a single tablet FDC
- Recommended by WHO for people at substantial risk of HIV infection

SA registers a two-in-one pill that can prevent HIV
# Why FTC/TDF for PrEP?

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Pre-Clinical</th>
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<tbody>
<tr>
<td></td>
<td>• Tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) have long intracellular half-lives (40 to 100 hours)(^1)</td>
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<tr>
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<td>• TDF and FTC effectively prevented infection in non-human primate studies(^2)</td>
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<thead>
<tr>
<th>Clinical</th>
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<tr>
<td></td>
<td>• Durable efficacy(^2)</td>
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<tr>
<th>Safety</th>
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<tr>
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<td>• TVD has favorable safety and tolerability profile(^2,3,5,6)</td>
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<td></td>
<td>• TDF and FTC: approved in Europe in 2002 and 2004, respectively, for treatment of HIV(^4)</td>
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<tr>
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<td>• TDF: ~10 million patient-years; FTC: ~7 million patient-years (in the commercial or clinical study settings)(^4)</td>
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<td>• TDF: High barrier to resistance and limited cross-resistance(^3,5)</td>
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<td>• No interactions with hormonal contraception(^5)</td>
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<thead>
<tr>
<th>Pharmacokinetics</th>
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<tr>
<td></td>
<td>• TVD is one pill, once daily(^5)</td>
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<td>• TVD to be given with food (preferably) but also without food(^5)</td>
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<tr>
<td></td>
<td>• TFV and FTC concentrations in the genital tract exceed those in blood plasma(^3,6)</td>
</tr>
</tbody>
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5. Data on File HIV052 – May 2016  
6. EU Truvada SmPC, August 2016
Differences in Half-Lives of Regimen Components

PrEP: Better adherence correlates with higher efficacy

Trials where the majority of subjects were adherent demonstrated HIV protection, with higher protection estimates when more of the population was adherent.

Southern African guidelines on the safe use of pre-exposure prophylaxis in persons at risk of acquiring HIV-1 infection
Who is PrEP intended for?

PrEP should be considered for people who are HIV-negative and at significant risk of acquiring HIV infection. This includes:

- Key populations: most at risk of HIV - including sex workers, men who have sex with men (MSM), adolescent girls and young women (AGYW), intravenous drug users (IDUs), transgender people, prisoners
- Serodiscordant couples
- Bottom line: **ANYONE** who perceives themselves to be at substantial risk

Also depends on **country-specific** guidelines:

- What's approved?
- What's available in the private sector?
- What's available in the public sector?

In South Africa: phased rollout starting with sex workers, then MSM, then...

There are also many demonstration/research projects looking at PrEP provision for AGYW.
Self perception of HIV risk is low

Persons (N=3,533; >90% African-American) undergoing HIV rapid testing in Philadelphia were surveyed between July 2012 and Dec 2013

A large proportion of patients at high-risk for HIV infection do not perceive themselves at high risk
Contra-indications to PrEP

1. Pre-existing HIV infection
2. Creatinine clearance <60 mL/min
3. Adolescents <35 kg or <15 years who are not ≥Tanner stage 3 (sexual maturity)
4. Unwilling or unable to adhere to daily PrEP
5. Pregnant or breastfeeding women (as per Truvada PI)
Risk assessment

In the past six months:

1. Have you had sex with men, women or both?
2. How many men/women have you had sex with?
3. How many times did you have sex without a condom?
4. How many of your partners were HIV-positive or of unknown HIV status?
5. With these positive/unknown status partners, how many times did you have sex without wearing a condom?
Or more simply...

In the past six months:
1. Have you had sex?
2. Have you had unprotected (condom-less) sex?
3. Have you had sex with partners who are HIV-positive or whose HIV status you did not know?
4. Have you had sex under the influence of alcohol and/or drugs?
Or even more simply...

In the past six months:
1. Have you had sex?
2. Have you had unprotected (condom-less) sex?
Eligibility criteria

1. No contraindications to TDF or FTC
2. HIV-negative
3. No suspicion of acute HIV infection
4. Willing and able to adhere to PrEP
Starting PrEP

Screening

PrEP initiation visit

One month follow-up

Three-monthly maintenance visits
Screening visit

- Educate: risks and benefits of PrEP
- Assess risk and eligibility
- HCT/creatinine/HBV/STI screen/pregnancy
- Contraception/condoms/lube
- Arrange follow-up
Managing abnormal screening results

• Abnormal renal function (CrCl <60 mL/min)
  • No PrEP
  • Recheck after 2 weeks – if normal can start PrEP

• HBV screening – see table

• Treat STIs as per national guidelines
Hepatitis B immune status and PrEP

- Acute/chronic HBV: LFT monitoring

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>HBsAb</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative (-)</td>
<td>Negative (-)</td>
<td>Start PrEP, vaccinate concurrently</td>
</tr>
<tr>
<td>Negative (-)</td>
<td>Positive (+)</td>
<td>Start PrEP, no vaccine needed</td>
</tr>
<tr>
<td>Positive (+)</td>
<td>N/A</td>
<td>Refer for evaluation</td>
</tr>
</tbody>
</table>

N/A, not applicable; PrEP, pre-exposure prophylaxis.
PrEP initiation visit

- HCT
- Eligibility (incl labs and CrCl)
- HBV vaccination? STI treatment
- Educate
- Follow-up date
- PrEP side effects
  - Acute HIV infection
  - Bone health
  - Effective use of PrEP
One month follow-up

- PrEP initiation visit PLUS:
  - Tolerability / side effects
  - Effective use
- Manage side effects

3 months TDF/FTC Follow-up

- Contraception / condoms / lubricant
- Creatinine clearance
**Maintenance visits**

- Repeat procedures done at one month
- CrCl: every 3 months for the first year, then 12-monthly
- STI screen and treatment every visit
- Complete HBV immunisation at 6 months?
Adherence

• PrEP: seasons of risk (ART = lifelong)
• Effective use of PrEP requires daily usage for a specified period
  • attainment of full protection
  • daily use for the duration of possible exposure
  • continuous use for one month after cessation of exposure
• Good quality counselling fosters adherence
• Combination prevention package
Exclude acute HIV infection

- HIV test before commencing or restarting PrEP
- Ask about missed doses
- Negative HIV test
  - Clinical screen for symptoms acute HIV
  - Targeted examination
- Time between last potential exposure and window period of tests used
Stopping PrEP

1. Positive HIV test
2. Non-adherent to PrEP
3. Does not need or want PrEP
4. Safety concerns
   • Creatinine clearance <60 mL/min
   • Risks outweigh benefits
5. No longer meets eligibility criteria
Starting and stopping PrEP and effectiveness

Risk via **anal sex**: need **7 days** of daily dosing with oral PrEP to reach adequate anal/rectal tissue levels

Risk via **vaginal sex**: need **20 days** of daily dosing with oral PrEP to achieve protective vaginal tissue levels

- During this period, other protective precautions must be used, such as abstinence or condoms.
- This needs to be taken into account in **users who stop and start PrEP** according to their periods of risk.
- PrEP medications should be continued **for 28 days after** the last potential HIV exposure in those wanting to cycle off PrEP.

**How long does it take for PrEP to work?**

It takes up to **20 days** to be fully protected. PrEP must be taken daily!

**Can I take PrEP for one night only?**

No. You need to take the pill once a day for at least 20 days before you are fully protected.
Women: PK differences in various mucosal tissues

- TFV concentrates 10-100X more in rectal tissue than in cervicovaginal tissue

\[ \text{Concentration (ng/g)} \]

- TFV concentration is sustained longer in rectal tissue in women

\[ \text{Days post single-dose} \]

- TFV exposure was 2- to 160-fold greater in rectal tissue than cervical/vaginal tissue in women
- FTC-DP exposure was 80- to 280-fold greater in cervical/vaginal tissue than rectal

**Minimally effective use for FGT-rectal tissue exposure = 7 doses/week**

<table>
<thead>
<tr>
<th>Dose per week</th>
<th>TFV concentrates 10-100X more in rectal tissue than cervical/vaginal tissue in women</th>
<th>FTC-DP exposure was 80- to 280-fold greater in cervical/vaginal tissue than rectal</th>
</tr>
</thead>
</table>

Cottrell M. R4P 2015;Cape Town, South Africa. #22
HIV incidence & drugs concentrations in MSM

Modeling data from subjects in randomized placebo-controlled iPrEx, ATN 089, or US PrEP safety trials were enrolled in the 72-week open label extension (iPrEx OLE).

The recommended dose of TVD for PrEP in HIV-1 uninfected adults is one tablet once daily taken orally with or without food.

2. Grant RM et al. AIDS 2014, TUAC0105LB
3. EMA Truvada SmPC, September 2016
Stopping PrEP

PrEP should be stopped:

• HIV test is positive
• PrEP user decides to stop
• Safety concerns (particularly if creatinine clearance < 60 mL/min)
• If the risks of PrEP outweigh the potential benefits
Stopping PrEP

If a client decides to stop PrEP

• Explore risk and alternative prevention/risk reduction strategies with them
• Advise client that an HIV test will be required to reinitiate PrEP
• PrEP needs to be used for 28 days after last exposure to HIV
Cycling on and off PrEP

- PrEP is not a lifelong drug-taking intervention
- PrEP should be used only if there is possible exposure to HIV
  - Risk levels expected to change
  - People will use PrEP for variety of reasons
  - Case example e.g. student vs. SW
- People can cycle off PrEP
- This is NOT non-adherence
- But, remember lead in and lead out times
  - 7/20 days from initiation, 28 days after last exposure to HIV
Cycling on and off PrEP

Duration of PrEP use may vary from person to person

- Start and stop PrEP depending on personal needs
- Perceived risk at different periods in a person's life
  - Changes in relationships
  - Behaviours
  - Ability to adhere to a PrEP maintenance programme

Key points to remember:

- It takes **7/20 days** of daily TDF/FTC to reach adequate tissue levels
- Use other methods of protection during this time
- **When stopping** continue PrEP for 28 days after last HIV exposure
Integrated delivery of PrEP and ART: Sustained near elimination of HIV transmission in African HIV serodiscordant couples

Open-label, prospective interventional study of integrated ART and PrEP delivery for HIV prevention among N=1013 heterosexual high risk HIV serodiscordant couples

**HIV Incidence: Expected and Observed**

- **PrEP as a Bridge to ART**
  - HIV+ partner
  - PrEP prior to viral suppression in HIV+ partner
  - Protection through sustained ART use →
  - 6 Months

- **ART delayed**
  - HIV+ partner
  - PrEP prior to ART initiation and then prior to viral suppression in HIV+ partner
  - Protection through sustained ART use →
  - 6 Months

**Integrating delivery of ART and PrEP in HIV serodiscordant couples demonstrated:**

- 95% reduction in observed HIV incidence compared to expected
- time-limited PrEP as a bridge to ART is feasible and highly effective in preventing HIV transmission


**Discordant Couples**
PrEP in pregnancy: Guidelines Vary

**WHO Guidance:**

‘Although additional surveillance is important, at the present time, given the available safety data, there does not appear to be a safety-related rationale for discontinuing PrEP during pregnancy and breastfeeding for HIV-uninfected women receiving PrEP who become pregnant and remain at continuing risk of HIV acquisition’.

**South Africa NDOH Guidance:**

PrEP is contraindicated by the MCC, until we have further guidance from WHO and MCC we will continue to not offer PrEP to pregnant women.

**Southern African HIV Clinician Society Guidance:**

The use of TDF/FTC as PrEP in pregnant or breastfeeding women is contra-indicated. However, as the risk of seroconversion during pregnancy is high, the risks and benefits of PrEP should be discussed with potential PrEP users, allowing these women at high risk of HIV acquisition to make an informed decision regarding PrEP use.

WHO Guidance July 2016
In SA: TDF/FTC PrEP CI in pregnant or breastfeeding women
Birth defects with TDF or FTC

<table>
<thead>
<tr>
<th>HIV+ Women on ART</th>
<th>Any FTC-containing regimen</th>
<th>Any TDF-containing regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancies enrolled, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First trimester</td>
<td>1728</td>
<td>2478</td>
</tr>
<tr>
<td>Second trimester</td>
<td>525</td>
<td>670</td>
</tr>
<tr>
<td>Third trimester</td>
<td>206</td>
<td>351</td>
</tr>
<tr>
<td>Defects/live births, n/N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First trimester exposure</td>
<td>35/1543 (2.3%)</td>
<td>47/2141 (2.2%)</td>
</tr>
<tr>
<td>Second/third trimester exposure</td>
<td>15/729 (2.1%)</td>
<td>21/1021 (2.1%)</td>
</tr>
</tbody>
</table>

Among pregnant women in the US reference population, the background rate of birth defects is 2.7%.

There was no association between FTC or TDF and overall birth defects observed in the APR.

http://www.apregistry.com/
Other considerations

• Standard TB medications do not interact with PrEP
  • No need for dose modifications

• Risk of renal side effects with MDR-TB medications
  • Avoid PrEP until end of treatment

• Standard hormonal contraception does not affect efficacy of PrEP
  • PrEP does not affect contraceptive effectiveness
Risks and side effects

- GI effects
- ARV resistance
- Renal
- HBV management
- BMD
- Risk compensation
Side effects

• Mild: headache, malaise
• GI side effects
  • Nausea, weight loss
• Renal toxicity
  • Transient increases in serum creatinine
  • Decreased GFR
• Extremely small risk of lactic acidosis and hepatic steatosis or steatohepatitis
• Decreased BMD
  • Less cf HIV-infected individuals on TDF
  • No differences in fracture rates
Summary algorithm

HIV testing and screening
(HTS guidelines)

HIV-negative:
Eligible for PrEP?

HIV-positive:
Refer for immediate ART

Risk reduction counselling
Confirm interest in PrEP
Summary algorithm cont.

Creatinine clearance
HBV screening
Pregnancy test

Creatinine clearance >60 mL/min:
Initiate PrEP

Creatinine clearance <60 mL/min:
Review in 2 weeks

One month prescription

Ongoing PrEP education and counselling

Book follow-up appointment within 28 days
Some final thoughts

• PrEP is seasonal
• PrEP isn’t for everyone
• PrEP use requires commitment
• Risk reduction counselling
• PrEP users are NOT patients
Should people use condoms when using PrEP? Your thoughts?
Blesser Levels

Level 0
- Airtime & Data

Level 1
- Clothing & Brazilian Hair

Level 2
- iPhones & iPads

Level 3
- Cars & Apartments

Level 4
- Trips to Dubai

Level 5
Combination prevention to break the Cycle of HIV transmission

Men 25-40 years (N=79)
Knew HIV status: 21.5%
VL > 50,000 : 37.1%

Male circumcision for HIV negative men <25 & Antiretroviral therapy for HIV positive men

Young women <25 years (N=43)
PrEP

Women 25-40 years (N=56)
Changing community norms on age-disparate sex & patriarchy
Test & Treat
Thank you for your attention!

It always seems impossible until it’s done
- Nelson Mandela
Acknowledgements

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Wits Reproductive Health and HIV Institute
Anova Health Institute