An Introduction to Pre-Exposure Prophylaxis (PrEP) for HIV Prevention in Barbados

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BARBADOS
Prologue; HIV Treatment as Prevention

HIV remains a significant global public health problem despite advancements made in treatment and prevention.

We still see unacceptably high HIV incidence globally and in the Caribbean.

Based on HPTN 052, a person with HIV taking effective ART consistently can reduce the likelihood that they pass it on to their uninfected partner by 96%.

Today we have more HIV prevention tools at our disposal than ever before.
This presentation will cover:

1. The HIV situation in Barbados and the need to strengthen prevention
2. What PrEP is
3. The evidence in support of PrEP
   a) Eligibility criteria
   b) Monitoring procedures
HIV situation in Barbados

HIV prevalence in 15-49 year olds in Barbados (2016) = 1.6%

Prevalence is higher in certain sub-groups:
- HIV prevalence among MSM = 11.8% (2017)
- Presumably higher HIV prevalence among FSW and TG

Sustained high prevalence of other STIs:
- Chlamydia: 13.1% (2016)
- Gonorrhea: 3.4% (2016)

Syphilis outbreak between 2011 and 2013
- Annual rates of new cases stabilized since then
- Outbreak predominated by men (72%)
- Majority (72%) of cases comprised persons between 15 and 49 years old
HIV situation in Barbados (2)

According to KABP survey 2013/2014:

HIV knowledge is relatively high

Behaviors among participants:

◦ Condom use at last sex (anal or vaginal) = 45%
◦ Multi-partnering was common, 41% in the last 12 months
◦ Never had an HIV test = 29%
Prevention of HIV is complex thus we need an HIV Combination Prevention approach

- **BIOMEDICAL**
  - Interventions that use clinical and medical methods, e.g.
    - condoms and lubricants
    - antiretroviral treatment as prevention
    - pre-exposure prophylaxis (PrEP)
    - voluntary medical male circumcision
    - needle and syringe programmes

- **STRUCTURAL**
  - Interventions that promote an enabling environment, e.g.
    - decriminalising sex work, homosexuality and drug use
    - addressing gender inequality and violence
    - laws to protect the rights of people living with HIV and key populations
    - interventions to reduce stigma

- **BEHAVIOURAL**
  - Interventions that encourage safe behaviour, e.g.
    - risk reduction counselling
    - comprehensive sexuality education
    - peer education programmes
    - social marketing campaigns, e.g. to promote condoms

- **RIGHTS-BASED**

- **EVIDENCE-INFORMED**

What is PrEP?

Oral PrEP is the use of ARV drugs by people who do not have HIV infection to prevent the acquisition of HIV.

Oral PrEP involves the use of FTC+TDF (Emtricitabine plus Tenofovir) available as Truvada®.

FTC+TDF:

- Reverse transcriptase inhibitors
- Co-formulated as single once-daily pill marketed as Truvada®
- Safe, well tolerated, and potent
- Has a long plasma (10 to 17 hours) and intracellular (40 to ≥60 hours) half-lives
- Long half-life allows forgiveness for imperfect daily use
- Have even higher penetration in vaginal and rectal tissues
Evidence from Clinical Trials of HIV PrEP
Features of the clinical trials for Oral PrEP

Design

Community Consultation

Randomized controlled trials with assignment to TDF or TDF+FTC vs placebo

Symptom assessment and laboratory monitoring

HIV testing, risk reduction and adherence counselling

Primary endpoint was acquisition of HIV

Outcomes

*PrEP significantly reduced the risk of HIV transmission!*

There was greater efficacy in those with blood levels of the drugs
What is the evidence for oral PrEP?

This was meta-analysis
18 studies from 39 articles and 6 conference abstracts
15 RCTs and 3 Observational or demonstration projects
  - Seven RCTs were double-blind placebo-controlled trials evaluating the efficacy and safety of daily oral PrEP.
  - Two studies randomized participants to receive immediate or delayed PrEP and one study compared daily PrEP with both placebo and ‘no-pill’ arms
19,491 participants, of whom 11,901 received active PrEP, with follow-up times ranging from 24 weeks to 5 years.

Populations included: PWID, serodiscordant couples, MSM, TGW, women and heterosexual men.

Trials occurred in low, middle and high-income settings.
### Meta-analysis results assessing the effectiveness of PrEP

#### Results from meta-analysis

<table>
<thead>
<tr>
<th>Analysis</th>
<th>No. of studies</th>
<th>Total N</th>
<th>Risk Ratio (95% CI)</th>
<th>P value</th>
<th>$I^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCTs comparing PrEP with placebo</td>
<td>Overall$^a$</td>
<td>10</td>
<td>17 423</td>
<td>0.49 (0.33–0.73)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mode of Acquisition</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal</td>
<td>4</td>
<td>3 166</td>
<td>0.34 (0.15–0.80)</td>
<td>0.01</td>
<td>29.1</td>
</tr>
<tr>
<td>Vaginal/penile$^b$</td>
<td>6</td>
<td>14 252</td>
<td>0.54 (0.32–0.90)</td>
<td>0.02</td>
<td>80.1</td>
</tr>
<tr>
<td>Adherence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (&gt;70%)</td>
<td>3</td>
<td>6 149</td>
<td>0.30 (0.21–0.45)</td>
<td>&lt;0.001</td>
<td>0.0</td>
</tr>
<tr>
<td>Moderate (41–70%)</td>
<td>2</td>
<td>4 912</td>
<td>0.55 (0.39–0.76)</td>
<td>&lt;0.001</td>
<td>0.0</td>
</tr>
<tr>
<td>Low (≤40%)</td>
<td>2</td>
<td>5 033</td>
<td>0.95 (0.74–1.23)</td>
<td>0.70</td>
<td>0.0</td>
</tr>
<tr>
<td>Biological sex$^c$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>7</td>
<td>8 704</td>
<td>0.38 (0.25–0.60)</td>
<td>&lt;0.001</td>
<td>34.5</td>
</tr>
<tr>
<td>Women</td>
<td>6</td>
<td>8 714</td>
<td>0.57 (0.34–0.94)</td>
<td>0.03</td>
<td>68.3</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 years</td>
<td>3</td>
<td>2 997</td>
<td>0.71 (0.47–1.06)</td>
<td>0.09</td>
<td>20.5</td>
</tr>
<tr>
<td>≥25 years</td>
<td>3</td>
<td>6 291</td>
<td>0.45 (0.22–0.91)</td>
<td>0.03</td>
<td>72.4</td>
</tr>
<tr>
<td>Drug regimen$^d$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF</td>
<td>5</td>
<td>86 19</td>
<td>0.49 (0.28–0.86)</td>
<td>0.001</td>
<td>63.9</td>
</tr>
<tr>
<td>FTC/TDF</td>
<td>7</td>
<td>11 381</td>
<td>0.51 (0.31–0.83)</td>
<td>0.007</td>
<td>77.2</td>
</tr>
<tr>
<td>Drug dosing$^e$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>8</td>
<td>16 951</td>
<td>0.54 (0.36–0.81)</td>
<td>0.003</td>
<td>73.6</td>
</tr>
<tr>
<td>Intermittent</td>
<td>1</td>
<td>400</td>
<td>0.14 (0.03–0.63)</td>
<td>0.01</td>
<td>0.0</td>
</tr>
<tr>
<td>RCTs comparing PrEP to no PrEP</td>
<td></td>
<td>2</td>
<td>723</td>
<td>0.15 (0.05–0.46)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

#### Results from metaregression

<table>
<thead>
<tr>
<th></th>
<th>Meta-regression (MR)</th>
<th>MR standard error</th>
<th>MR P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCTs comparing PrEP with placebo</td>
<td>Overall$^a$</td>
<td>ref</td>
<td>0.51</td>
</tr>
<tr>
<td>Mode of Acquisition</td>
<td></td>
<td>ref</td>
<td>0.23</td>
</tr>
<tr>
<td>Adherence</td>
<td></td>
<td>ref</td>
<td>0.21</td>
</tr>
<tr>
<td>Biological sex$^c$</td>
<td></td>
<td>ref</td>
<td>0.35</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>ref</td>
<td>0.46</td>
</tr>
<tr>
<td>Drug regimen$^d$</td>
<td></td>
<td>ref</td>
<td>0.45</td>
</tr>
<tr>
<td>Drug dosing$^e$</td>
<td></td>
<td>ref</td>
<td>0.06</td>
</tr>
</tbody>
</table>
PrEP works!

Results from meta-analysis demonstrated a **51% reduction in risk of HIV infection comparing PrEP with placebo**
- risk ratio = 0.49, 95% confidence interval (CI): 0.33–0.73, \( P = 0.001 \).

Results from meta-regression suggest **adherence was a significant moderator of PrEP effectiveness**
- regression coefficient = -0.02, \( P < 0.001 \).

**PrEP was most effective in studies with high adherence, where HIV infection risk was reduced by 70%**
- risk ratio = 0.30, 95% CI: 0.21–0.45, \( P < 0.001 \).

**PrEP also significantly reduced infection risk in studies with moderate adherence levels, but showed no effect in studies with low adherence**
- risk ratio = 0.95, 95% CI: 0.34–1.23, \( P = 0.70 \).

In studies comparing immediate with delayed PrEP, PrEP was protective against HIV infection
- risk ratio = 0.15, 95% CI: 0.05–0.46, \( P = 0.001 \).

**Reductions in HIV incidence were also seen in observational studies**
TDF alone appears as effective as TDF+FTC

**TDF**

<table>
<thead>
<tr>
<th>Study name</th>
<th>Subgroup within study</th>
<th>Comparison</th>
<th>Risk ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC (SPH, StU)</td>
<td>TDF</td>
<td>Daily PrEP vs. placebo</td>
<td>0.143 (0.076-0.274)</td>
</tr>
<tr>
<td>West Africa Study</td>
<td>TDF</td>
<td>Daily PrEP vs. placebo</td>
<td>0.202 (0.134-0.294)</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>TDF</td>
<td>Daily PrEP vs. placebo</td>
<td>0.347 (0.187-0.642)</td>
</tr>
<tr>
<td>BIK/TDF Study</td>
<td>TDF</td>
<td>Daily PrEP vs. placebo</td>
<td>0.490 (0.279-0.871)</td>
</tr>
<tr>
<td>VOICE</td>
<td>TDF</td>
<td>Daily PrEP vs. placebo</td>
<td>0.872 (0.388-1.973)</td>
</tr>
</tbody>
</table>

**TDF-FTC**

<table>
<thead>
<tr>
<th>Study name</th>
<th>Subgroup within study</th>
<th>Comparison</th>
<th>Risk ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Igggay</td>
<td>TDF-FTC</td>
<td>Intermittent PrEP</td>
<td>0.314 (0.233-0.428)</td>
</tr>
<tr>
<td>REN Kenya Study</td>
<td>TDF-FTC</td>
<td>Multiple PrEP dosing</td>
<td>0.470 (0.297-0.744)</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>TDF-FTC</td>
<td>Daily PrEP vs. placebo</td>
<td>0.805 (0.468-1.383)</td>
</tr>
<tr>
<td>TDF-2 Main</td>
<td>TDF-FTC</td>
<td>Daily PrEP vs. placebo</td>
<td>0.847 (0.489-1.451)</td>
</tr>
<tr>
<td>MTN</td>
<td>TDF-FTC</td>
<td>Daily PrEP vs. placebo</td>
<td>0.665 (0.328-1.363)</td>
</tr>
<tr>
<td>VOICE</td>
<td>TDF-FTC</td>
<td>Daily PrEP vs. placebo</td>
<td>0.882 (0.279-2.882)</td>
</tr>
</tbody>
</table>

**Graphs**

- Favors PrEP
- Favors placebo
### PrEP and adverse events

**Table 3. Meta-analysis results for effects of preexposure prophylaxis on any adverse event.**

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Any adverse event</th>
<th>Any grade 3 or 4 adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of studies</td>
<td>Pooled risk ratio (95% CI)</td>
</tr>
<tr>
<td>RCTs comparing PrEP with placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>10</td>
<td>1.01 (0.99–1.03)</td>
</tr>
<tr>
<td>Mode of acquisition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal</td>
<td>3</td>
<td>1.01 (0.97–1.06)</td>
</tr>
<tr>
<td>Vaginal/penile</td>
<td>7</td>
<td>1.01 (0.99–1.04)</td>
</tr>
<tr>
<td>Adherence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>2</td>
<td>0.97 (0.87–1.08)</td>
</tr>
<tr>
<td>Medium</td>
<td>2</td>
<td>1.01 (0.98–1.04)</td>
</tr>
<tr>
<td>High</td>
<td>2</td>
<td>1.02 (0.99–1.04)</td>
</tr>
<tr>
<td>Biological sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>2</td>
<td>1.00 (0.98–1.03)</td>
</tr>
<tr>
<td>Women</td>
<td>3</td>
<td>1.00 (0.92–1.07)</td>
</tr>
<tr>
<td>Drug regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF</td>
<td>4</td>
<td>0.98 (0.92–1.04)</td>
</tr>
<tr>
<td>FTC/TDF</td>
<td>8</td>
<td>1.02 (1.00–1.04)</td>
</tr>
<tr>
<td>Drug dosing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>9</td>
<td>1.00 (0.97–1.03)</td>
</tr>
<tr>
<td>Intermittent</td>
<td>3</td>
<td>1.05 (0.99–1.11)</td>
</tr>
</tbody>
</table>

*The FEM-PrEP study did not present results for the outcome ‘any grade 3 or 4 event.’ For this analysis, results from the outcome ‘any serious adverse event’ were used.

PrEP, preexposure prophylaxis.
PrEP and adverse events (2)

• Across studies, proportions of adverse events comparing PrEP with placebo were similar
  • OR = 1.01, 95% CI: 0.99–1.03, P = 0.27).
  • No differences were seen across subgroups based on mode of acquisition, adherence, sex, drug regimen, dosing or age

Several studies reported small, subclinical decreases in renal function among PrEP users.

Although function mostly returned to normal following PrEP discontinuation. Additionally, some studies reported small, subclinical decreases in liver function, and bone mineral density while taking PrEP
PrEP and drug resistance

Among participants in the trials who seroconverted post-randomization, there were few FTC or TDF-resistant infections, so little statistical power.

Some potential risk of increased drug resistance, but appears relatively minimal.

Bear in mind:
- If you take PrEP, little chance of HIV acquisition
- If you don’t take PrEP, you may acquire HIV with small chance of resistance to PrEP drugs
PrEP and reproductive health outcomes

Partners PrEP and FEM-PrEP
- FEM-PrEP required hormonal contraceptive use; Partners PrEP provided contraceptive counseling
- Discontinued PrEP use once pregnancy confirmed

Both studies reported higher rates of pregnancy in PrEP vs. placebo arms, but there was no difference in adjusted analyses.

Both studies showed **no difference in adverse pregnancy-related events in PrEP vs. placebo arms**
- Results remained insignificant when stratified by adherence and PrEP regimen.
History of Implementation of PrEP

- WHO recommends PrEP for all persons at substantial risk of HIV (2015/2016)
- CDC developed clinical guidelines for PrEP (2014)
- Called for demonstration projects (2012)
- FDA approval of Truvada® for PrEP in 2012
Current WHO recommendations (2016)

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**.
(Proposed) Guidelines on the use of PrEP for HIV Prevention in Barbados

CLINICAL GUIDANCE ADAPTED FROM THE CDC AND WHO
It is the Policy of the MOH that PrEP for HIV prevention may be offered to any person in Barbados who is deemed to be at substantial risk for HIV.
PrEP Eligibility criteria

1. HIV-negative;
2. No suspicion of acute HIV infection;
3. Substantial risk of HIV infection;  
   ◦ Refer to Indications for the use of PrEP
4. No contraindications to PrEP medicines;
5. Willingness to use PrEP as prescribed, including periodic testing for HIV and STIs.
Indications for the use of PrEP

1. **Adult person** (> 18 years old) **who is also**
2. **HIV negative** and with no suspicion of acute HIV infection

AND at least one of the following in the last 6 months:

a) Is in an ongoing sexual relationship with an HIV-positive partner who is not virally suppressed
b) Is a MSM engaging in unprotected anal sex with another man (receptive or insertive)
c) Is a TG individual engaging in unprotected sex (vaginal or anal)
d) Exchanges sex for money or goods and engages in unprotected sex (vaginal or anal)
e) Is a MSM, TG individual or a person that exchanges sex for money or goods with diagnosed or reported STI
f) Has unprotected sex (vaginal or anal) with 1 or more partners of unknown HIV status who are known, or believed, to be at substantial risk of HIV infection
g) Had PEP for sexual exposure.
Contraindications for use of PrEP

1. HIV-positive
2. Renal impairment
   - Estimated creatinine clearance <60 ml/min
3. Signs or symptoms of acute HIV infection, probable recent exposure to HIV
4. Allergy or contraindication to any medicine in the PrEP regimen.
PrEP drug regimen =

TDF 300 mg + FTC 200 mg once a day

Available as Truvada®

● One tablet a day
When initiating PrEP

1. HIV test
2. Serum creatinine
3. HBsAg
4. HCV antibody
5. STI screening – Syphilis, chlamydia, gonorrhea
6. Pregnancy testing
7. Review vaccination history
8. Counselling
Clinical Follow-Up and Monitoring Procedures

At least every 3 months to
- Repeat HIV testing and assess for signs or symptoms of acute infection to document that patients are still HIV negative
- Repeat pregnancy testing for women who may become pregnant
- Provide a prescription for daily TDF/FTC for no more than 90 days (until the next HIV test)
- Assess side effects, adherence, and HIV acquisition risk behaviours
- Provide support for medication adherence and risk-reduction behaviours
- Respond to new questions and provide any new information about PrEP use

At least every 6 months to
- Monitor eCrCl
- Conduct STI testing (syphilis, gonorrhea, chlamydia)

At least every 12 months to
- Evaluate the need to continue PrEP as a component of HIV prevention
Summary of PrEP

1. Oral PreP with TDF+FTC (Truvada®) is highly effective in reducing the risk of HIV acquisition as part of combination HIV prevention

2. One-pill a day regimen

3. Minimal side effects

4. Safe in pregnancy
WHO tool kit for PrEP implementation

http://who.int/hiv/pub/prep/prep-implementation-tool
Strong Global and Regional Political Commitments Towards Ending AIDS by 2030

TARGETS

By 2020

90–90–90
HIV treatment

500,000
New adult HIV infections

ZERO
Discrimination

By 2030

95–95–95
HIV treatment

200,000
New adult HIV infections

ZERO
Discrimination
References


Presentation content based on:

1. CDC Grand Rounds on HIV PrEP as seen at https://www.youtube.com/watch?v=R6Saff_u-xY

2. Presentation by Dr Caitlin Kennedy, JHU - Pre-exposure prophylaxis (PREP) for HIV prevention: where are we now? Feb. 2017


Thank you for your attention!

- Questions?
- Comments?

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