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

82ND UWI / BAMP CME CONFERENCE,

LLOYD ERSKINE-SANDIFORD CENTRE

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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
4. Guidelines on the use 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)

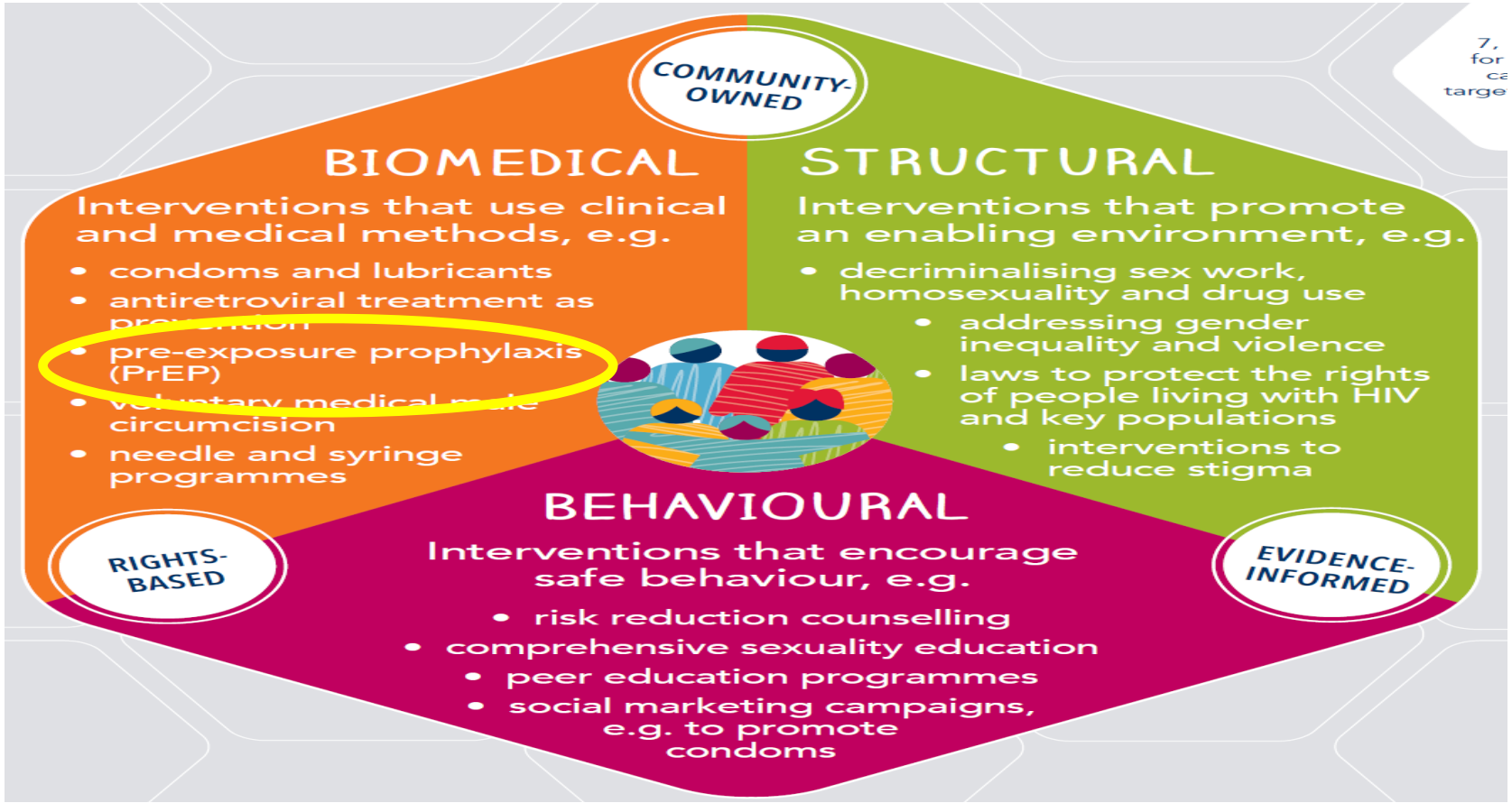
According to KABP survey 2013/2014:

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



Source: International HIV/AIDS Alliance and UNAIDS. An advocacy brief for community-led organisations. Advancing combination HIV prevention. 2016

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?

Effectiveness and safety of oral HIV preexposure prophylaxis for all populations

Virginia A. Fonner[c], Sarah L. Dalglish[a], Caitlin E. Kennedy[a], Rachel Baggaley[b], Kevin R. O'Reilly[c], Florence M. Koechlin[b], Michelle Rodolph[b], Ioannis Hodges-Mameletzis[b] and Robert M. Grant[d]

Objective: Preexposure prophylaxis (PrEP) offers a promising new approach to HIV prevention. This systematic review and meta-analysis evaluated the evidence for use of oral PrEP containing tenofovir disoproxil fumarate as an additional HIV prevention strategy in populations at substantial risk for HIV based on HIV acquisition, adverse events, drug resistance, sexual behavior, and reproductive health outcomes.

Design: Rigorous systematic review and meta-analysis.

Methods: A comprehensive search strategy reviewed three electronic databases and conference abstracts through April 2015. Pooled effect estimates were calculated using random-effects meta-analysis.

Results: Eighteen studies were included, comprising data from 39 articles and six conference abstracts. Across populations and PrEP regimens, PrEP significantly reduced the risk of HIV acquisition compared with placebo. Trials with PrEP use more than 70% demonstrated the highest PrEP effectiveness (risk ratio = 0.30, 95% confidence interval: 0.21–0.45, $P < 0.001$) compared with placebo. Trials with low PrEP use did not show a significantly protective effect. Adverse events were similar between PrEP and placebo groups. More cases of drug-resistant HIV infection were found among PrEP users who initiated PrEP while acutely HIV-infected, but incidence of acquiring drug-resistant HIV during PrEP use was low. Studies consistently found no association between PrEP use and changes in sexual risk behavior. PrEP was not associated with increased pregnancy-related adverse events or hormonal contraception effectiveness.

Conclusion: PrEP is protective against HIV infection across populations, presents few significant safety risks, and there is no evidence of behavioral risk compensation. The effective and cost-effective use of PrEP will require development of best practices for fostering uptake and adherence among people at substantial HIV risk.

AIDS 2016, **30**:1973–1983

Keywords: HIV, HIV prevention, meta-analysis, preexposure prophylaxis, systematic review, tenofovir

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

Analysis	No. of studies	Total *N*	Results from meta-analysis: Risk Ratio (95% CI)	*P* value	I^2	Results from metaregression: Meta-regression (MR) coefficient	MR standard error	MR *P* value
RCTs comparing PrEP with placebo								
Overall[a]	10	17 423	0.49 (0.33–0.73)	0.001	70.9			
Mode of Acquisition								
Rectal	4	3166	0.34 (0.15–0.80)	0.01	29.1	*ref*		
Vaginal/penile[b]	6	14 252	0.54 (0.32–0.90)	0.02	80.1	0.47	0.51	0.36
Adherence								
High (>70%)	3	6149	0.30 (0.21–0.45)	<0.001	0.0	−1.14	0.23	<0.001
Moderate (41–70%)	2	4912	0.55 (0.39–0.76)	<0.001	0.0	−0.55	0.21	0.01
Low (≤40%)	2	5033	0.95 (0.74–1.23)	0.70	0.0	*ref*		
Biological sex[c]								
Men	7	8704	0.38 (0.25–0.60)	<0.001	34.5	*ref*		
Women	6	8714	0.57 (0.34–0.94)	0.03	68.3	0.46	0.35	0.19
Age								
<25 years	3	2997	0.71 (0.47–1.06)	0.09	20.5	*ref*		
≥25 years	3	6291	0.45 (0.22–0.91)	0.03	72.4	0.45	0.42	0.29
Drug regimen[d]								
TDF	5	8619	0.49 (0.28–0.86)	0.001	63.9	*ref*		
FTC/TDF	7	11 381	0.51 (0.31–0.83)	0.007	77.2	0.06	0.40	0.88
Drug dosing[e]								
Daily	8	16 951	0.54 (0.36–0.81)	0.003	73.6	*ref*		
Intermittent	1	400	0.14 (0.03–0.63)	0.01	0.0	−1.32	0.90	0.14
RCTs comparing PrEP to no PrEP								
Overall	2	723	0.15 (0.05–0.46)	0.001	0.0			

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

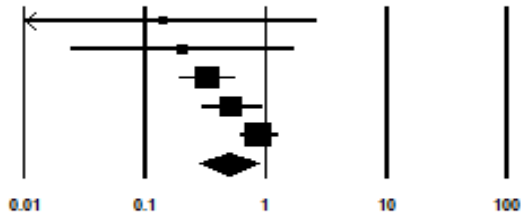
- risk ratio = 0.15, 95% CI: 0.05–0.46, P = 0.001.

Reductions in HIV incidence were also seen in observational studies

TDF alone appears as effective as TDF+FTC

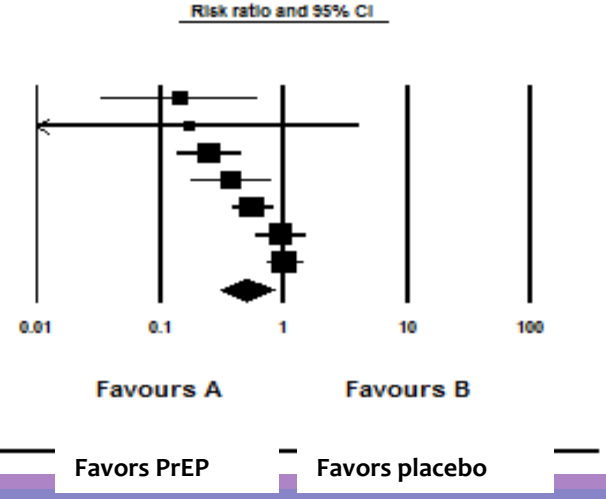
TDF

Study name	Subgroup within study	Comparison	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
CDC Safety Study	TDF	daily PrEP vs. placebo	0.141	0.007	2.704	-1.299	0.194
West Africa Study	TDF	daily PrEP vs. placebo	0.202	0.024	1.725	-1.461	0.144
Partners PrEP	TDF	daily PrEP vs. placebo	0.327	0.190	0.562	-4.037	0.000
BKK TDF Study	TDF	daily PrEP vs. placebo	0.517	0.290	0.924	-2.229	0.026
VOICE	TDF	daily PrEP vs. placebo	0.872	0.608	1.251	-0.745	0.457
			0.490	0.279	0.861	-2.482	0.013



TDF-FTC

Study name	Subgroup within study	Comparison	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Ipergay	TDF-FTC	Intermittent PrEP	0.144	0.033	0.627	-2.584	0.010
IAVI Kenya Study	TDF-FTC	multiple PrEP dosing	0.170	0.007	4.025	-1.097	0.272
Partners PrEP	TDF-FTC	daily PrEP vs. placebo	0.250	0.137	0.458	-4.496	0.000
TDF2- Main	TDF-FTC	daily PrEP vs. placebo	0.373	0.175	0.795	-2.554	0.011
IPrEx- Main	TDF-FTC	daily PrEP vs. placebo	0.561	0.376	0.838	-2.826	0.005
Fem-PrEP- Main	TDF-FTC	daily PrEP vs. placebo	0.950	0.595	1.517	-0.214	0.831
VOICE	TDF-FTC	daily PrEP vs. placebo	1.031	0.730	1.456	0.174	0.862
			0.506	0.308	0.831	-2.689	0.007



PrEP and adverse events

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

	Any adverse event				Any grade 3 or 4 adverse event			
Analysis	No. of studies	Pooled risk ratio (95% CI)	*P* value	I^2	No. of studies	Pooled risk ratio (95% CI)	*P* value	I^2
RCTs comparing PrEP with placebo								
Overall	10	1.01 (0.99–1.03)	0.27	38.1	11[a]	1.02 (0.92–1.13)	0.76	16.5
Mode of acquisition								
Rectal	3	1.01 (0.97–1.06)	0.60	6.0	5	1.09 (0.84–1.41)	0.52	19.0
Vaginal/penile	7	1.01 (0.99–1.04)	0.39	51.6	6	1.00 (0.88–1.15)	0.96	28.9
Adherence								
Low	2	0.97 (0.87–1.08)	0.60	85.6	2	1.08 (0.71–1.64)	0.71	58.0
Medium	2	1.01 (0.98–1.04)	0.46	13.9	2	0.95 (0.82–1.10)	0.48	0.0
High	2	1.02 (0.99–1.04)	0.23	28.4	3	1.05 (0.78–1.39)	0.76	51.9
Biological sex								
Men	2	1.00 (0.98–1.03)	0.85	0.0	4	1.07 (0.83–1.39)	0.59	22.8
Women	3	1.00 (0.92–1.07)	0.92	80.2	2	1.08 (0.71–1.64)	0.71	58.0
Drug regimen								
TDF	4	0.98 (0.92–1.04)	0.47	88.5	3	0.95 (0.80–1.13)	0.56	54.1
FTC/TDF	8	1.02 (1.00–1.04)	0.06	0.0	10	1.07 (0.94–1.21)	0.32	17.4
Drug dosing								
Daily	9	1.00 (0.97–1.03)	0.78	65.6	9	1.01 (0.91–1.13)	0.81	21.2
Intermittent	3	1.05 (0.99–1.11)	0.14	0.0	3	1.14 (0.60–2.18)	0.70	0.0
Age	No safety data stratified by age				No safety data stratified by age			
RCTs comparing PrEP to no PrEP								
Overall	Data not reported for PROUD and CDC Safety Study				Data not reported for PROUD; CDC Study included in PrEP vs. placebo analysis			

[a]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.

Fonner et al., AIDS 2016

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

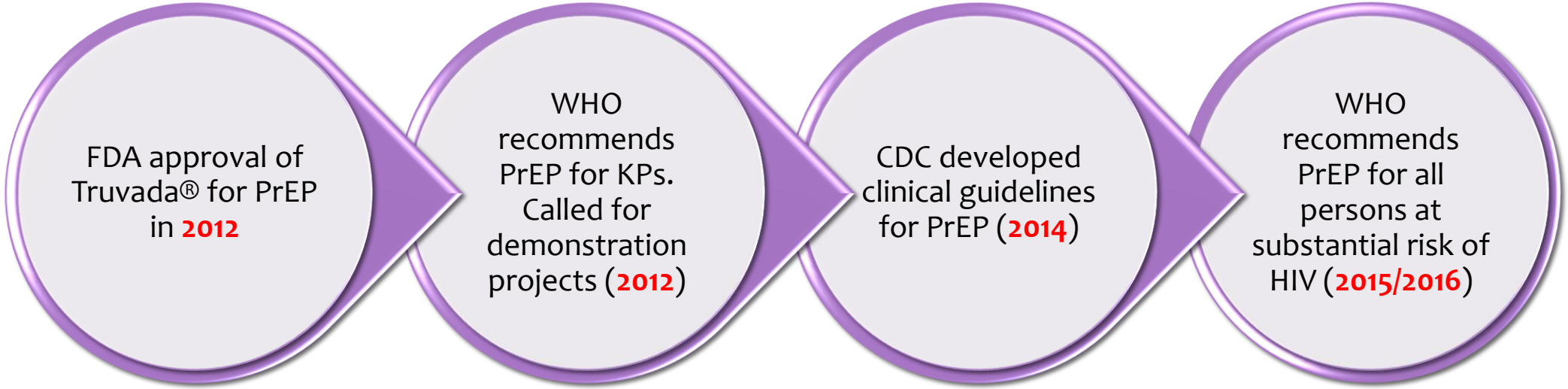
- FEM-PrEP required hormonal contraceptive use; Partners PrEP provided contraceptive counseling
- Discontinued PrEP use once pregnancy confirmed

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

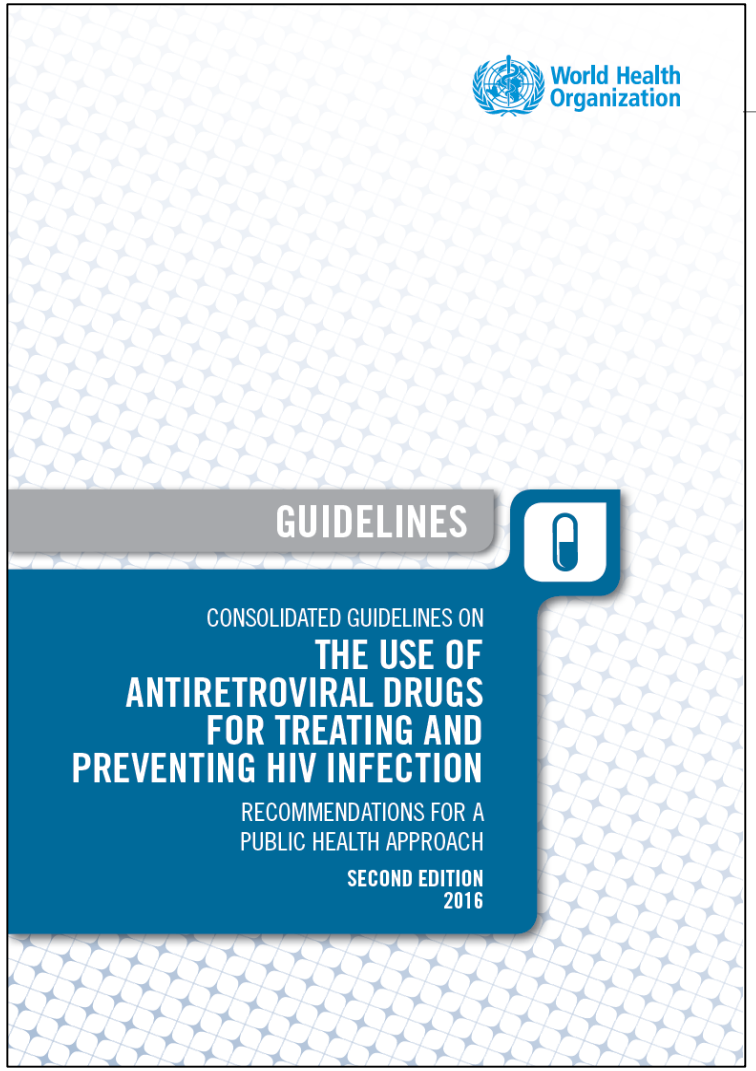
Both studies showed **no difference in adverse pregnancy-related events in PrEP vs. placebo arms**

- Results remained insignificant when stratified by adherence and PrEP regimen

History of Implementation of PrEP



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

(*Proposed*) Policy on PrEP for HIV Prevention in Barbados

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 supressed
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

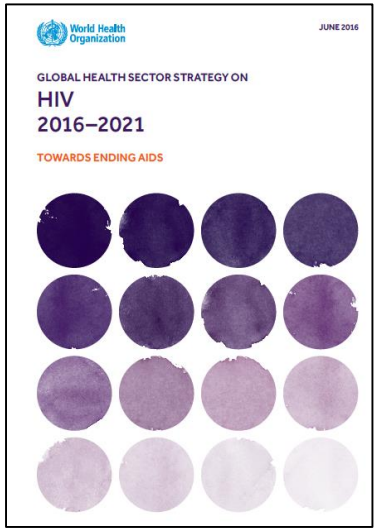
Summary of PrEP

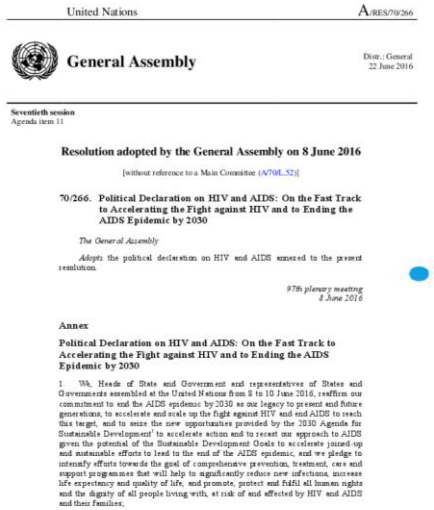
1. Oral PreP with TDF+FTC (Truvada®) is highly effective in reducing the risk of HIV acquisition as part of **combination HIV prevention**
2. One-pill a day regimen
3. Minimal side effects
4. Safe in pregnancy

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





United Nations A/RES/70/266

General Assembly

Distr.: General
22 June 2016

Seventieth session
Agenda item 11

Resolution adopted by the General Assembly on 8 June 2016

[without reference to a Main Committee (A/70/L.52)]

70/266. Political Declaration on HIV and AIDS: On the Fast Track to Accelerating the Fight against HIV and to Ending the AIDS Epidemic by 2030

The General Assembly

Adopts the political declaration on HIV and AIDS annexed to the present resolution.

97th plenary meeting
8 June 2016

Annex

Political Declaration on HIV and AIDS: On the Fast Track to Accelerating the Fight against HIV and to Ending the AIDS Epidemic by 2030

1. We, Heads of State and Government and representatives of States and Governments assembled at the United Nations from 8 to 10 June 2016, reaffirm our commitment to end the AIDS epidemic by 2030 as our legacy to present and future generations, to accelerate and scale up the fight against HIV and end AIDS to reach this target, and to seize the new opportunities provided by the 2030 Agenda for Sustainable Development[1] to accelerate action and to recast our approach to AIDS given the potential of the Sustainable Development Goals to accelerate joined-up and sustainable efforts to lead to the end of the AIDS epidemic, and we pledge to intensify efforts towards the goal of comprehensive prevention, treatment, care and support programmes that will help to significantly reduce new infections, increase life expectancy and quality of life, and promote, protect and fulfil all human rights and the dignity of all people living with, at risk of and affected by HIV and AIDS and their families;

TARGETS

By 2020	By 2030
90–90–90 HIV treatment	**95–95–95** HIV treatment
500 000 New adult HIV infections	**200 000** New adult HIV infections
ZERO Discrimination	**ZERO** Discrimination

Pan American Health Organization

World Health Organization
REGIONAL OFFICE FOR THE Americas

TAKE THE CHALLENGE
END AIDS

References

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3. CDC Grand Rounds Pre Exposure Prophylaxis of HIV https://www.cdc.gov/cdcgrandrounds/archives/2014/may2014.htm as accessed on Oct. 25th, 2017
4. Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2014 Clinical Practice Guideline
5. Effectiveness and Safety of Oral HIV Preexposure Prophylaxis for All Populations Fonner et al AIDS. 2016;30(12):1973-1983.

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
3. Presentation by Dr Ioannis Mameletzis, PrEP focal-point, WHO - WHO PrEP guidance March 2017
4. "PrEP in LAC" a presentation by Dr Maeve de Mello, Nemus Webinar Series, PAHO Oct. 2017

MINISTRY OF HEALTH
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Thank you for your attention!

- Questions?
- Comments?

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