How to administer PrEP;A typical clinical consultation.

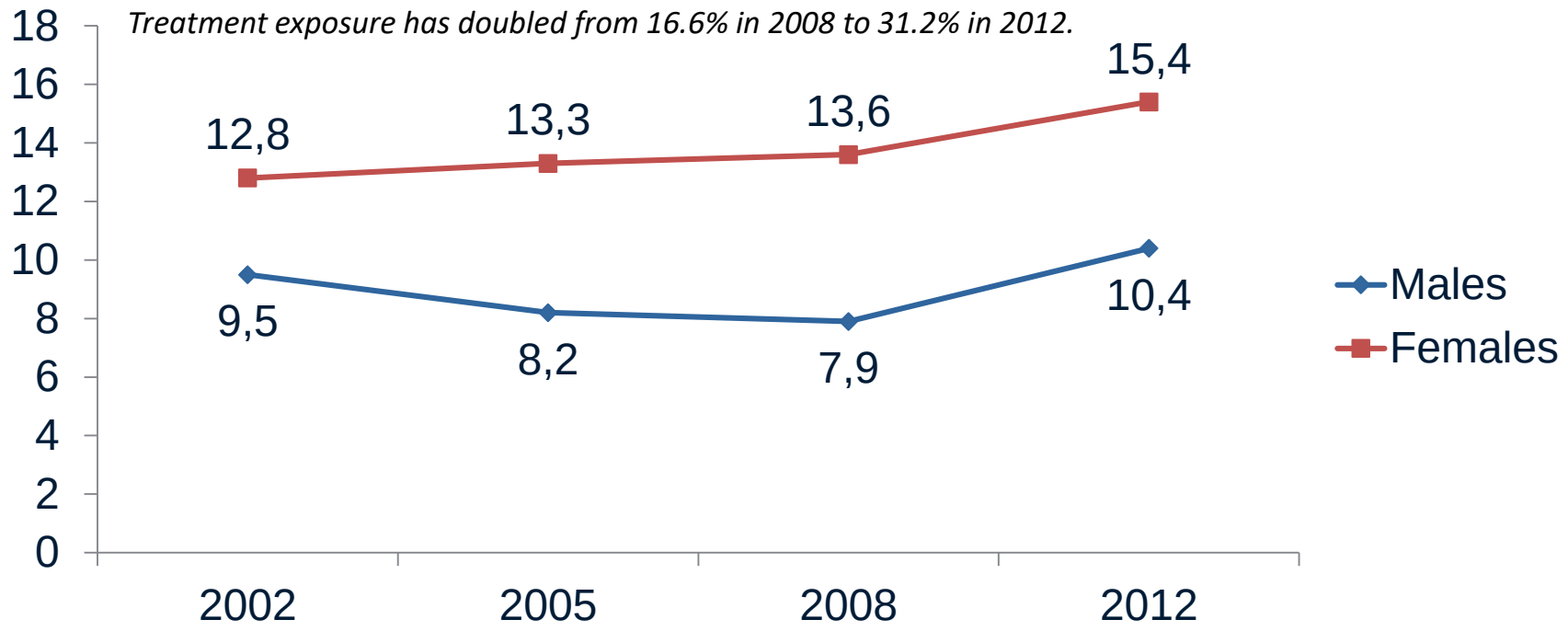
Dr Muhangwi Ben Mulaudzi
SAHCS
Gallagher Estate 24 October 2018

'Nothing will ever be attempted if all possible objections must first be overcome' – Samuel Johnson (1709-1784)

Disclosures

WHY PREP??

Ongoing HIV transmission despite expanding access to ART – SA

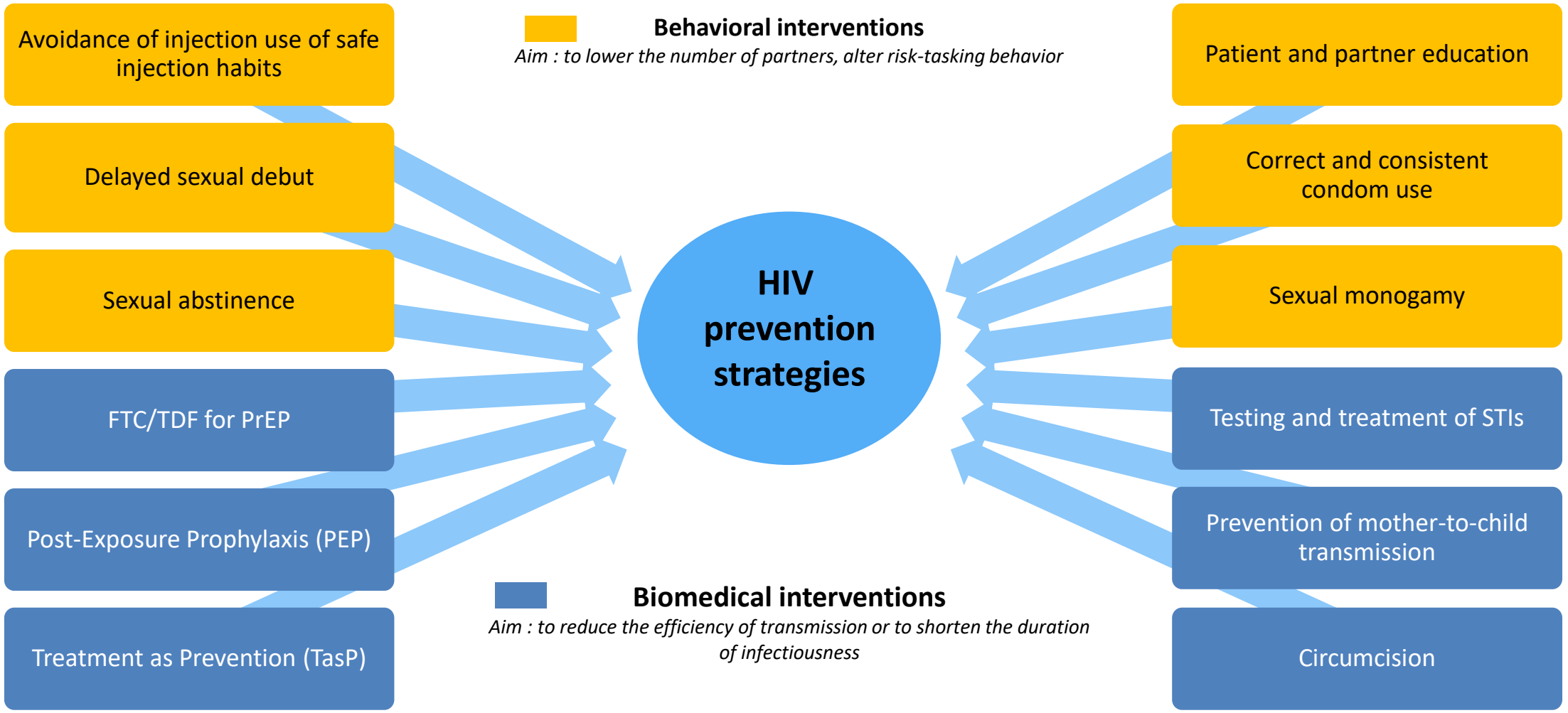


Source: HSRC, 2012

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



Cohen M, et al. *J Int AIDS Soc.* 2008;11:4. (adapted)
Cohen M, et al. Sexual HIV Transmission and Its Transmission. www.medscape.org/viewarticle/416415. Accessed March 10, 2016.

PrEP in South Africa

SA registers a two-in-one pill that can prevent HIV

- 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

Why FTC/TDF for PrEP?

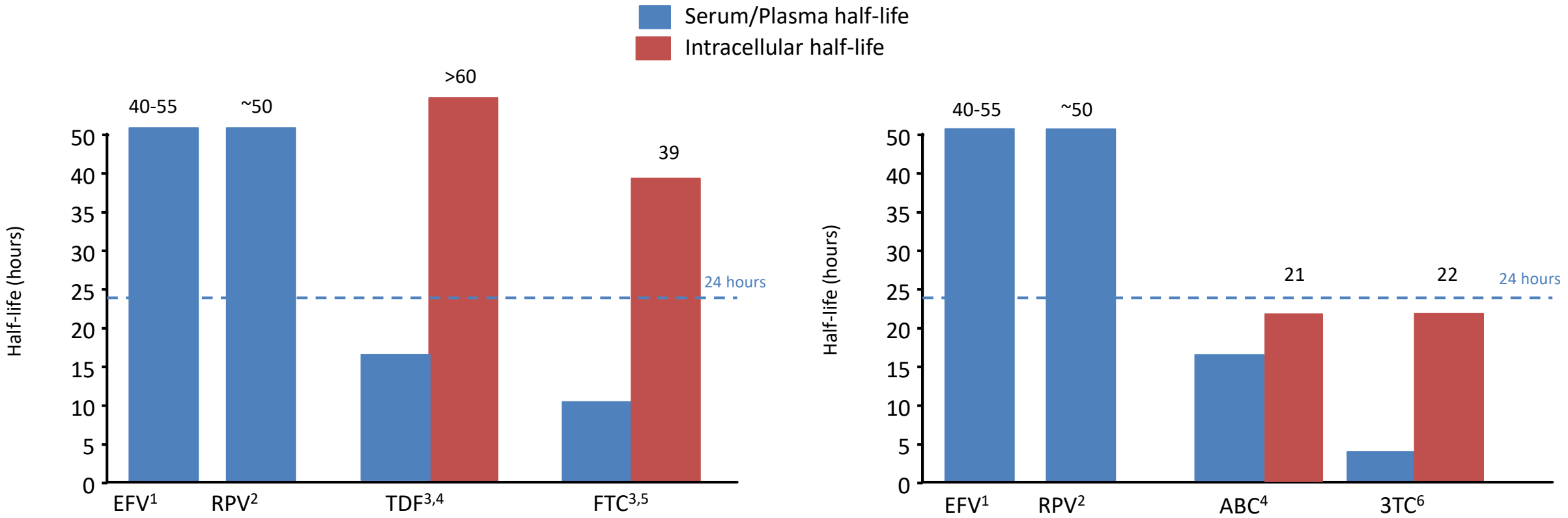
Efficacy	**Pre-Clinical** • Tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) have long intracellular half-lives (40 to100 hours)[1] • TDF and FTC effectively prevented infection in non-human primate studies[2] **Clinical** • Durable efficacy[2]

Safety	• TVD has favorable safety and tolerability profile[2,3,5,6]
	• TDF and FTC: approved in Europe in 2002 and 2004, respectively, for treatment of HIV[4]
	  • TDF: ~10 million patient-years; FTC: ~7 million patient-years (in the commercial or clinical study settings)[4]
	  • TDF: High barrier to resistance and limited cross-resistance[3,5]
	• No interactions with hormonal contraception[5]

Pharmacokinetics	• TVD is one pill, once daily[5] • TVD to be given with food (preferably) but also without food[5] • TFV and FTC concentrations in the genital tract exceed those in blood plasma[3,6]

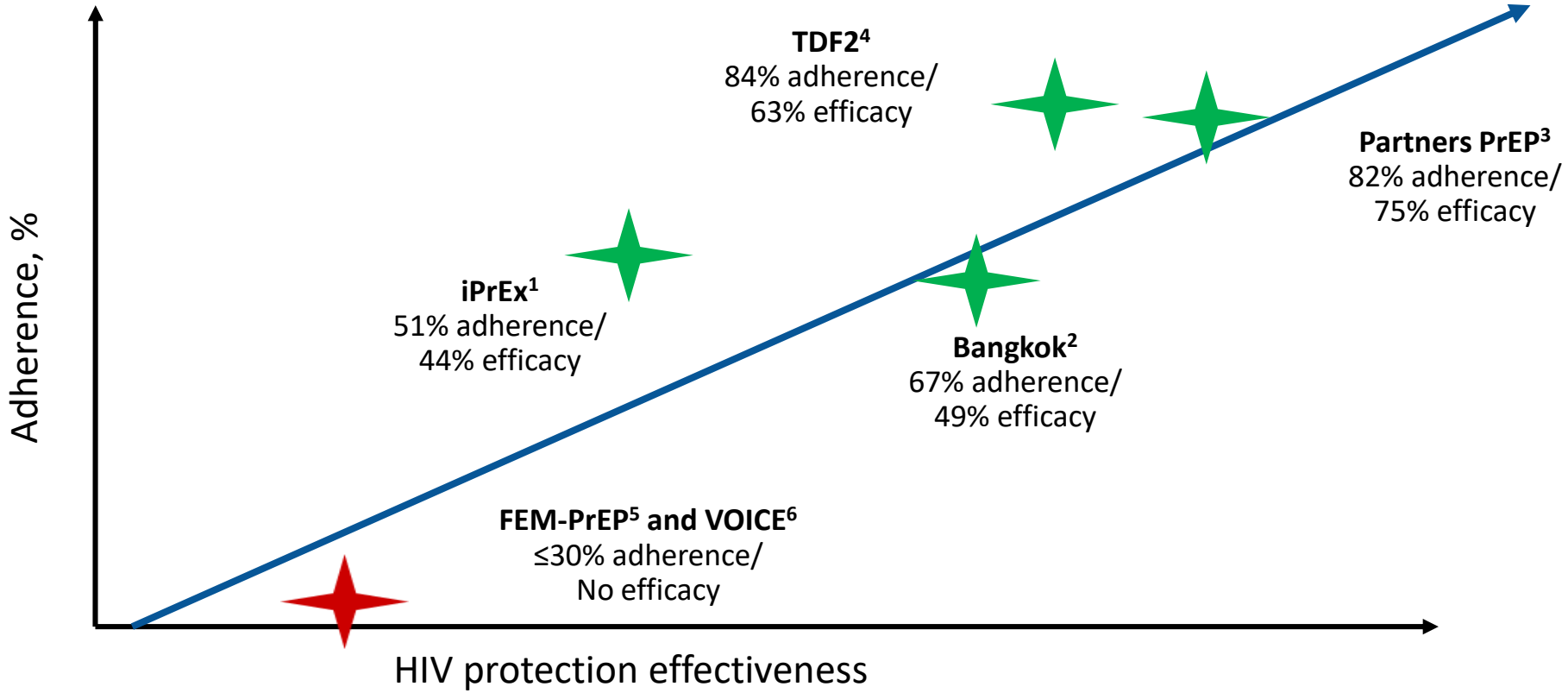
1. Garcia-Lerma J, et al. *Trends Pharmacol Sci* 2009; 31(2): 74-81
2. Okwundu CI et al. Cochrane Database Syst Rev. 2012 Jul 11;(7):CD007189
3. Chirenje Z, et al. Expert Rev. Anti Infec Therap 2010; 8(10): 1177-86.
4. Data on File HIV052 – May 2016
5. EU Truvada SmPC, August 2016.
6. Cohen MS, et al. *Ann Intern Med.* 2007;146:591-601.

Differences in Half-Lives of Regimen Components



1. Sustiva® US Prescribing Information. Bristol-Myers Squibb Company. August 2012
2. Complera® US Prescribing Information. Gilead Sciences Inc. May 2015
3. Mathias A, et al. J Acquir Immune Defic Syndr 2007;46:167-173
4. Hawkins T, et al. J Acquir Immune Defic Syndr 2005;39:406–411
5. Wang LH, et al. IAC 2002. Barcelona. #4546
6. Anderson PL, et al. AIDS 2003;17:2159-2168

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

1. Grant R, et al. *N Engl J Med* 2010;363:2587-99. 2. Choopanya K, et al *The Lancet*. June 13, 2013. 3. Baeten J, et al. *N Engl J Med* 2012;367:399-410. 4. Thigpen M, et al. *N Engl J Med* 2012;367:423-34. 5. Van Damme L, et al. *N Engl J Med* 2012;367:411-22. 6. Van der Straten A, et al. *AIDS* 2012;26(7):F13-F19

GUIDELINES

Southern African guidelines for the safe use of pre-exposure prophylaxis in men who have sex with men who are at risk for H

GUIDANCE ON PRE-EXPOSURE ORAL PROPHYLAXIS (PrEP)
FOR SERODISCORDANT COUPLES, MEN AND TRANSGENDER
WOMEN WHO HAVE SEX WITH MEN AT HIGH RISK OF HIV:
Recommendations for use in the context of demonstration projects

July 2012

World Organ

GUIDELINE ON WHEN TO START ANTIRETROVIRAL THERAPY AND

US Public Health Service

P PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV

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 ?

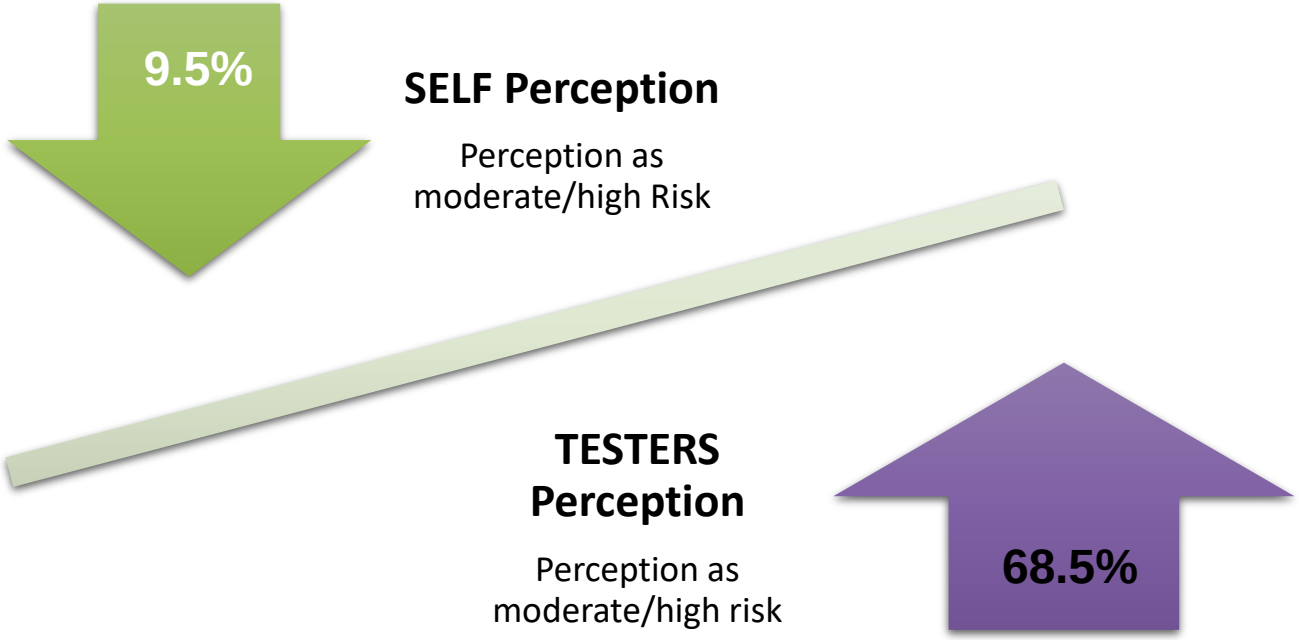
What's available in the public sector?

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

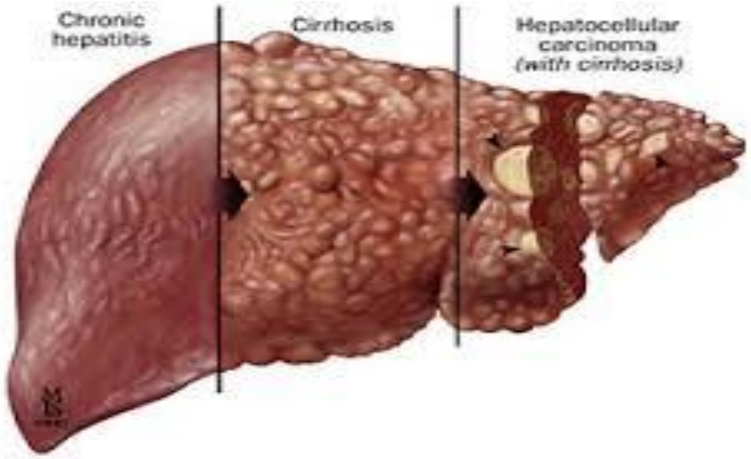
Three-monthly maintenance visits

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

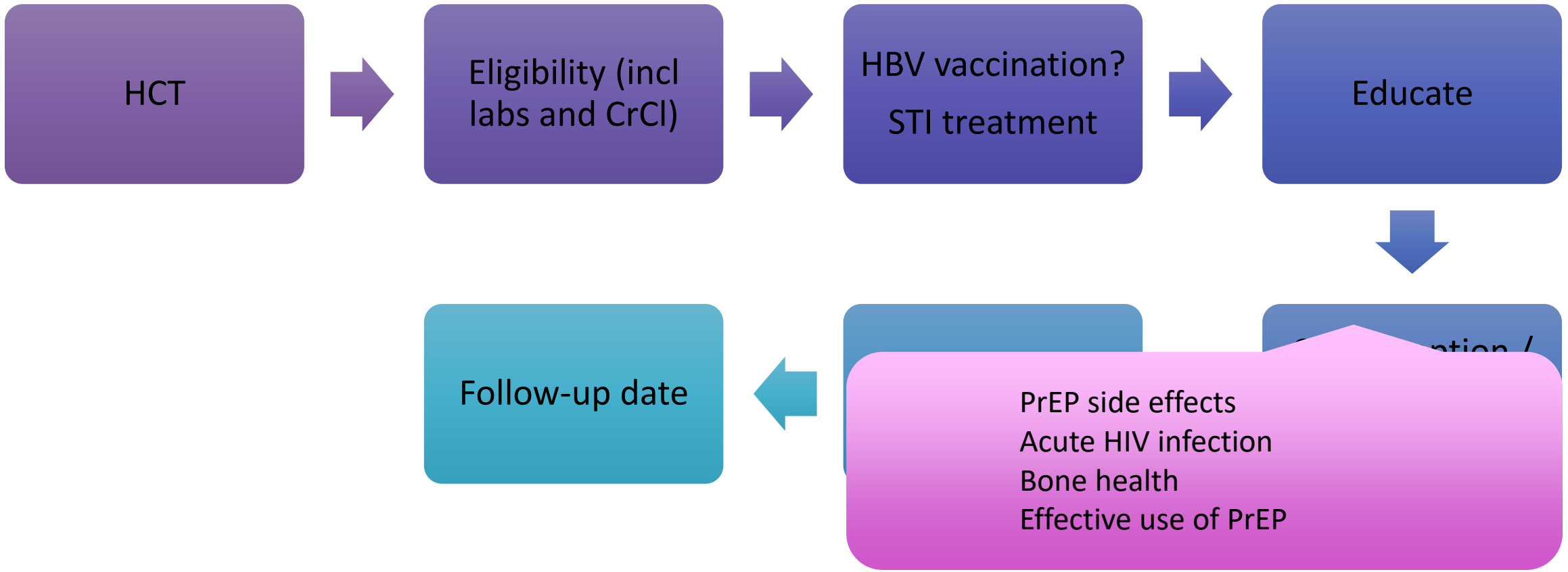
TABLE 3: Hepatitis B immune status and pre-exposure prophylaxis eligibility.

Hepatitis B surface antigen (HBsAg)	Hepatitis B surface antibody (HBsAb)	Action
Negative (-)	Negative (-)	Start PrEP, vaccinate concurrently
Negative (-)	Positive (+)	Start PrEP, no vaccine needed
Positive (+)	N/A	Refer for evaluation

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

- Acute/chronic HBV: LFT monitoring

PrEP initiation visit



One month follow-up

PrEP initiation visit PLUS:

→ Tolerability / side effects

Effective use

→ Manage side effects

↓

Creatinine clearance

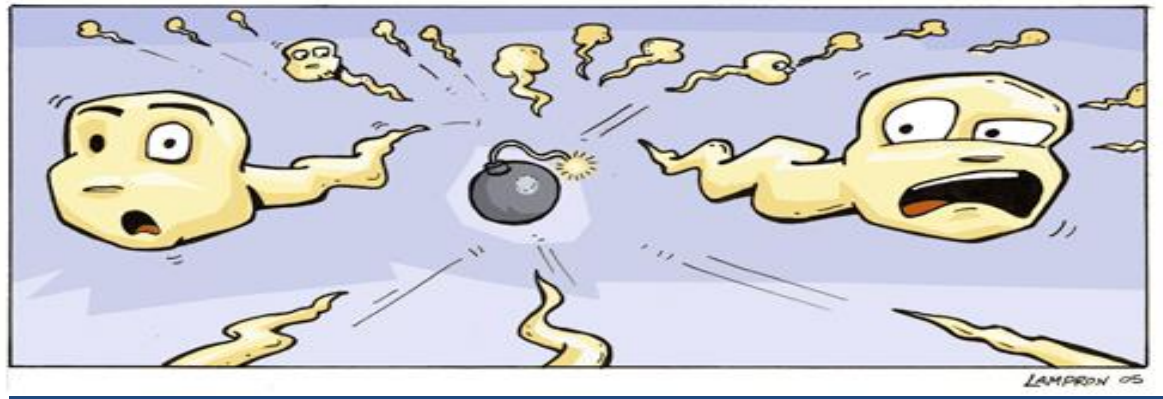
← Contraception / condoms / lubricant

← 3 months TDF/FTC

Follow-up

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

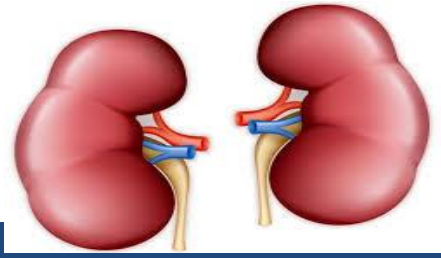
- PrEP: seasons of risk (ART = lifelong)
- Effective use of PrEP requires daily usage for a specified period
  - attainment of full protection
  - daily use for the duration of possible exposure
  - continuous use for one month after cessation of exposure
- Good quality counselling fosters adherence
- 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?

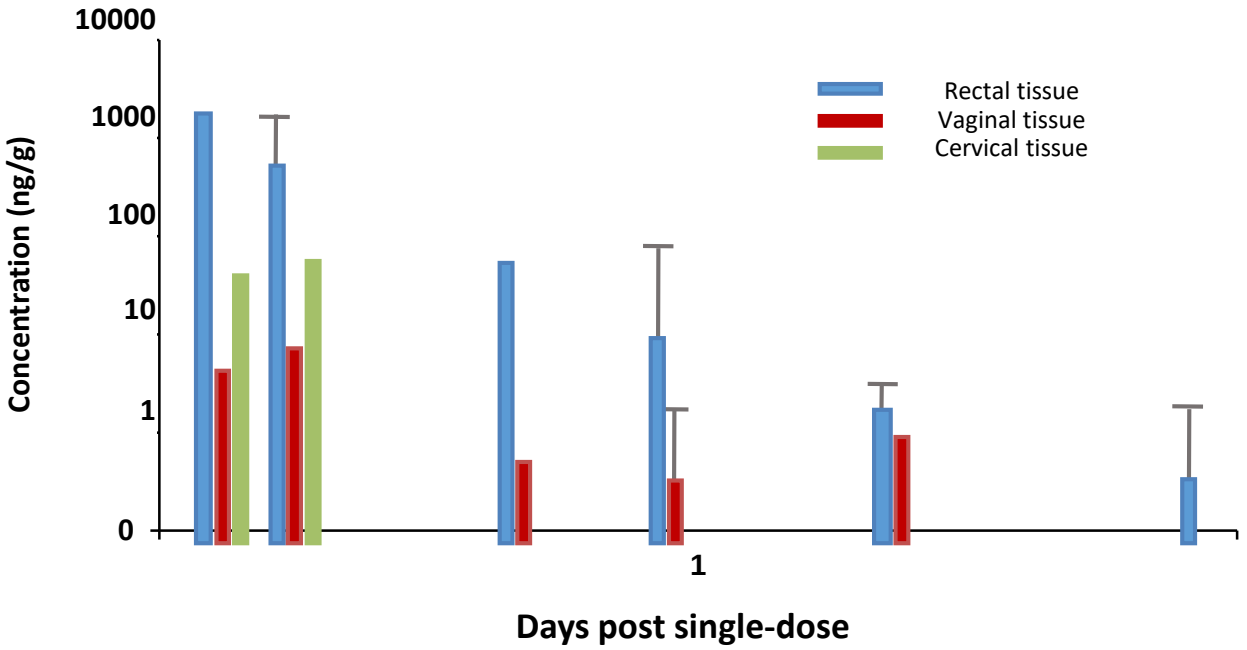
It takes up to **20 days** to be fully protected. PrEP must be taken daily!

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.

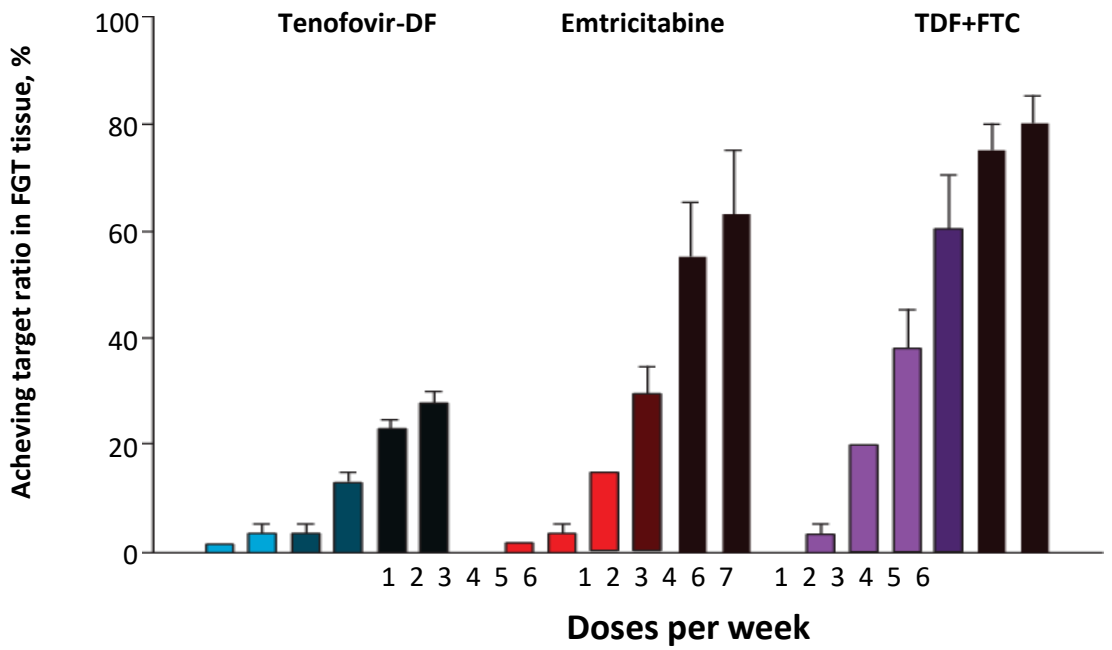
Women: PK differences in various mucosal tissues

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



- TFV concentration is sustained longer in rectal tissue in women

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

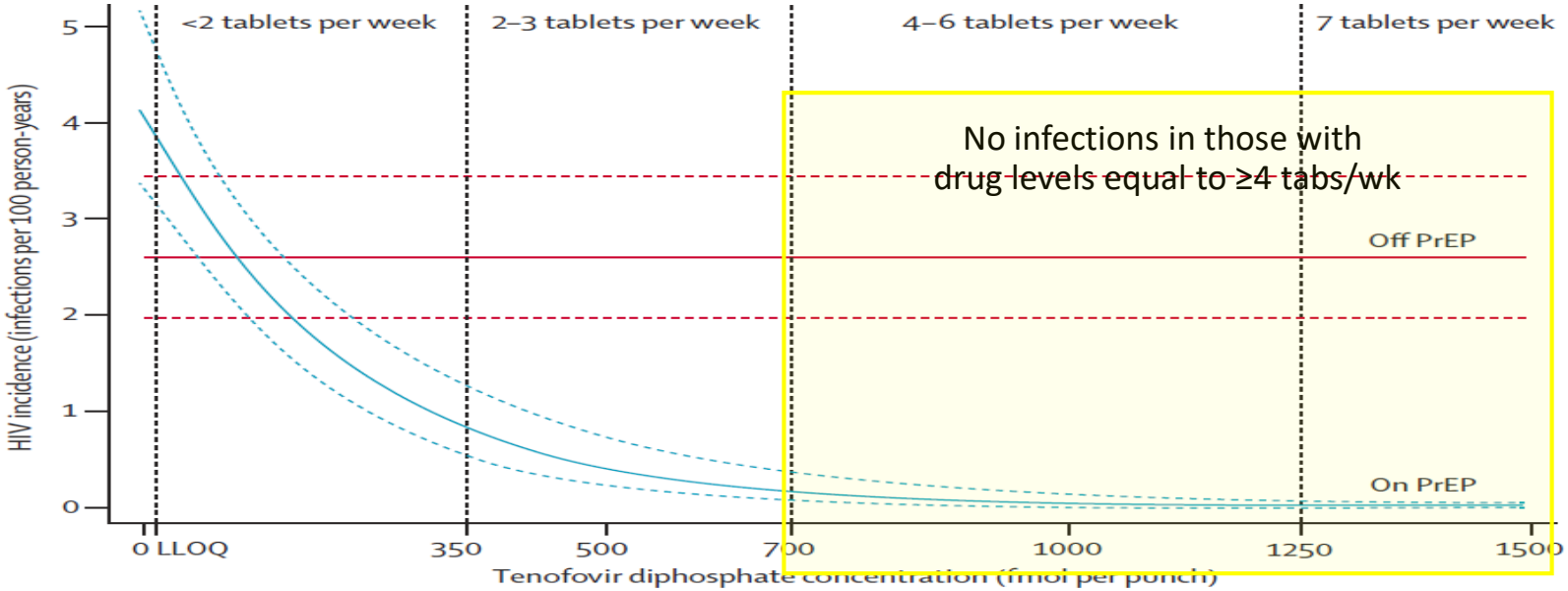


- TFV exposure was 2- to 160-fold greater in rectal tissue than cervical/vaginal tissue in women
- FTC-DP exposure was 80- to 280-fold greater in cervical/vaginal tissue than rectal

Patterson K, et al. Sci Transl Med. 2011;;3(112):112re4
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)



Drug Concentration	none	<2 pills/week	2-3 pills/week	≥ 4 pills/week	7 pills/week
HIV Incidence per 100 PY (95%CI)	*4.7 (2.99-7.76)*	*2.25 (1.19-4.79)*	*0.56 (0.00-2.50)*	*0*	*0*
Risk Reduction (95%CI)		*44% (-31-77)*	*84% (21-99)*	***100% (86-100)***	

The recommended dose of TVD for PrEP in HIV-1 uninfected adults is one tablet once daily taken orally with or without food[3]

1. Grant RM, et al. Lancet ID 2014;14(9):820-829
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 persons life
  - Changes in relationships
  - Behaviours
  - Ability to adhere to a PrEP maintenance programme

Key points to remember:

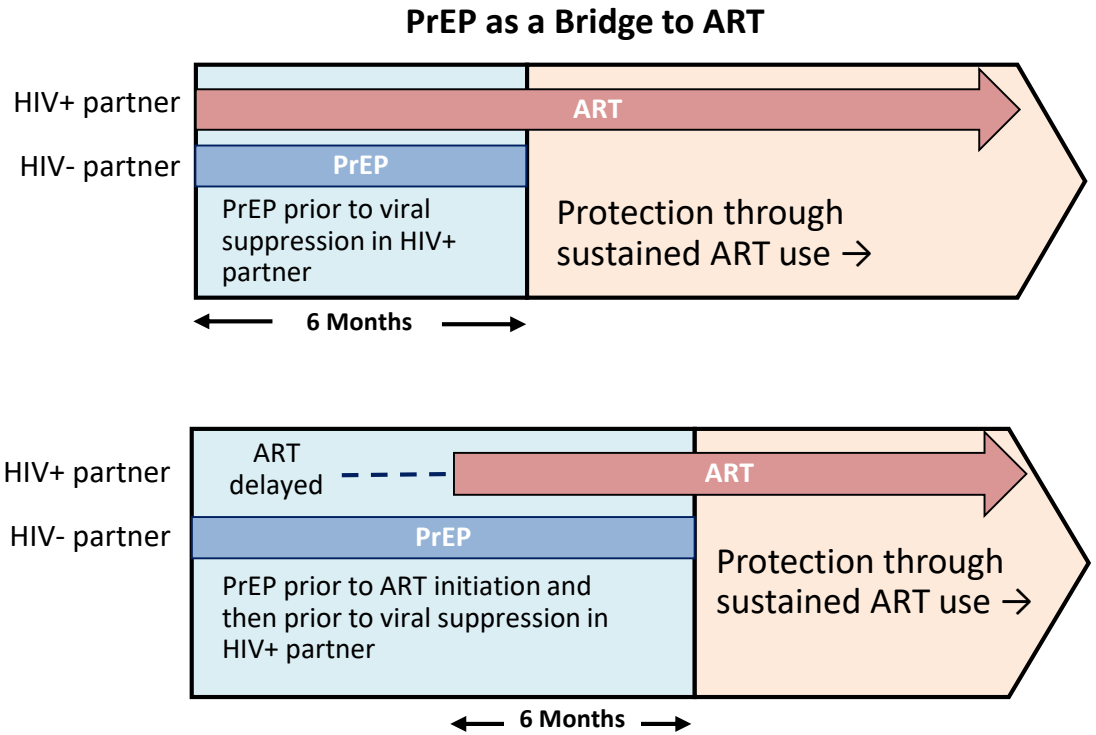
- It takes **7/20 days** of daily TDF/FTC to reach adequate tissue levels
- Use other methods of protection during this time
- **When stopping** continue PrEP for 28 days after last HIV exposure

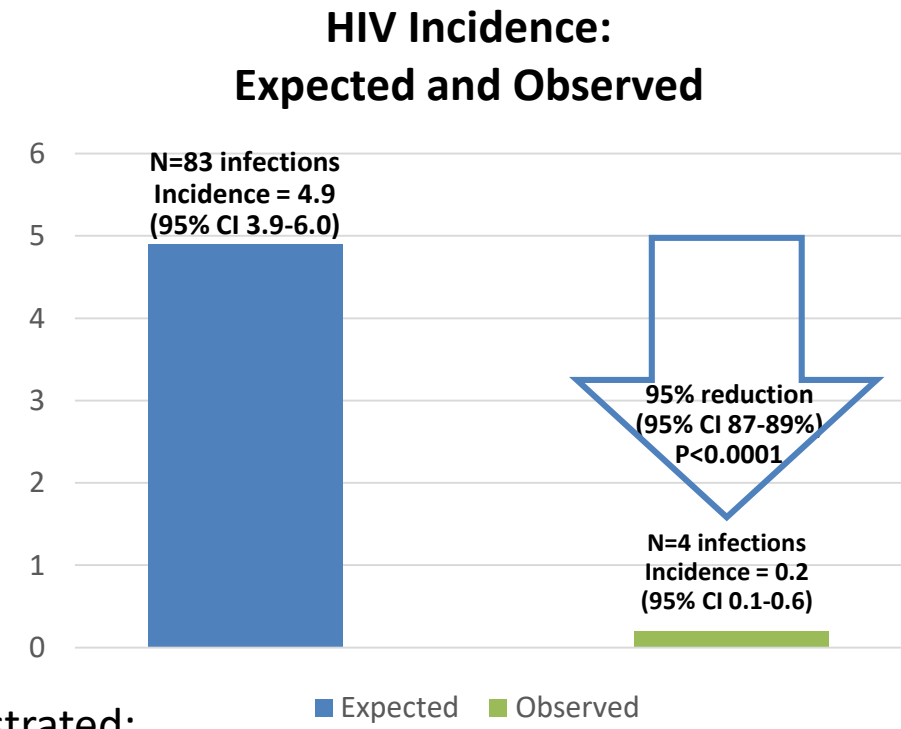
Integrated delivery of PrEP and ART: Sustained near elimination of HIV transmission in African HIV serodiscordant couples

Discordant Couples

Partners Demonstration Project

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

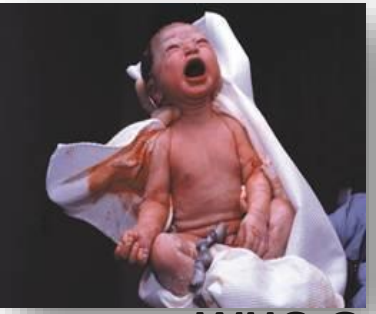




Integrated delivery of ART and PrEP in HIV serodiscordant couples demonstrated:

- 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

Baeten J, et al. AIDS 2016



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.

Mofenson L, et al. AIDS 2016
WHO Guidance July 2016
Bekker LG, et al. SA Journal of HIV Med. 2016

In SA: TDF/FTC PrEP CI in pregnant or breastfeeding women

Birth defects with TDF or FTC

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

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

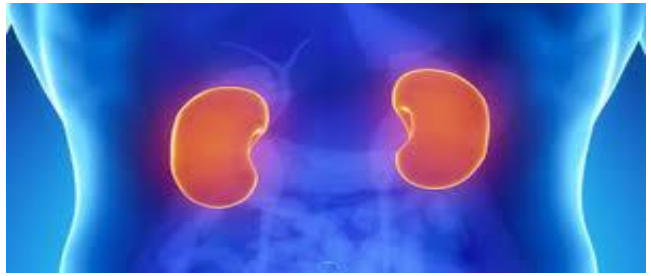
Risks and side effects

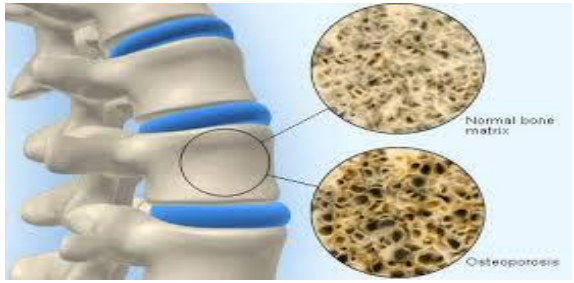
GI effects

ARV resistance

HBV management

Renal



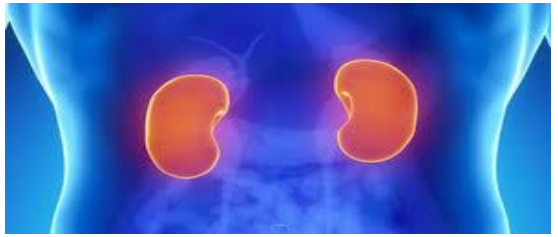


BMD

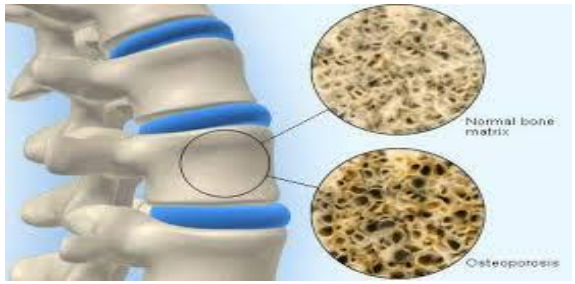
Risk compensation

Side effects

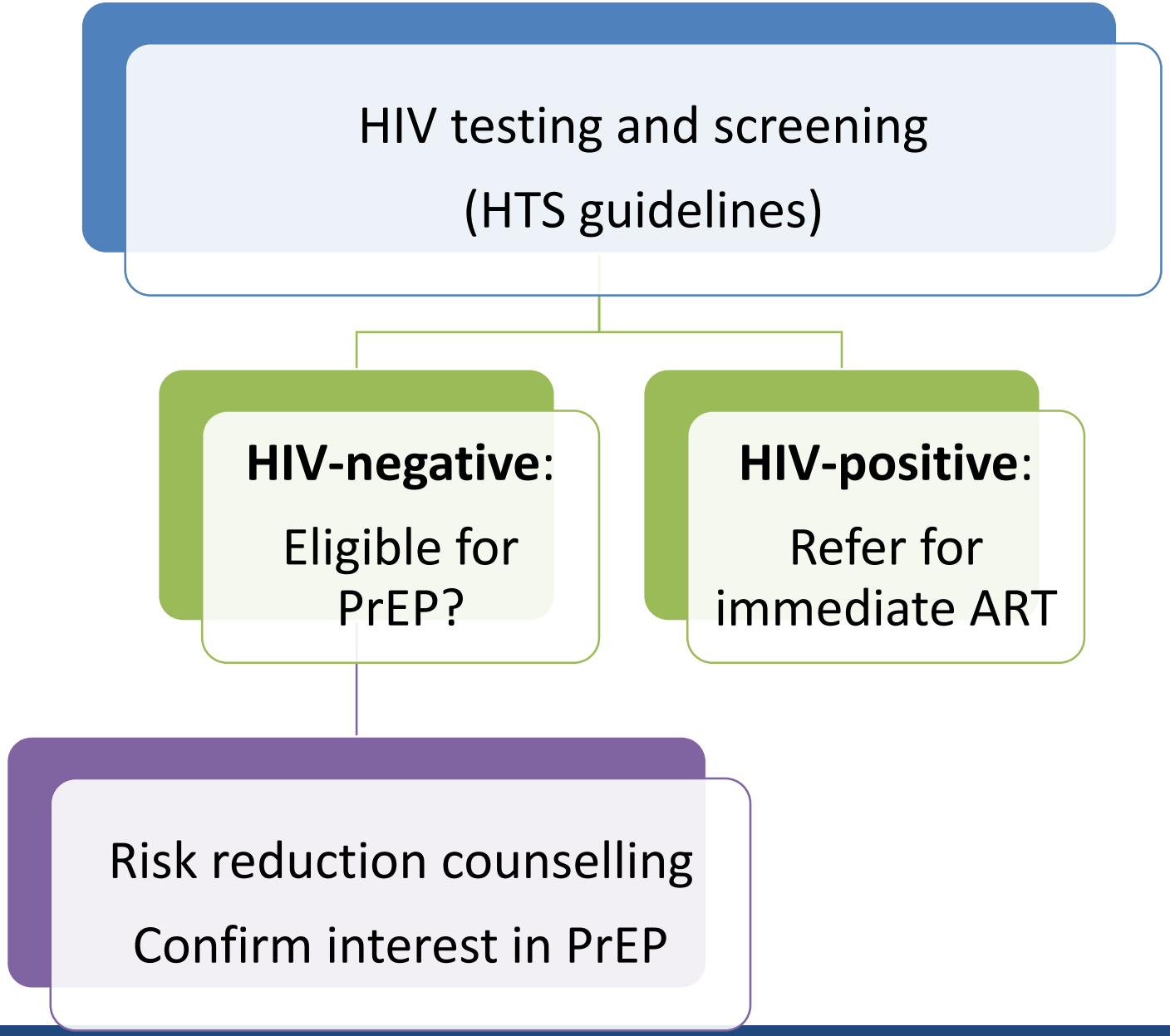
- Mild: headache, malaise
- GI side effects
  - Nausea, weight loss
- Renal toxicity
  - Transient increases in serum creatinine
  - Decreased GFR



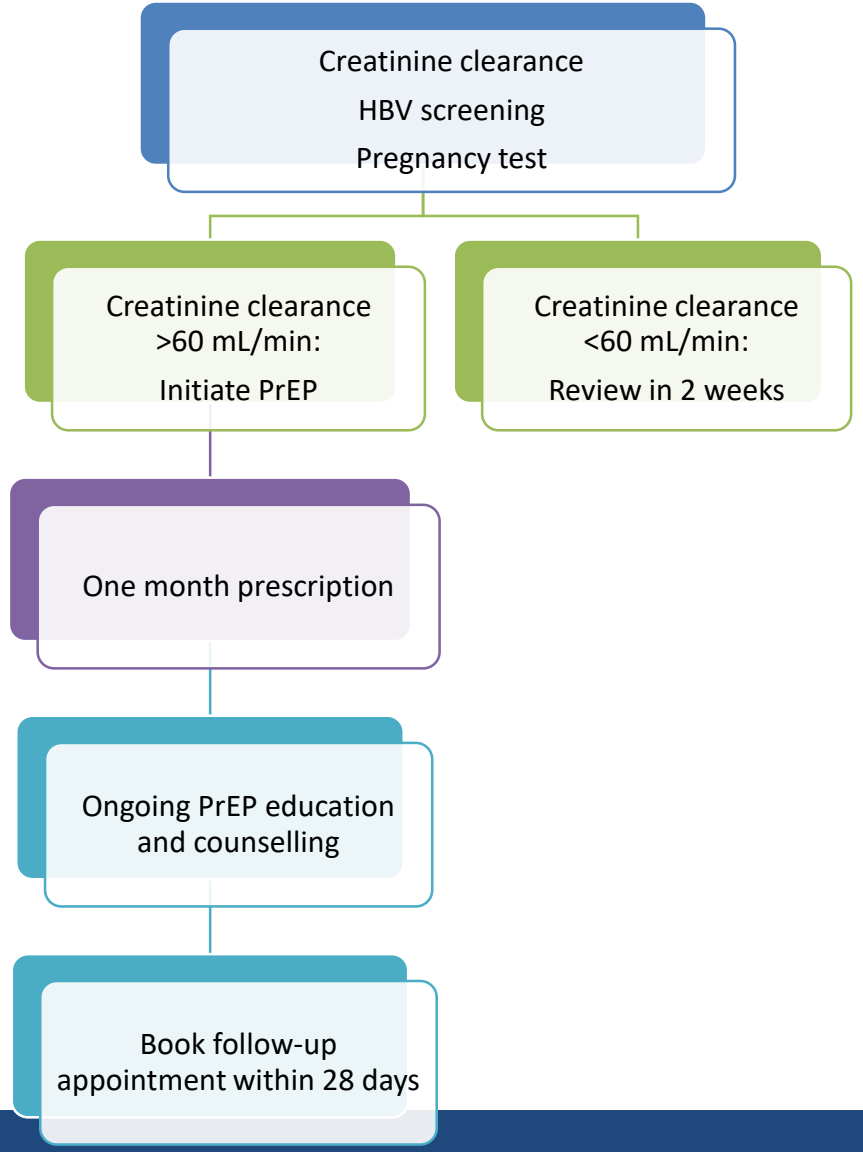
- Extremely small risk of lactic acidosis and hepatic steatosis or steatohepatitis
- Decreased BMD
  - Less cf HIV-infected individuals on TDF
  - No differences in fracture rates



Summary algorithm



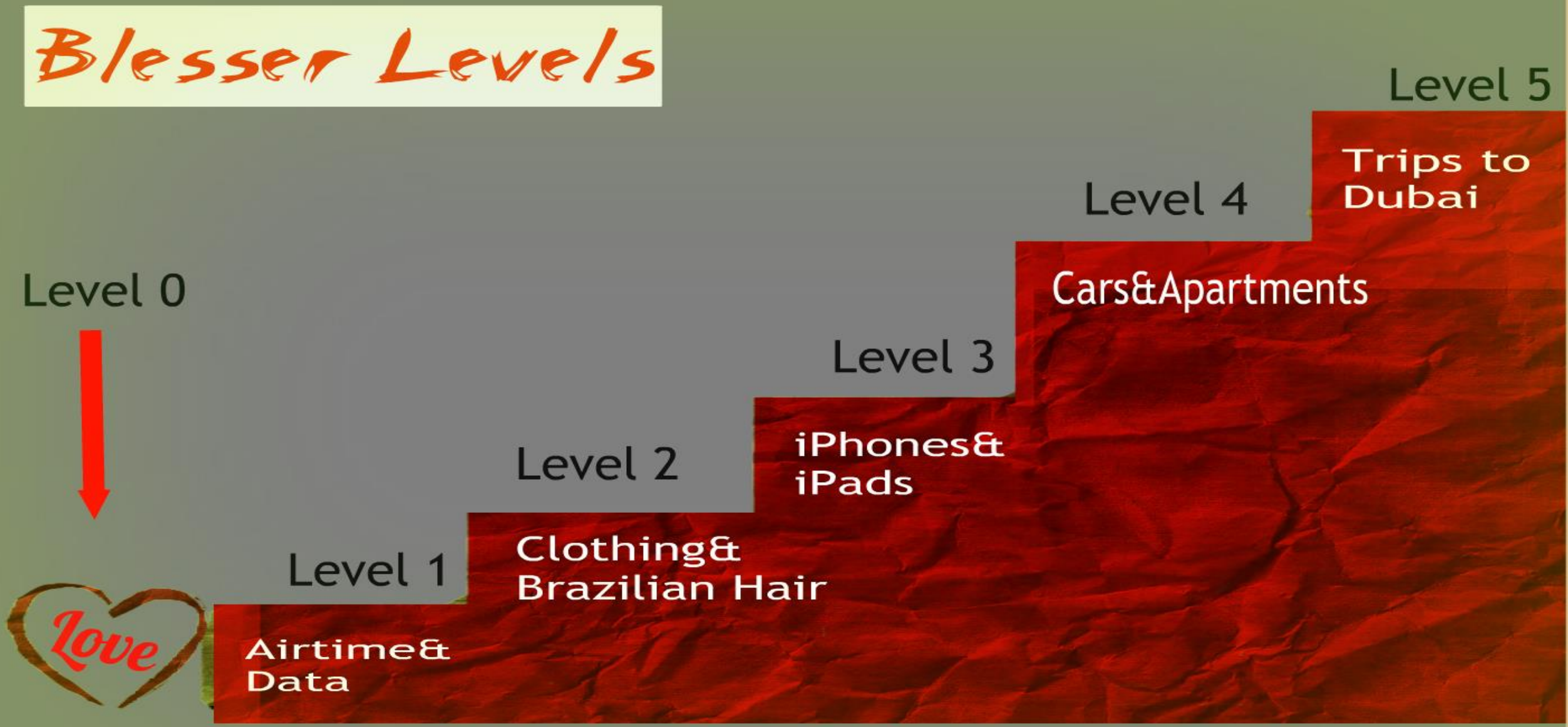
Summary algorithm cont.



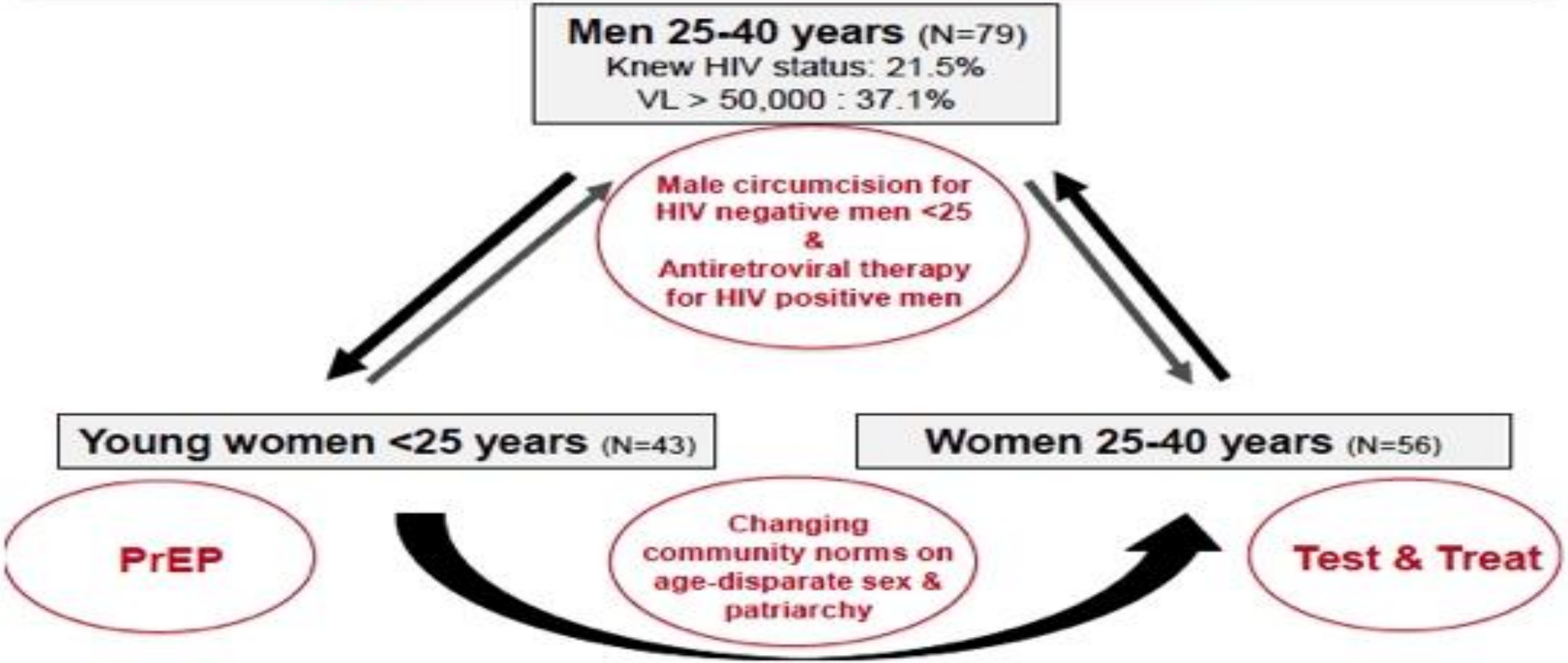
Some final thoughts

- 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
Love
Level 1
Airtime&
Data
Level 2
Clothing&
Brazilian Hair
Level 3
iPhones&
iPads
Level 4
Cars&Apartments
Level 5
Trips to
Dubai

Combination prevention to break the Cycle of HIV transmission



Thank you for your attention!

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Anova Health Institute