PREP IS 4

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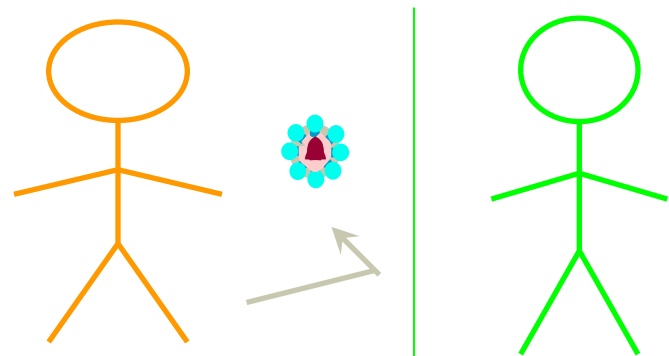
PRE-EXPOSURE PROPHYLAXIS (PREP)

An HIV uninfected individual takes antiretroviral medication (oral or topical) ahead of ongoing HIV exposures. By having these medications in the bloodstream/tissues, HIV may be unable to establish infection.



US WOMEN ARE BEING PRESCRIBED PREP

- **Between Jan 2011 – March 2013 pharmacy data from aprox 55% US pharmacies assessed for PrEP prescriptions.**
- **Total of 1,774 subjects were identified as starting TVD for PrEP.**
  - 47.7% were women

Mera RM et al.ICAAC 2013

KNOWLEDGE AND ACCEPTABILITY OF PREP AMONG HIV+ INDIVIDUALS (DREXEL UNIVERSITY COLLEGE OF MEDICINE)

Cross sectional survey between 1/2013 and 6/2013 of HIV+ persons

- 206 subjects included

Survey was based on a CDC validated survey which examined knowledge, attitudes and acceptability of PrEP

Results:

- Only 15% were aware of PrEP
- MSM (p=0.014) and males (p=0.013) were significantly more likely to be aware of PrEP than women
- Once educated about PrEP 89% said that would be extremely likely/likely to recommend PrEP to a negative partner
- Of those subjects who had HIV negative partners and who had not missed a dose of their ART in the last 7 days (p=.05), were more likely to have heard of Prep (p=.05) and were more likely to recommend this for their partner (p=.049).

PREP AT DREXEL COLLEGE OF MEDICINE HIV CLINIC, PHILA

- **Majority of persons who have expressed interest are pregnant women with HIV+ partners, and HIV- male partners of HIV+ pregnant women**
  - 10 HIV- pregnant women of HIV+ partner
  - 8 HIV – male partners of HIV+ pregnant women
  - 5 HIV- women who are attempting conception
- **Excellent adherence to meds and apts**
  - 85% reported no missed meds in last 7 days.
  - No transmissions
- **8 of the women received PrEP in the OB/GYN clinic associated with the HIV clinic**
  - OB/GYN attendings, residents, NPs and midwives have been trained o prescribe PrEP independently

PREP IS A CHOICE

"IT IS ONLY WHEN YOU EXERCISE YOUR RIGHT TO CHOOSE THAT YOU CAN ALSO EXERCISE YOUR RIGHT TO CHANGE."

HIV PREVENTION: OPTIONS/CHOICES

Safe sexual practices

Male condoms

Female condoms

Male circumcision

Partner is on HIV medications and has a suppressed viral load.

Pre-exposure Prophylaxis

HPTN-052: TREATMENT FOR PREVENTION

- Couples were randomized to immediate treatment or delayed treatment when CD4 counts decreased to <250 or had an AIDS defining illness.
- Early treatment was 96% effective for prevention of HIV transmission to the uninfected partner.

ABSTRACT CROI, 2014

- 750 mixed status couples, heterosexuals and same sex
- HIV+ partner on ART
- No linked HIV transmissions

BENEFITS OF PREP DURING ATTEMPTED CONCEPTION BETWEEN HIV- WOMEN AND HIV+ MALE PARTNERS: A MODELING APPROACH

PrEP provided little added benefit when all are true:

- The HIV-infected male partner is on ART
- Unprotected intercourse is limited to the period of ovulation
- STIs are diagnosed and treated in both partners

ART treatment of the HIV+ male partner drives the differences between strategies

This model shows that HIV prevention can be achieved without the addition of PrEP if all of the above modifiable risk factors are used.

HOFFMAN ET AL IAS 2013

NOT ALL PERSONS WITH HIV ARE READY TO START ART

- **772 serodiscordant couples in Partners PrEP study**
- **"Would you be willing to start ART if it would lower your chance of giving HIV to your partner"**
  - HIV+Men: 58% - Yes 42% - No
  - HIV+ Women: 70% Yes 30% No
- **Concerns: Side effects, stigma, pill burden potential for ART resistance if the person becomes + during PrEP administration** **Heffron JAIDS 2012**
- **PrEP could be used as a bridge to ART as a public health strategy**
- **The HIV neg partner can not always depend on the fact that their partner is on ART with an undetectable VL and no resistance**

WHY WE NEED NEW PRODUCTS FOR PREVENTION FOR WOMEN

- Receptive sexual partners have a higher vulnerability to HIV from vaginal and anal sex
- Receptive partners often do not have control over condom use
- Treatment for prevention is success, but not all HIV+ persons may not want treatment
- PrEP is a way for women to control their risk of infection

Contraceptives: Many Choices

FAMILY PLANNING MODEL

Family planning services is prevention:

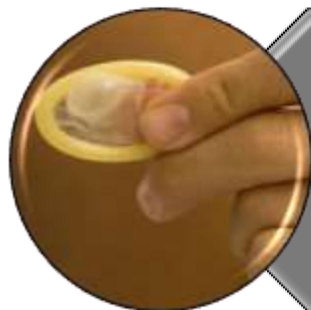
- Prevention of unwanted pregnancy
    - Birth Control provided on site
    - Preconception counseling provided for those interested in conception
- Prevention of STDs
    - STD treatment provided on site for patients and their partners
- Prevention of HIV
    - HIV testing and counseling
    - Condom supply
    - **PrEP counseling**

PREP is a choice in this prevention model

HOW WILL MICROBICIDES OR PREP BE DELIVERED?

Like managing hypertension treatment?

Like getting Depo-Provera?



Like buying condoms?

LESSONS FROM THE PREP TRIALS IN WOMEN

SUMMARY OF PREP AMONG WOMEN: ADHERENCE IS EVERYTHING!

- **1% TDF gel**
  - VOICE: no difference vs. placebo (why?)
  - CAPRISA: 54% ↓ if >80% adherent
- **Oral TDF**
  - VOICE: no difference vs. placebo (why?)
  - Partners PrEP: 67% ↓ vs. placebo
- **Oral TDF/FTC**
  - FEM-PrEP: no difference vs. placebo; adherence!
  - Partners PrEP: 95% ↓ if >80% adherent
  - TDF-2: 76% ↓ if drug supply confirmed

VOICE TRIAL

- Study of over 5000 women
- The study products showed no effectiveness
- Daily approach – gel or tablet – was not right for the population of women in VOICE
- Younger (under 25), unmarried women were least likely to use the products and the most likely to acquire HIV 3-10 times higher
- The women who need safe and effective HIV prevention methods must also be willing and able to use them – and they must actually use them

WHY WAS TRUVADA NOT TAKEN?

- Why didn’t women use the study products?
- Why did they go to great lengths to hide their non use from the study sites?
- Why did they join the trial if the did not want the products?
- What happened to the unused products?
- Why did they not use it even after they found out that the products worked?
- Was there stigma associated with taking the medications?

WHAT ARE THE REASONS THAT WOMEN WERE NOT ADHERENT?

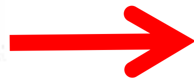
- **Acceptability**
  - Preference for oral tablets or vaginal gel?
  - Gel perceived to improve sex by many African women (Qualitative interviews)
- **Adherence**
  - Daily dosing is a barrier
- **Stigma**
  - Taking an ART is thought to be associated with having HIV

QUALITATIVE INTERVIEWS OF WOMEN IN VOICE TRIAL

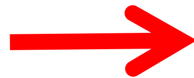
- Reimbursement be removed, just make sure they can get to the clinic
- Women were told about side effects, so that women in the study thought if they did not get side effects then they were on placebo
- Liked getting tested for HIV monthly
- Liked having free cervical check up
- Consent forms emphasized side effects and discouraged use
- The women made conscious decisions not to take the drug.

- **PrEP, when used with high adherence, is a highly effective prevention strategy for women.**
- **Can be used for safe pregnancy planning**

PROTECTION AGAINST HIV TRANSMISSION DURING CONCEPTION AMONG SERODISCORDANT COUPLES



Options include self insemination or assisted reproduction



Optimal procedures are often prohibitive due to cost and lack of widespread availability (sperm washing + adjunctive)

Less costly menu of options: Timing of intercourse, STI treatment, PrEP, ART for positive partner.

PREP IN COUPLES PLANNING PREGNANCY

USING PREP-CONCEPTION

- Evaluated timed intercourse with PrEP in 46 heterosexual HIV-discordant couples where the female was HIV-uninfected
- The male HIV-infected partner received ART and had undetectable plasma HIV RNA levels.
- One dose of oral tenofovir was taken by the women at luteinizing hormone peak and a second oral dose was taken 24 hours later.
- None of the women became HIV infected and pregnancy rates were high, reaching a plateau of 75% after 12 attempts.

Vernazza, Graf et al 2011

PREGNANCY STUDIES OF TENOFOVIR: SUMMARY

PK of single-dose TFV gel in term pregnancy shows levels similar to nonpregnant women

Tenofovir applied topically does get to fetal compartment but at 40X lower levels than with oral dosing (Beigi, et al, Microbicides 2010)

Antiretroviral Pregnancy Registry demonstrates no teratogenicity in first trimester among women who are HIV + and pregnant on Tenofovir.

PREP DURING BREASTFEEDING

- In the USA: guidelines recommend against breastfeeding
- Sub-Saharan Africa exclusive breastfeeding for 6 months is recommended by WHO
    - Breastfeeding is closely tied to infant survival in sub-Saharan Africa
- Women at greatest risk for HIV are in their childbearing years
    - Exposed to both HIV infection & pregnancy
    - HIV – women in serodiscordant couples are at risk for seroconversion if breastfeeding
    - High rates of transmission if seroconvert during pregnancy and breast feeding

TOPICAL & SYSTEMIC DELIVERY: MORE OPTIONS

Pill

Gel with applicator

Vaginal film

Vaginal ring (sustained delivery)

Injectable (long-acting)

- ✓ Ideal: long acting, safe, effective, low cost and user-friendly
- ✓ Maximize choice & optimize effectiveness
- ✓ Potential for combination ARVs to increase effectiveness
- ✓ Potential to combine ring or injections with contraception

NEW APPROACHES

Injectable formulations :

- Integrase Inhibitor Dolutegravir provides prolonged protection against intrarectal simian HIV in macaques in injectable formulation (GSK1265744)
  - Half life 21-50 days Andrews et al Science 2014
- Rilpivirine monthly injection (TMC 278)

Vaginal Rings

- Dapivirine and Marvorac vaginal rings over one month

Topical and oral:

- Marvorac +/- FTC/TDF (HPTN 069)
- Topical and oral raltegravir

How Can We Make Prevention Products More Fun to Use?

IS INTERMITTENT PREP FEASIBLE?

Intermittent dosing: periods of risk (e.g., periconception), event-driven, or scheduled fixed dosing

Do we know enough about PK and PD to predict frequency of fixed, intermittent dosing or optimal timing of dosing pre-exposure?

- May vary by drug & by compartment (vaginal, rectal, blood)

How much sex is planned, & could be protected by event-driven PrEP?

Would adherence be higher with fixed intermittent dosing than daily dosing?

HOW TO INCREASE PROMOTION OF PREP

- Social marketing of prevention
- Normalize product
- Ensure access to PrEP treatment in clinical settings
- Make is easier (like hand washing products)
  - Broad availability
  - Low costs
  - Products portable and widely avialable

HAND WASHING: A PUBLIC HEALTH PREVENTION

- CDC: Clean Hands Save Lives
- Social marketing: Dispensers every where, Hand sanitizers are portable and widely available
- No stigma associated. Positive prevention behavior
- Normalized

STEPS FOR A NATIONAL AGENDA FOR PREP IMPLEMENTATION

- **Educational campaign to increase awareness for persons who might benefit from PrEP use**
- **Educational campaign to train providers interested in offering PrEP to their patients**
  - Systematic training in medical, family planning, HIV, and OB/GYN clinics
- **Monitor PrEP use and its health impact**
- **Disburse information on models of implementation**
- **Disburse information on clinical research**
- **Ensure insurance policies reimburse billing codes**
- **Coverage for uninsured needs to be worked out: lab costs, coverage for visit etc.**

PATIENT INFORMATION SITES

Project Prepare Website: www.projectprepare.net

http://www.prepwatch.org/#women

Centers for Disease Control and Prevention: http://www.cdc.gov/hiv/prep/

Project inform: http://www.projectinform.org/pdf/prep_msm.pdf

San Francisco Department of Public Health: www.prepfacts.org

PrEP watch: http://www.prepwatch.org/#guidance

Bay Area Perinatal AIDS Center: Positive Reproductive Outcomes for Men: hiv.ucsf.edu/care/perinatal/pro_men.html

National HIV/AIDS Clinicians' Consultation Center
UCSF – San Francisco General Hospital

Perinatal HIV Hotline (888) 448 - 8765

National Perinatal HIV Consultation & Referral Service

Advice on testing and care of HIV-infected pregnant women and their infants

Referral to HIV specialists and regional resources

Warmline (800) 933 - 3413

National HIV Telephone Consultation Service

Consultation on all aspects of HIV testing and clinical care

PEPline (888) 448 - 4911

National Clinicians' Post-Exposure Prophylaxis Hotline

Recommendations on managing occupational exposures to HIV and hepatitis B & C

HRSA AIDS ETC Program & Community Based Programs, HIV/AIDS Bureau
& Centers for Disease Control and Prevention (CDC)

www.nccc.ucsf.edu