HIV, PREP AND PREGNANCY IN SERO-DISCORDANT RELATIONSHIPS

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Disclosures

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Background

- Serodiscordant couple= refers to an intimate partnership in which one person is HIV+ and the other is HIV negative.
  - In sub-Saharan Africa, up to half of those living with HIV report a serodiscordant partnership[1,2]
  - In lower prevalent area, may be as high as 75%
  - One US study (Houston)- 212 HIV pos pregnant women
    - 40% serodiscordant partner
    - 34% partner with unknown HIV status

- 20-50% of HIV-infected men and women desire children[3-5]
- Childbearing desires can lead to unprotected sex and/or nondisclosure of HIV status[6-8]
- Up to 60% of new infections occur between stable, heterosexual, discordant couples in countries in sub-Saharan Africa, including Kenya[9,10]
- HIV transmission risk is up to 2x greater among discordant couples who conceive, compared to those who do not[11]

1. Chemaitelly STI 2012; 2. Guthrie Curr HIV Res 2007; 3. Chen Family Planning Perspective 2001; 4. Ogilvie AIDS 2007; 5. Frodsham Fertil Steril 2006; 6. Brubaker HIV Medicine 2011; 7. Chen Family Planning Perspective 2011; 8. Ujji BMC Women's Health 2010; 9. Dunkle Lancet 2008; 10. Coburn Lancet Infect Dis 2011 11. Brubaker HIV Medicine 2011

Reproductive rights and counseling

- With treatment, men and women with HIV are living longer, healthier lives, and can expect to see their children grow into adulthood.
- Safer conception counseling for HIV discordant couples is a reproductive right and should be included as a public health strategy to reduce HIV incidence among men, women, and their children
- Ethically:
  - The ethical dilemma in providing safer conception strategies to HIV affected couples includes the possibility of mother-to-child HIV transmission and the risk of HIV transmission to an uninfected partner.
  - Some have argued that it would be unethical to withhold proven HIV prevention strategies to HIV-affected couples who desire pregnancy

Matthews AIDS Behavior 2011; Mantel Journal Public health Policy 2009

Summary of relevant Trials

FEM-PrEP Trial[3]	Phase 3 randomized, double-blind, placebo-controlled study among heterosexual women -1951 Heterosexual women	TDF/FTC Vs Placebo	-Adherence was low -TDF detected in fewer than 50% -correlated with low efficacy -trial stopped after interim analysis determined unlikely difference in efficacy between the two groups.
Vaginal and Oral Interventions: VOICE[4]	Phase 2B randomized, open-label, placebo-controlled study . 5029 Heterosexual women -young- ave age 25 -single- 79%	oral TDF or oral TDF/FTC or topical TDF vaginal gel Vs Corresponding placebo	TDF only detected in: -30% o in TDF group -29% in TDF/FTC -25% Gel Ultimately not assoc w/ risk of reduction. -TDF/FTC- 4% increase -TDF- 49% increase -Gel- 15% decrease (not statistically significant)

Summary of relevant Trials

Study Name	Design	Medication	Key Findings
Partners Demonstration Project (Partners PrEP)[1] Africa	Open-label; daily oral PrEP among ART-naive heterosexual serodiscordant, high-risk couples -4758 couples -38% HIV neg female -68% HIV neg male	TDF/FTC Vs TDF alone Vs Placebo	-TDF- 62% reduction -TDF/FTC- 73% reduction -detectable plasma TDF levels was associated with 90% reduction in risk of HIV acquisition -no drug resistance detected in those infected after enrollment
TDF2[2] Botswana	Phase 3 randomized, double-blind, placebo-controlled study in 1,219 heterosexual 55% male 45% female 90% unmarried 90% aged 21-29	TDF/FTC Vs Placebo	-62% reduction in HIV acquisition (95% CI 22-83; P=0.03) -Adherence was 84% in both arms.
HPTN 052 Africa, Brazil, India, Thailand	Randomized clinical trial designed to evaluate cART by HIV-infected individuals to prevent sexual transmission of HIV among serodiscordant couples. -1763 Heterosexual couples 50% HIV neg female	cART- immediate or delayed	cART led to a 96% reduction in transmission of HIV to the uninfected partner.

MCA Case

- 28 year old HIV+ male referred to MCA for preconception counseling. CD4 415, Viral load 285 on cART for 5 years. Wife is 23 years old, married for 1 year. Last tested negative two months ago. Couple has inconsistent condom use and desires to have a baby.

Reproductive Health Services for Serodiscordant Couples

- Preconception counseling
- PMTCT services
- Assisted reproductive services
  - Sperm washing
  - IUI/IVF
- Biomedical approaches
  - TasP
  - Prep and Prep-C
  - STI testing and treatment

Guidelines on Safer Conception

- US Public Health Service PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES - 2014 A CLINICAL PRACTICE GUIDELINE
  - PrEP use periconception and during pregnancy by the uninfected partner may offer an additional tool to reduce the risk of sexual HIV acquisition.
  - Both the FDA labeling information[1] and the perinatal antiretroviral treatment guidelines[2] permit this use.
  - However, data directly related to the safety of PrEP use for a developing fetus are limited

1. Gilead Sciences. Truvada Package Insert. 2013; 2. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. 2014

Safer Conception

HIV Transmission/goal	Method	Risk Reduction
Female HIV positive Goal: decrease perinatal transmission (MTCT)	ARV in the mother ARV to child after birth	95-98%
Female HIV positive Goal: decrease female to male transmission	Non-intercourse vaginal insemination Voluntary medical male circumcision	Unknown (100%) 66%
Male positive Goal: decrease male to female transmission	Sperm washing + intrauterine insemination or IVF	100%
Either partner positive Goal: decrease transmission to negative partner	Sex without condoms limited to peak fertility ART for infected partner PrEP (oral, daily FTC/TDF) Treatment of STIs	Unknown 96% 63-73% 40%

Conception Options for mixed-status couples

- Having a HIV-negative baby is possible with careful planning.
- Your conception options will vary depending on which partner is HIV-positive.
- Preconception counseling is crucial
  - Preparing and planning for a healthy pregnancy before you are pregnant
- Optimal health should be obtained before attempting conception
  - Use contraception until healthy
  - Manage underlying medical conditions: DM, HTN
  - Stop smoking

Preconception Counseling

- Assess HIV status
  - Which partner is infected?
  - Is the HIV+ partner on ARVs? Adherence?
  - What is the HIV+ partners viral load? CD4?
  - Has there been disclosure to the HIV neg partner?
  - Partner HIV testing
- How often do you and your partner use condoms?

Preconception Counseling (contd)

- HIV positive individual: Attempting to get pregnant or being pregnant may increase the risk of passing HIV to the uninfected partner
- HIV negative individual: attempting to get pregnant or are already pregnant may put you at high risk of getting HIV from your infected partner
  - If female- risk of transmitting to baby is very high if seroconvert during pregnancy.

Preconception strategies: Reducing risk of HIV Transmission

- ARV therapy (TasP)
  - Goal of sustained, undetectable viral load
  - CD4 count above 350
- Prep
- Are healthy
  - No opportunistic infections
  - Not using drugs or alcohol
- Screen for STI
- Safest options for becoming pregnant
  - Avoid or limit condomless sex
- **No options** have been shown to be **100% effective**, but some can greatly reduce the chance of transmission

TasP

- HIV-infected partner should be receiving cART and demonstrated sustained suppression of viral load.
- Use of cART reduces but may not completely eliminate the risk of HIV sexual transmission in couples who conceive through unprotected intercourse
- Effective cART that decreases plasma viral load to undetectable levels is also associated with decreased concentration of virus in genital secretions.
  - Discordance between plasma and genital viral loads has been reported, and individuals with an undetectable plasma viral load may have detectable genital tract virus.
  - Antiretroviral (ARV) drugs vary in their ability to penetrate the genital tract.

Loutfy MR J Int Assoc Provid AIDS Care. 2013; Cu-Uvin S AIDS. 2010;24(16):2489-2497; Sheth PMAIDS. 2009;23(15):2050-2054; Politch JA AIDS. 2012; Taylor S Curr Opin HIV AIDS. 2010;5(4):335-343

HIV Discordance: Female is HIV positive/ male HIV negative

- Safest:
  - Artificial insemination
    - Artificial insemination protects the male partner from HIV-infected bodily fluids. His sperm is inserted into the woman's vagina using a syringe.
    - Artificial insemination is most effective when a woman is ovulating (releasing an egg). Ovulation occurs about 14 days after a woman's period starts.
  - Home insemination
    - Man ejaculates into a condom (w/o spermicide).
    - Use non-needle syringe or baster to deposit the semen deep inside the vagina
  - Condom use advised at all times.

HIV Discordance: Male is HIV positive and Female is HIV negative

Safest:

- Donor sperm from an uninfected HIV man with artificial insemination
- Sperm washing
  - HIV-infected semen cannot infect your baby, but can infect your partner
  - Sperm washing is a procedure that separates HIV-free sperm from the HIV-infected seminal fluid
  - HIV-free sperm can be inserted into the woman's vagina by artificial insemination – eliminating any risk of HIV infection
  - Washed sperm can also be used to fertilize the woman's egg by in vitro fertilization (IVF)
- Access to sperm washing and IVF can be limited in some settings.
  - $10,000-20,000

What about couples that do not have access to these reproductive services?

HIV treatment and planned unprotected sex

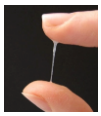
- Both types of mixed-status couples could take HIV treatment and conceive naturally with comprehensive counseling.

TIMED, PERIOVULATORY UNPROTECTED INTERCOURSE AFTER:

- Undetectable viral load for 6 months
- The HIV-negative partner can take PrEP prior to unprotected sex in some cases *(however, the risk of HIV infection still exists)*.
  - PrEP is one of several options to protect the uninfected partner during conception and pregnancy,
- Adherence to treatment is essential
- No sexually transmitted infections (STIs)
- Semen analysis- to evaluate for low sperm count, low motility, low semen volume
  - Avoid unnecessary exposure for prolonged periods when likelihood of conceiving is low or nonexistent

Ovulation: Fertile Period

- Calendar Days
- Cervical Mucus
- LH Testing
- Basal Body Temperature
- US



Timed Intercourse with Prep-C

- Switzerland study:
  - Vernazza et al: 46 Heterosexual HIV-discordant couples with an HIV-uninfected female partner.
    - Males on cART with undetectable viral load
    - One dose of TDF at peak LH and 2nd dose 24hours later.
      - No HIV infections
      - High rate of pregnancy- 75% after 12 attempts
- Further studies are needed.

Prep- C

- TDF/FTC is FDA approved for only daily dosing
  - Guidelines: "option for serodiscordant couples during conception and pregnancy"
- Adherence is critical
- The exact time to optimal protection using daily doses of TDF/FTC is not known.
  - maximum intracellular concentrations are reached in cervicovaginal tissues at approximately 20 days
  - rectal tissue at approximately 7 days

Prep-C

- HIV-negative women:
  - Referral to clinical site offering comprehensive care including prevention of MTCT.
    - Risk of HIV transmission increases during pregnancy
    - Risk of transmission to infant increases if mother infected during pregnancy or breastfeeding.
    - Regular counseling regarding consistent condom use
    - Counseling regarding symptoms of acute HIV.
  - ART to positive male partner to achieve undetectable viral load
  - Daily dosing of TDF/FTC beginning one month before conception attempt, continue for 1 month after conception (or longer)
  - Condomless sex **limited** to peak fertility time identified by lab tests for ovulation.

Mugo NR. AIDS 2011; 25 (15): 1887-95

Prep-C

- Monitoring HIV neg pregnant patient
  - HIV testing: 4th generation/ plasma HIV RNA VL
    - Routine prenatal lab and during 2nd and 3rd trimester
    - Depending on ability to negotiate condom use, we test more frequently.
  - Assess adherence: Pharmacy/SW
  - Frequent counseling on risk of sero-conversion
    - Risk reduction counseling
  - Monitoring of partners HIV VL
  - Discussion on plans for breastfeeding
    - Low vs High risk for seroconversion

PreP- C Risk

- Pregnancy and breastfeeding are not contraindications to PreP
  - Long term safety during pregnancy or during breastfeeding is not yet determined
  - No increased risk of birth defects found in infants exposed to HIV positive mothers taken as part of treatment.
    - One study showed increased risk of preterm birth- unclear if related to TDF/FTC.
- Partner Prep study: IAS 2013
  - 288 pregnancies
  - babies conceived when the mother was taking either TDF or TDF/FTC.
    - No differences in: miscarriages; stillbirths; preterm delivery; birth weight; congenital abnormalities; Infant growth

EMBRACE MTN 016

- Observational study to learn whether HIV prevention products containing ARVs can affect a woman's pregnancy outcome or her baby's general growth and development.
  - CROI presentation 2016
    - 27 women at substantial risk for HIV infection in SF/ Bronx.
      - 18 identified when already pregnant
      - 8 identified pre-conception
      - 1 post-partum
      - All but one had HIV positive partner, remaining women had partner that also had sex with men.
        - 73% were on Art
        - 42% had documented viral suppression
        - 39% had known detectable virus
    - Of the 24 women offered PreP
      - 67% (16) chose to use it; median length of time- 30 wks.
      - 33% chose to use condoms
      - Over half relied on their partners TasP
      - No Prep related pregnancy complications
      - Half on Prep chose to breast feed.
      - One seroconversion in women not taking PreP.

Research: Much to learn

Long acting PrEP
- Maraviroc (MVC)
- Rilpivirine (RPV)
- Integrase Inhibitors
- Tenofovir alafenamide (TAF) subdermal implant

PrEP vaginal rings
- Dapivirine
- Maraviroc (MVC)

HIV vaccine

Financial Considerations

- Most private and employee-sponsored health plans cover TDF/FTC
- Medicaid and Medicare typically cover PreP
- Public insurance may vary
- Medication assistance programs
- Cost: $1300/month

http://www.projectinform.org/pdf/PrEP_Flow_Chart.pdf

Resources

MCA "A Family Clinic"

- MCA Clinic: Prep referral
  - Call or text: 323 455-9454
  - Email MCAclinic@usc-mca.org

- Offering PrEP in Family Planning Clinics
  Mon, October 31, 2016, 9:00 AM – 10:00 AM
  www.hiveonline.org