CLINICIAN CONSULTATION CENTER
National rapid response for HIV management and bloodborne pathogen exposures.

CROI 2013 National Perinatal HIV Hotline lunch discussion

PrEP & Women: Pregnancy, breastfeeding, implementation

Facilitated discussion with Renee Heffron and Nelly Mugo
Perinatal HIV Hotline: Shannon Weber and Deborah Cohan

PrEP and pregnancy: What do we know?

ARV Pregnancy Registry data on the prevalence of birth defects among children with:

- 1st trimester Emtricitabine exposure: 27/1068 live births, prevalence 2.5%, 95% CI 1.7%, 3.7%
- 1st trimester Tenofovir exposure: 39/1612 live births, prevalence 2.4%, 95% CI 1.7%, 3.3%
- 2nd/3rd trimester ARV exposure: 2.8 per 100 live births, prevalence 1.06%, 95% CI: 0.88, 1.28
- General population birth defect prevalence: 2.72% of live births, 95% CI: 2.68, 2.76

Studies of HIV-infected women using tenofovir for treatment

- Data suggest no clinically significant risks for poor birth outcomes or infant growth
- Recent study found a small difference in head circumference (0.3cm smaller) and length (0.4cm shorter) among infants exposed to tenofovir, relative to infants without exposure. (Siberry AIDS 2012)

Studies of HIV-uninfected women using tenofovir as PrEP

- Limited data from first trimester suggest no increased risk for poor birth outcomes and no delays in infant growth (Mugo CROI 2012)

PrEP and pregnancy: What do we need to know?

More data are needed from HIV-uninfected women using tenofovir-based PrEP during the entire pregnancy to:

- Evaluate safety of PrEP on birth outcomes
- Evaluate safety of PrEP on infant growth
- Evaluate effectiveness of PrEP to protect women against HIV infection during pregnancy

PrEP and pregnancy: Discussion

- In PrEP clinical trials, women who became pregnant stopped study drug. But we have some data of women who were on study drug in their first few months of pregnancy. There are no concerns from the data regarding safety of Truvada as

PrEP during pregnancy. We also have data of HIV-infected women who have used Truvada during pregnancy. The data from the US Antiretroviral Pregnancy Registry does not show an increase in birth defects or adverse pregnancy outcomes for pregnant women using Truvada for treatment. We know we have limited data but what we see does not cause concern for PrEP use during pregnancy.

- From the Partners PrEP data, we have been following women for up to one year who had early exposure to tenofovir during periconception. From preliminary data, there was no risk during pregnancy. There is follow up of infants for up to one year with visits every three months, gathering head circumferences, weight and length. These preliminary data are not showing any adverse outcomes.

- CDC PrEP for heterosexuals interim guidance: If women are either pregnant before initiating PrEP or become pregnant while being prescribed PrEP, health-care providers should discuss currently available information regarding potential risks and benefits of continuing PrEP so that an informed decision can be made. (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6131a2.htm)

- A 2013 CROI presentation from the French cohort looks at teratogenicity and antiretrovirals found potential teratogenicity with AZT and EFV, they found no increased risk of birth defects associated with TDF or FTC use.

Upcoming Data

- Concerns about fetal exposure to ARV effecting bone density. CDC has an ongoing study of pregnant women using PrEP who are HIV and HepB co-infected studying the infant outcomes. The data are expected in the next few years.

- Partners PrEP as part of their demonstration study is now following women taking PrEP during pregnancy and following the exposed infants for a year to obtain more safety data. One of the FDA mandates to Gilead about Truvada use is to collect data on 400 women, 200 who use Truvada during pregnancy and 200 who discontinue Truvada use. The Partners PrEP demonstration study expects to contribute data from 40-50 pregnancies to those data and other studies and the ARV registry and other clinical trials will contribute the remaining data.

- The ARV Pregnancy Registry is collecting data on HIV-negative women who are pregnant using ARVs for PEP or PrEP. Though these data are limited to teratogenicity not toxicity. There are however some birth measures included in the registry, including birth weight, length and head circumference. There is a dearth of data on ARV use in HIV-negative women in the US. **It is highly recommended for US based clinicians to contribute to safety data by registering eligible HIV-infected and HIV-uninfected pregnant women with the ARV Pregnancy Registry.**

Comments from CROI discussion participants:
What type of counseling do you provide for women considering PrEP and pregnancy?

- "I have an HIV-negative pregnant teen with a perinatally infected male partner who is not always adherent to his ARV regimen and they are not using condoms regularly and I have prescribed PrEP. If the male partner was completely suppressed and they use condoms regularly, I would wait for more data before considering PrEP."

- It is less of an issue with HIV-positive women with an HIV-negative male partner. But more of a concern with an HIV-positive man even with an undetectable viral load and an ovulation predictor kit. Even if they are attempting timed coitus there is the question how many days before and after should she be taking PrEP. There are the UK data showing 2 peri-coital pills but many in the US considering 30 days of Truvada after attempted conception just as you would prescribe PEP.

- "I recommend timed intercourse, ovulation tracking and daily Truvada with condoms the rest of the time. Most of the couples who come to our program are selected out for their motivation to complete this regimen. If there was ongoing risk (viral load detectable or inconsistent condom use) we would re-evaluate the use of Truvada after pregnancy is achieved. We are fairly conservative about risk anyway. There is another group of couples who do not select for this type of program and we'd probably differentiate for prescribing PrEP."

- "We have only initiated it among pregnant women four times. Very few of the couples I see use condoms. We prescribe PrEP during pregnancy because of ongoing risk. We really work to engage the man, make sure he is on treatment, get monthly viral loads, much of the attention is on her and the PrEP but even more is on the HIV-positive male partner's treatment and engagement in care. We have our first PrEPception case and he is actually not undetectable because of being on an inappropriate regimen through a community clinic. We are working on his regimen and getting him undetectable and have also prescribed her PrEP."

- "We focus strongly on counseling and I see the couples personally. We counsel them on avoiding risk, but usually see them once they are already pregnant. I have offered PrEP to several HIV-negative female/HIV-positive male couples but none have elected to take PrEP. I also try to engage the male partner and talk about protecting their partner and child. So far we have had success in avoiding infection in the women and the babies."

- "In the UK we use very little PrEP. Health care is free. For discordant couples with an HIV-positive male and HIV-negative female, sperm washing is available but not covered under the national health care. The couples must afford this themselves. For most couples, when the man's viral load is undetectable, they are attempting natural conception with timed intercourse. We have not had any transmissions, yet. No PEP, either. Most of us in the UK believe the Swiss Statement. But we do not know how much we can believe what our patients tell us."

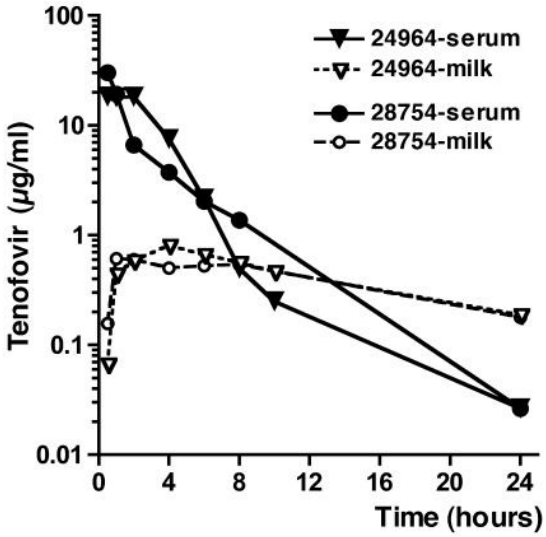
- "PrEP is more cost-effective in Australia even with the IUI government subsidy. We will probably not offer IUI anymore. It will just be PrEP or IVF-ICSI for those with fertility issues."

When prescribing PrEP what kind of HIV testing do you do during pregnancy?

- "Depending on the sexual activity of the couple it may be monthly viral loads for the women and we are reasonably aggressive with testing during this high risk period."

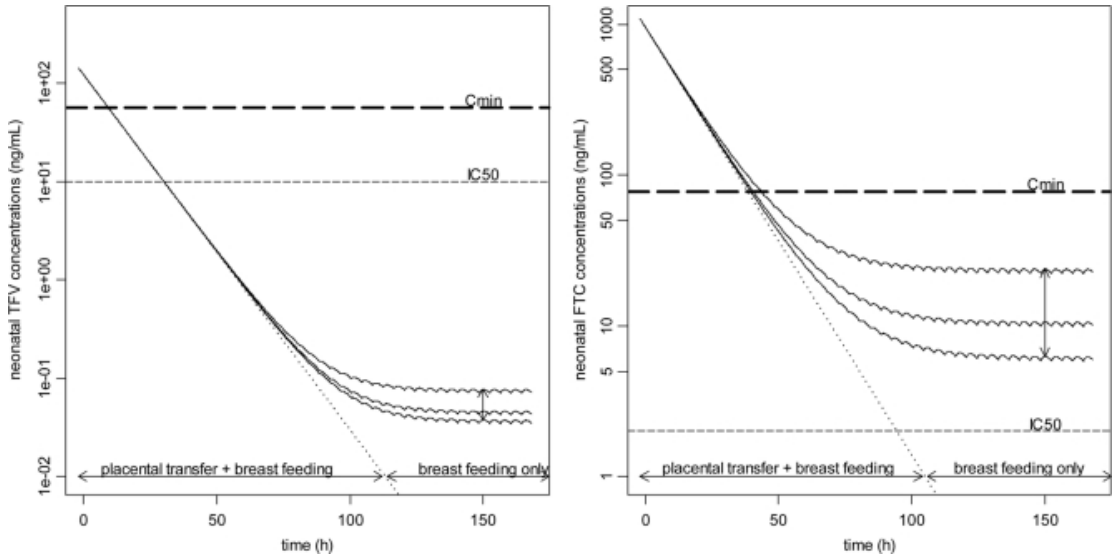
PrEP and breastfeeding: What do we know?

- Women at greatest risk for HIV are in their childbearing years: exposed to both HIV-1 infection & pregnancy.
- Breastfeeding is closely tied to infant survival in sub-Saharan Africa.
- No published data on infant safety with TDF or FTC PrEP exposure through breastfeeding.
- Experience with TDF and pregnancy outside of clinical trials has been among HIV-1 infected women for PMTCT & maternal health.
- The US Perinatal HIV guidelines recommend against breastfeeding.
- In sub-Saharan Africa WHO recommendations: Exclusive breastfeeding for 6 months, then continue breastfeeding for 1 year .
- Early breastfeeding cessation is associated with increased infant mortality and morbidity.
- Tenofovir crosses through to breast milk in low concentrations.



Concentration of TDF in serum and breast milk following a single sub-cutaneous dose of 30mg of TDF/kg body weight (Two Rh macaques)
Koen K., et al. Antimicrob Agents Chemother. 2005; May.

Administered one tablet of NVP (200 mg) plus two tablets of TDF (300 mg)-FTC (200 mg) at the start of labor and one TDF-FTC daily tablet for 7 days postpartum.



5 HIV-1 infected women in Cote d'Ivoire, NVP & TDF/FTC at labor onset, one tablet TDF/FTC daily 7/7

(ANRS 12109 TEmAA Study, Step 2 Benaboud S., Antimicrobial Agents 2011)

PrEP and breastfeeding: What do we need to know?

- Infants exposed to TDF in-utero have been followed up one year of infancy possible extrapolation of safety in pregnancy to breastfeeding (see pregnancy section above).
- The use of PrEP during breastfeeding still begs for more data
- Tenofovir crosses through to the breast milk but appears in suboptimal levels, which causes a concern of TDF resistance in the exposed infant in the case of incident HIV during breastfeeding. However, the levels may also be so low that there is less risk of adverse outcomes for the infant. The amount of these ARVs in breast milk is so small it may be safe for women to breastfeed. This is based on limited data in women in addition to monkey data.
- We do not have data from infants who have been breastfeed while the mothers have taken tenofovir.

PrEP and breastfeeding: Discussion

- Suggestion to find these data from monoinfected high viral load HepB infected pregnant women. In Australia about ¼ of these patients are taking tenofovir to reduce perinatal transmission. There may be sufficient numbers from this cohort. This is also standard of care in the UK. This cohort is recommended to breastfeed.

- "For HepB we recommend tenofovir as we believe the concentration in breast milk is not harmful, in spite of the product information."

- "In Africa, most of the women are followed for six weeks following delivery and this post partum period is also a risky period for the mother to acquire HIV. We should continue PrEP after delivery and we do not want to stop African women from breastfeeding. "

- With truvada, babies are not just exposed to tenofovir but also emtricitabine. We do not have data on emtricitabine.

- It would be beneficial to have data on children exposed to ARVs through breast milk. Do they have renal abnormalities or bone density issues?

- What about Malawi B+ rollout? Will this large-scale up of mothers taking ARVs provide additional data points to inform this conversation?

- "One thing we have learned from this conference is the importance of adherence. So I would have a discussion with her. If she is already on PrEP, one of the key questions is was she taking the medication and her being very honest about whether she was taking the pills at the time of the exposure. Your clinical recommendation will change if she has been missing doses vs taking the PrEP daily."

- "Even low literacy patients can appreciate these variables and appreciate the subtleties enough to make a decision that works for them. Studies show that the provider opinion influences the patient decision-making."

There were no recommendations for regimens or protocols from this group; no one has implemented PrEP during breastfeeding in clinical practice.

PrEP Implementation – slides by Erika Aaron

- Billing Code V107: exposure to an infectious disease including HIV
- Report HIV-negative women to Antiretroviral Pregnancy Registry
- HIV clinic culture change from front desk to provider room
- EMR template
- PrEP protocal
  Use CDC interim guidelines as a guide

- Medication Access – Medicaid has paid for PrEP but Medicaid differs by state
- Truvada.com for MAP (Medication Assistance Program)
- PrEP is delivered as part of a compreshensive HIV prevention package:
  Condom use
  Behavioral intervention (CDC-DEBI)
  Positive partner on ART, screened/treated for STDs
  Screening and treating patient for STDs
  Reproductive health counseling, pregnancy and breastfeeding counseling
- How to make PrEP welcome from front desk to office visit; retraining not just providers but also support staff to be aware and open to serving HIV-negative persons and partners of HIV-positive individuals.

What are the gaps in terms of funding and tools that need to be developed?

- Regarding insurance coverage, if you call and ask "do you cover PrEP?" they may say no. However, when providers bill insurance it is being covered. Is Truvada on the insurance formulary? If so, they cover it because it is now FDA approved.

- Medicaid in some places has put restrictions as a cost control measure that HIV status must be documented and ARVs are only covered for HIV-positive individuals. However, better to assume they cover it and try and if they do not then go to the Gilead MAP plan. If insurance denies the claim, show Gilead the proof of denial and Gilead will give automatic coverage.

- Adult HIV providers think they do not want to pay attention to PrEP as it is a whole other practice. Or just not thinking about the HIV-positive men and their female partners. Very important to get providers of HIV-positive men in the conversation. Once they join, they get excited. No one is talking to the HIV-positive men about whether they want to have kids. We have created posters and put them up in the lobby depicting men holding children that say "Do you want to have kids? Let's talk about it."

- BAPAC (Bay Area Perinatal AIDS Center) has launched a PRO Men (Positive Reproductive Outcomes for HIV+ Men) initiative at SFGH's Ward 86 HIV clinic. A 9-minute video "HIV+ Men: Healthy sex lives, Healthy Families", 2 patient brochures and a provider algorithm are available at: http://hiv.ucsf.edu/care/perinatal/pro_men.html

- Ask at the first visit and get a decent sexual history. Do you have sex with men, women or both? Do you want to have children? Repeat this conversation often.

- In Australia, we are implementing an "annual assessment of reproductive intent for men and women" because circumstances change and if you ask at the beginning the answer may have changed over time. Otherwise it is easy to go two or three years and forget to ask these questions.

- Standard of care suggests Prevention with Positives is an incredibly important program. I suggest we ask at every visit what is going on for the patient sexually. This does not always have to be the physician. In our clinic we had physicians who just could just not ask about sex. So we identified members of the health care team who would ask at each visit in a real non-judgmental way. "Who do you have sex with? How is it going? Are you having any issues?"

- Just asking folks about their reproductive desires normalizes these desires and opens the door for them to come back to talk with us. We talk about condoms so much that it conveys the message there is no option for having children.

- We have a script in Epic about sexual health and family planning. People can implement these scripts if they have electronic medical records.

- We need patient materials in additional languages such as Spanish.

What successes have you had with PrEP implementation?

- Building a relationship with an obstetrician to provide PrEP to a woman. It turned out to be really fun for us to work together and the Ob did the prescribing because the woman was his patient. In other situations we have had to find interesting sources to find the PrEP and the prescriber. I've done this about 5 times and it is fun to work with these couples.

- We are implementing PrEP education at the HIV testing site. It is a cultural change to go from a prevention message of only condoms to include PrEP in the conversation.

Patient and Provider PrEP Resources

Project Prepare Website: www.projectprepare.net
CDC: 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
Is PrEP right for me? A primer for women:
http://hiv.ucsf.edu/care/perinatal/resources.html
The Well Project:
http://www.thewellproject.org/en_US/Treatment_and_Trials/Things_to_Consider/PrEP_for_Women.jsp

PRO Men (Positive Reproductive Outcomes for HIV+ Men), a BAPAC initiative based at SFGH's Ward 86 HIV Clinic, videos & patient + provider resources:
http://hiv.ucsf.edu/care/perinatal/pro_men.html

Gilead MAP (Medication Assistance Program):
http://start.truvada.com/Content/pdf/Medication_Assistance_Program.pdf

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