IATT Webinar: Pregnancy and PrEP
August 11, 2016

A total of 76 participants from Jamaica, Zimbabwe, South Africa, Uganda, Malawi, Lesotho, Sudan, Panama and many other countries attended the IATT webinar on August 11, 2016 to learn about the use of pre-exposure prophylaxis (PrEP) during pregnancy. Based on available evidence, the benefits of providing PrEP during for women at high risk of HIV infection seem to outweigh the risks, as it presents an opportunity to reduce the risk of HIV transmission and keep people healthier. More in-depth and nuanced research is needed on adherence, safety, and incorporating PrEP as part of a combination prevention strategy. Involving community members in these discussions and providing clear, consistent and community-friendly messages about PrEP was also recommended to ensure women understand that PrEP is an option, not the option. The recording of the webinar can be found here.

Main Discussion Points from Presentations

1. Efficacy & Eligibility of HIV PrEP: Considerations for Pregnant Women

   Dr. Nelly Rwamba Mugo (Kenya Medical Research Institute (KEMRI), University of Washington-ICRC, Department of Global Health, Partners in Health Research and Development (PHRD)-Thika). Dr. Heather Watts, Office of the Global AIDS Coordinator (OGAC) presented the slides on behalf of Dr. Mugo.

   - Randomized trials, notably Partners PrEP study in Kenya and Uganda of 5,000 serodiscordant[1] couples (women living with HIV and women with partners living with HIV) demonstrated 75% efficacy for tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) and 67% efficacy for TDF alone.
   - TDF2 trial in Botswana with heterosexual couples demonstrated 62% efficacy.
   - Some trials have not shown efficacy, namely VOICE and Fem Prep trial, due to poor adherence.
   - As adherence increases so does the efficacy for HIV prevention.
   - Open-label studies may demonstrate higher rates of efficacy because people are sure they are receiving active medication (as opposed to clinical trials with placebos) and are more likely to adhere to the regimen.
   - Partners Demonstration Project presented at IAS 2016, only 4 individuals seroconverted, none of whom were on PrEP, compared with 83 infections expected in a counterfactual simulation model. Resulted in 95% reduction in HIV incidence.
   - PrEP is not necessarily a lifetime medicine, it is "for seasons of risk,"
     - Target young women during the high risk portion of their life, they don't have to continue PrEP forever if they eventually enter into a monogamous relationship with someone who has tested negative, as opposed to ART which is often lifelong medication. Or if they have an HIV-positive partner who is willing to start on ART, they can take PrEP until VL suppression is achieved in their partner.
   - Risk of HIV acquisition during pregnancy and lactation is quite high
     - Across many studies in Africa, 4.7 per hundred person-years among pregnant women, and 2.9 during breastfeeding
     - Above the 3% threshold in the current WHO guidelines depending on location and population
     - However, many of these studies pre-date scale-up of lifelong ART
   - Risk of transmission during pregnancy due to high viral load and lack of maternal antibodies
     - Risk ranges from 10-30% during pregnancy, but the risk can be lowered to 2-5% with early initiation of ART once someone tests positive and seeks treatment.
     - Issue is that many clinics are not consistently conducting follow up tests for pregnant or lactating women, so peripartum transmission risk remains as high as 18%
     - 26% transmission risk during breastfeeding due to seroconversion.
     - Transmission risk could be mitigated if infections recognized earlier but prevention even better.

[1] Serodiscordant can also be referred to as serodifferent.

- 2015 WHO Guidelines on PrEP recommend that oral PrEP containing TDF should be offered as **an additional prevention choice for people at substantial risk of HIV infection** (incidence >3 100-person years in absence of PrEP) as part of the combination prevention approach including condoms and voluntary male circumcision.
    - Pregnant women at substantial risk in Southern and Eastern Africa where HIV exists in endemic proportions, and in serodiscordant couples in which infected person not on treatment and without consistent condom use
    - In concentrated epidemics, may include sub-populations at high risk including female sex workers, fishing communities, partners of truck drivers
- Partners Demonstration Project showed the 88% of HIV uninfected pregnant women chose to continue to take PrEP. This is important considering that 40% of pregnancies are unplanned and may occur while people are on treatment.
- Serodiscordant couples want to conceive while minimizing risk of infection
- Need for enhanced methods of HIV protection both in peri-conception and in pregnancy, need to examine and balance risks and benefits in determining whether to administer PrEP to pregnant women.
    - We have improved PMTCT and antenatal care, but PrEP during pregnancy needs to be safe, cost-effective, and adhered to.
    - Risk of giving start of the art treatment to pregnant women and risk of not giving interventions
    - PrEP is safe and cost-effective in pregnant women and potentially important tool for EMTCT, but must put in place **methods to ensure adherence** to minimize risk infection nor resistance develop.

2. Review: **Safety of Tenofovir PrEP in Pregnant and Breastfeeding HIV-Uninfected Women and Their Infants,** Lynne M. Mofenson, M.D. Elizabeth Glaser Pediatric AIDS Foundation

Discussion on safety considerations for TDF-based PrEP used data available from three groups of women:

- HIV-Infected Women receiving TDF-based ART
- HIV Uninfected Pregnant Women with Hepatitis B mono therapy who received TDF alone and
- PrEP studies in which HIV-uninfected woman became pregnant while on PrEP

Overall TDF in Pregnancy

- TDF used in the third trimester by women with HBV infection is recommended and allowed by US, Europe, UK, WHO guidelines. WHO grade as low level of evidence.

Systematic Review of TDF in HIV Infected Pregnant Women (28 papers reviewed [Dr. Mofenson notes further updates including several new papers will be available soon]; outcomes inconsistently reported)

a. Pharmacokinetics
    - Standard doses of TDF appear to be safe during pregnancy and breastfeeding, amount adjusted for body weight
    - TDF concentrates in amniotic fluid, strong transplacental passage with levels near or higher than maternal levels. Infant definitely exposed to TDF in utero,
    - TFV found in breastmilk, but studies show very minimal penetration into milk and unmeasurable levels in infant, with 0.02-0.03% exposure to the drug

b. Comparative studies of Pregnancy Outcome and Infant Growth
    i. Overall with only a few exceptions (PROMISE study), birth defects, low birthweight, pre term birth, neonatal death, birth, length and head circumference and z-scores, and growth age rates show no significant difference regardless of TDF compared with any other treatment in HIV infection, HBV mono-infection and PrEP studies.
    ii. Studies on maternal adverse events showed no difference between TDF and AZT/sdNVP.

iii. Bone mineral density can decrease in HIV infected women taking TDF, but in the PrEP studies in MSM, after an initial decrease, bone mineral density then stabilizes over time (not a continual decrease) and density usually reverts to normal levels when treatment is reversed.
iv. For detailed information on the specific outcomes across HBV, ART and PrEP studies see presentation.

Conclusions

- Significant exposure in utero as TDF found in amniotic fluid and cord blood.
- Safety data from TDF use is reassuring, but most data is **not related to HIV-uninfected women,** the population of interest. Most studies are conducted on HIV-positive women on ART, who already have higher maternal adverse effect outcomes than HIV-uninfected women, even in the ART era.
- For women living with HIV, TDF-based ART appears similar to other ART regimens in terms of maternal, pregnancy and infant growth outcomes.
- Potential for decrease in BMD among HIV infected women. With PrEP, BMD stabilizes over time and reverse when stopped
- Significantly overall lower adverse events observed in HIV uninfected women, with no differences observed between TDF and other drugs (lamividuine, 3TC, for HBV infection) or the control groups
- There is a need to continue research on TDF, **though currently based on research to date, the known benefits seem to outweigh the theoretical risks, especially for women at a high risk of HIV infection.** Always potential risk when taking a drug. However, these risks are not high enough to outweigh ability to prevent it.
- Continued surveillance on maternal and infant outcomes to continue to assess safety that current research suggests.

Community Perspectives, Teresia Otieno, ATHENA Network

- To assess communities' understanding of the concept of PrEP during pregnancy, engaged with community members through online consultations with young women. Treatment must be balanced with the full knowledge of risks in order for PrEP to empower HIV uninfected women. Important to involve sex workers, transgender women, and women who use drugs in the discussion about PrEP.
- Concerns expressed during the online consultation are highlighted below:
    - Women are concerned about the long term risks of PrEP and lifelong ART.
    - Reality is that PrEP is not usually available widely for all women at health facilities across all settings.
    - **Prevention should be comprehensive**. Need to integrate PrEP with other prevention efforts: pregnancy, safe sex practices, condoms, education and empowerment of young women. **For sero-discordant couples, PrEP should be an option, not *the* option.**
    - Desire to see more data and research on PrEP, especially if PrEP might reduce a woman's treatment options in the future.
    - Include key affected populations who stand to benefit the most from PrEP in discussions and decision-making
    - Biological difference between TDF use in men and women and long-term affect with prolonged use of PrEP
    - Truvada trials have not included pregnant women, so there is no knowledge of its side effects and effect on the unborn child.
    - Questions also raised on the ethics of conducting trials on pregnant women and eventual resistance to Truvada.
    - Combined with investment in other structural interventions (i.e. Condom use, empowerment, education, etc.) to ensure young women remain HIV negative.

Community Perspectives, Angelina Namiba, Salamander Trust

- Opportunities identified through the online consultation.
- Condom negotiation training, gender-based violence (GBV) reduction programmes, followed by PrEP as one part of the combination prevention effort.
- PrEP could provide peace of mind and better psychological health, but all women should be empowered to make their own choices about which prevention efforts they want.
- Need for more data on adolescents and young people.

- Using PrEP is a good opportunity to prevent vertical transmission, should be incorporated alongside treatment of STI's and provision of sexual reproductive health services,
- Requires investment in health systems strengthening and training of healthcare providers to be able to properly offer PrEP.
- Need to improve messaging about PrEP and pre-conception advice, because many communities don't have access to accurate scientific information.
- Quote from selected video clip, Winnie Ssanyu-SSeruma.

Q&A

1. Have there been any studies on adherence and why some women find it difficult?

There are a whole host of reasons, there were probably some women who enrolled into the trial (VOICE trial) for the benefits of the care and remuneration and less for the HIV prevention aspects. But, not knowing if they were on an active drug or a placebo, and therefore having less incentive to take the medication. In some cases, the TDF/FTC drugs looks like HIV treatment, and so some people would not want to carry those pills around which may imply their HIV status. Also, there were various levels of partner engagement can have an impact. These reasons must be explored as they may continue to have an impact on adherence. PEPFAR is looking at alternative packaging, co-packaging with contraceptives to make these drugs more acceptable, but it is multifactorial.

2. Why is the preference to have women living with HIV started on PrEP when we have moved to test and start? Is there research to show that PrEP is more effective than ART? What about the short v. long term effects and benefits?

The issue for serodiscordant couples (say the man is infected and the woman isn't), is to initiate treatment as early as possible to decrease transmission risk, but there will be a several month period while they're initiating treatment when they might still have a detectable viral load and be at risk for transmission. The reason for this is that before attaining viral suppression, there is still risk of HIV transmission. PrEP provides a bridge of protection to the HIV-uninfected partner and is used for a limited duration: approximately 6 months after ART initiation, or until a time the HIV-infected partner is prepared and initiates ART 6 months thereafter. Therefore, PrEP could provide immediate and continued protection for the woman, while the partner is getting on treatment and becoming suppressed. If one partner does not wish to start treatment, PrEP could be effective for the HIV-negative partner.

PrEP will only be for a limited duration of time and complements treatment for prevention. But we agree that the goal is to try and get to 90-90-90 targets and supress viral load, which would then obviate the need for the PrEP in the long run.

3. When I attended IAC 2016 in Durban and talked to market women, these women in urban South Africa, did not even know about ART for prevention (Cohen et al., 2011), much less pre-exposure prophylaxis! What are the solutions to this?

Lots more information needs to be getting out there about the benefits of: 1) knowing your HIV status; 2) getting on treatment early for maintaining health and reducing risk of transmission 3) options for prevention measures including condom use, PrEP, voluntary medical male circumcision, all of that. We need to do a better job with education everywhere.

4. Are there any plans for education for women about PrEP? In my experience as a community member there is no information.

There's a lot more that we need to do with education. We haven't done an extensive amount for PrEP, and we have a call from the community. Last year we conducted treatment literacy workshops. We also have a community based network in the UK, made up of about a hundred community based HIV organizations which is a forum where we update people on treatment, research, PrEP. We use Leaflets, booklets, Q&A's are in our

online forums in language understandable to communities to try and provide information, but we know that this doesn't always reach the people who might need this information.

5. Does PEPFAR have plans for treatment literacy communication in countries with policies in place to implement PrEP?

Through DREAMs, we are trying to facilitate information about PrEP in those countries that have it as policy and trying to expand where that will be. Through the Innovation Challenge Fund, several projects are slated for funding that aim to increase peer educators and community leader trainings for young women to become the knowledge points in their communities and have a multiplier effect. One of the key things is for all of our groups to coordinate, as we develop messages and documents, as we evaluate ways to share the information and make it widely available so people aren't having to reinvent the wheel in these different places.

6. Given that 22 million people still need ART, what is the balance between ART and PrEP?

Obviously that's a consideration everywhere and the balance between prevention versus treatment to prevent transmission and maintain health. We need to mobilize more resources, including donor resources and domestic resources in countries to respond to the epidemic, to step up with more treatment and prevention Each country in their setting is going to have to figure out their balance.

Treatment and prevention are two sides of the same coin, if we continue increasing the number of new infections at the current rate, we shall have real challenges accessing treatment resources. Preventing new infections, safeguards resources for treatment. The two should not be in competition, but complementary interventions towards the same goal. However, no HIV infected individual should ever be denied therapy; that stands as a priority.

7. The presentation compares clinical outcomes of different drug regimens with each other but does not compare these outcomes with those occurring in the general HIV-negative population; I think we need this type of information to evaluate the net benefits of providing PrEP to HIV-negative pregnant women. Is any information of this kind already available or does any of the studies presented include this type of information, and if so for what clinical indicators?

This is more shaded because HIV at risk population might be different than the general HIV uninfected population, they have different risk factors for things like preterm delivery so it's a little difficult to get this information. None of these studies compared to an HIV uninfected population in general.

However, if you compare rates of adverse pregnancy outcome in women with HIV infection to HIV-uninfected women with Hepatitis B mono-infection, the rates in in the HIV-uninfected women were very low. I don't think if you compared those to the general population they would be very different, because they were in the rates of 0-3%. While I don't have the data, if you look to the uninfected population, I don't think that there was an elevation in adverse outcomes in the uninfected group above and beyond that to non-pregnant populations.

WHO is pulling together the data to gain more clarity on this which was the impetus for the systematic review I presented. WHO is reviewing the evidence to develop a policy statement. The drug label says to start PrEP only if the benefits outweigh the risks and to stop if you're breastfeeding BUT that is for a population in resource-rich settings.

8. Is the approach to train peer educators to only talk about PrEP or to educate women about the options including access to ART?

The approach is always to do a broad prevention approach to educate women about condom use, to engage in safer sex practices, VMMC, partner testing, and treatment for partners or themselves if women are living with HIV. We have to always remember that PrEP should be part of a broader effort, and try to empower women to have control over their own health and make choices regarding their own bodies.

9. A challenge in utilization of PrEP is the knowledge and capacity of health care providers. How informed and comfortable are health care providers about PrEP in sub-Saharan Africa?

We still have a lot of work to do in that area. The WHO guidelines initially only addressed men who have sex with men, so we have a lot of work to do on the broader PrEP guidelines. We need to integrate PMTCT into the antenatal care setting, and provide treatment to women living with HIV when pregnant in these settings, including family planning, to educate providers to offer PrEP. We have a long way to go and many different groups are working on this.

10. What is the uptake of the WHO guidelines on PrEP for pregnant women within HIV National Strategic Plans, particularly within countries implementing DREAMS?

Kenya and South Africa have both approved PrEP in general. The issue of pregnant women remains to be worked out. We have to increase the use of PrEP in other county's national plans. That work is ongoing and pregnant women are a group that's still under discussion in South Africa. WHO is looking more in depth at this issue as shown by the commissioning of Lynne Mofenson's systematic review.

11. I think health care professionals have a vital role to play especially for people who may not have access to information from other sources, however they may not attend clinic appointments and that is an opportunity for education. It brings the point about peer mentors in clinics. It will be useful for science to also emphasise the importance of other forms of support together with medicine that makes a difference to the patient to promote the provision of wholesome care that complements medicine.

I totally agree, and from a PEPFAR perspective, when we're trying to look at HIV prevention in young women, we are not just looking at PREP and clinic-based interventions, but also GBV and gender education for both women and men, keep girls in school, a multifaceted approach. I agree that PrEP needs to be part of a broader package.

12. Given that girls 14-24 are at highest risk of incident infection, it seems that sexually active negative girls (and especially those who are pregnant) would be one of the groups who could most benefit from PrEP. However, many are concerned about bone mineral density in this young group and also about adherence. What are thoughts on this? Have any studies disaggregated by the younger age band? Any suggestions for messaging to HIV programs regarding advocating for PrEP in these young negative pregnant women as part of Prong 1 of PMTCT? There is a lot of hesitancy to offer PrEP among these young women for these and other reasons (often similar rationale to reasons for not offering FP to young women).

Yes, there are concerns about BMD but if you think back to the studies of MSM which looked at the bone mineral density, they show a mild decrease with initial TDF or TDF/FTC use that stabilizes while people are receiving PREP and when you stop it the BMD levels go back up. The Adolescent Trials Network (ATN) in the U.S. have done studies with adolescents MSM between ages of 15 and 24 which found the same thing. There is a decrease in BMD but when you stop the PrEP it goes back up. Once again the issue of risk v. benefit comes into play. If you have a mild decrease is that risk enough to be able to deny to a woman at high risk of HIV acquisition medication that could prevent HIV infection? There is always a risk when administering a drug. The important question to address is if the benefit outweighs the risk.

I think you clearly need to put into place measures that help people adhere regardless of age. Adherence is the key. While I agree that adolescents have more trouble with adherence compared to older people, that's not a reason to deny someone medicine if they are motivated to use the drug. In the ATN studies, the individuals who engaged in the highest risk behaviors were most adherent to PrEP. I think people will be different, but the challenges with adherence is not a reason to say that people can't be able to access it.

At this point, one clarification to make is that PEPFAR and the scientific advisory board are reviewing the data and developing recommendations about PrEP in pregnant women which will be released this fall. Currently, PEPFAR is not recommending PEPFAR funded programmes offer PrEP to pregnant women. WHO is organizing a consultation with experts in September 2016 to further address these questions. WHO currently does not consider PrEP should be stopped in pregnancy and BF if substantial HIV risk persists. Following the systematic

review and expert consultation, WHO will produce a policy brief on the use and safety of oral TDF containing PrEP in pregnant and breastfeeding women. Hopefully, these recommendations and discussions will be positive and help move the field along.