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▼ "IF ANYTHING IS SACRED THE HUMAN BODY IS SACRED." – WALT WHITMAN ▼

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AAB PREVENTION UPDATE

PrEP for HIV Prevention: Three MSM PrEP Trials at IAS 2015 Report on HIV Prevention, Adherence Issues and Intermittent PrEP Dosing Schedules

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The bi-annual International AIDS Society's (IAS) Conference on HIV Pathogenesis was held in Vancouver, Canada from July 19-22, 2015. There were a number of PrEP (Pre-Exposure Prophylaxis) presentations that continue to describe the use of PrEP in MSM.

The FDA has approved Truvada for both PrEP and HIV treatment. Currently, Truvada is the only FDA approved drug for PrEP. Truvada actually contains a combination of two HIV drugs in one pill, Viread and Emtriva, and is what is known as a fixed dose combination (FDC). Truvada for PrEP is dosed at one pill once per day. Condom use is also recommended by the Centers for Disease Control (CDC) while using PrEP.

Truvada is also used for HIV treatment in combination with other HIV antiretroviral (ARV) medications. Truvada plus a number of other HIV ARVs are necessary to treat people with HIV in order for the drugs to remain effective against HIV, thereby

preventing HIV drug resistance.

More and more PrEP issues are being studied and every year we learn more about the complicated scientific and behavioral issues around PrEP use. Initially, most PrEP studies were not conducted in the US or in MSM (Men who Have Sex with Men). This is changing rapidly and there is more US MSM data at every conference.

The first big MSM news came from the IPREX PrEP study that was presented at the July, 2014 International AIDS Conference held in Melbourne, Australia. IPREX is an MSM open label study (all participants receive Truvada) that included 1,603 people from the United States, Brazil, Peru, Ecuador, South Africa and Thailand. In the IPREX study which also included 70 transgender women, the efficacy of PrEP was 84% in people who took two to three doses per week and there were no HIV infections in people who took at least four does per week.

AT CROI (the Conference on Retroviruses and Opportunistic Infections held in Seattle, WA from February 23-26, 2015, there were two very important MSM PrEP studies that showed us that PrEP was highly effective in preventing HIV in MSM if they take their medication daily, that side effects were minimal, that HIV resistance is not an issue if people continued to be tested for HIV at regular intervals and that the number of sexual partners was not increased because of PrEP use.

Let's review the PrEP studies presented at CROI 2015. The PROUD Study was conducted in the United Kingdom MSM with a high risk of HIV infection. PROUD showed that daily oral PrEP administered at existing sexually transmitted disease clinics reduced the risk of HIV infection by 86%.

There were no surprise side effects in the PROUD

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study. Side effects were similar to those seen in other PrEP studies. Only three of the six participants who ended up being HIV positive during the study developed resistance, and had resistance only to Emtriva, one of the component parts of Truvada, and not to Viread, the other drug contained in Truvada.

Prior to enrolling in the study, participants self-reported that on average, they had 10 sexual partners within the previous 90 days, and that they had both condomless insertive and receptive sex. While there was no increase in the number of sexual partners or behavior differences between the two study arms, there was an increase in the number of participants who had high numbers of condomless sexual partners during the study. Researchers will need further data to ascertain whether this has clinical significance.

IPERGAY is the other important MSM PrEP study reported at CROI 2015. This study was conducted in six sites in France and one in Canada and looked at intermittent use of PrEP tied to sexual activity (event-driven dosing) rather than the once daily dose of Truvada. The purpose of this study was to determine if adherence which is closely tied to the effectiveness of Truvada for HIV prevention would be better if taken during periods of sexual activity (on demand), instead of the currently FDA recommended daily dosing. The cost-effectiveness of only using Truvada for PrEP for three days per week rather than daily was also an important study concern.

Most of the 400 IPERGAY high risk MSM study participants took either two Truvada pills or a placebo which is a pill containing no medication between two and 24 hours before having sex, one pill 24 hours after having sex and one pill 48 hours after the last pre-sex dose, instead of one pill once a day. Truvada dosing continued as long as sex continued. The overall study data suggests that participants were taking Truvada an average of three to four days per week. But some study participants who were more sexually active were actually taking Truvada daily.

Consistent with the PROUD study, Truvada was much more effective than placebo, reducing the risk of HIV infection by 86%. Again, side effects were again similar to those seen in other PrEP studies and those in the placebo arm of this study. Most side effects were mild and consisted of mainly nausea, diarrhea and stomach pain. This number of sexual contacts (10) two months prior to the study remained the same throughout the study with no increases.

The IPERGAY on demand dosing schedule was further investigated in a study presented at IAS 2015. The CDC PrEP Guidelines still recommend daily PrEP dosing and condom use. Although both the PROUD and IPERGAY studies have amended their original study designs so that all participants are now receiving PrEP, both are still ongoing studies. Both studies have released only preliminary data. It will be months before we have a full data analysis of both studies.

Keeping these previous studies in mind, let's review the important PrEP study information that was reported at IAS 2015 that further increases our knowledge base about PrEP use in MSM. Now we know even more about PrEP for HIV prevention, adherence issues and intermittent PrEP dosing.

The PrEP DEMO Project Study is a demonstration project sponsored by the NIH which enrolled more than 500 MSM and transgender women from public clinics in Washington, DC, Miami and San Francisco. The average age of participants was 35, but 20% were younger than 25. White people comprised 48% of the group studied, while 35% were Latino, 7% were black and only 2% were transgender women.

This study followed participants for 12 months and offered Truvada to all (open label) for 48 weeks. Most study participants followed up with their visits throughout the study. Participants that reported anal receptive sex without a condom and those who knew about PrEP before the study had higher study retention rates. Approximately 90% of participants

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reported good to excellent adherence at every visit. Owning or renting your own home and reporting two or more condomless anal sex partners in the preceding three months doubled the amount of people who were adherent. The number of condomless receptive sex acts did not change during the study.

Participants continued to contract sexually transmitted infections (STIs) during the study, indicating that they were sexually active. But only two people became HIV infected during the study. Both of the two seroconversions (HIV infections) occurred because these participants were not taking their PrEP medication as directed. No serious side effects or the bone breaks that occurred during the study were attributed to PrEP use. The three cases of elevated kidney function tests (creatinine levels) which are related to PrEP use were resolved without stopping PrEP.

PrEP DEMO Project researchers concluded that the low incidence of HIV infection despite the high incidence of STIs provides strong support for scaling up PrEP use in such public clinic settings. Quarterly STI testing was also recommended. But the underrepresentation of blacks and transgender people was also cited by the researchers as a study limitation.

There were a number of presentations resulting from the ADAPT Study or HPTN 067, from the NIH's HIV Prevention Trials Network. This study looked at the feasibility, acceptability, adherence and different dosing schedules of MSM in Harlem, NYC and in Bangkok, Thailand.

In the Harlem cohort, 179 people participated in the trial. Of that group, 98% were MSM, 2% were transgender women, 70% were black, 25% were Latino and 69% were unemployed. PrEP was given in a number over an extended period in three different dosing regimens. Participants were given PrEP by study personnel for the first six weeks and self-administered PrEP for 24 weeks. Thereafter, they were off PrEP for four weeks and had a final study visit.

There were three PrEP dosing groups. The first group was supposed to take PrEP on a daily basis (daily dosing). The second group took PrEP twice weekly and after sex acts (time driven dosing). The third group took PrEP before and after sex acts (event driven dosing). No more than two doses were taken daily or more than seven doses weekly.

Only one person in 179 became HIV infected (seroconverted) during the study. He was found to have no detectable Truvada in his system which means he was non-adherent (not taking his PrEP medication). The side effects were a bit higher in the daily dose group, but were not significantly greater than in the two intermittent dosing groups.

Daily dosing provided the best PrEP coverage for pre and post sex acts and showed the best adherence. In the time and event driven groups, there was incomplete coverage of sex act dosing, specifically related to post-sex dosing.

What researchers learned about the feasibility and acceptability of PrEP use in MSM is extremely important to understanding PrEP adherence in this population. The Harlem participants believe PrEP is a valuable new tool for HIV prevention. But many participants experienced or self-perceived that their sex partners believed they were HIV positive or were exceptionally promiscuous. Related stigma issues resulted in a limited willingness to disclose PrEP use to their sexual partners and limited their ability to adhere to post-sex PrEP dosing.

The results of 38 MSM in Bangkok, Thailand are also very illuminating. The following items all facilitated PrEP adherence:

- Understanding their regimens
- Being assigned to a regimen that fit their lifestyle
- Having reminder tools
- Disclosing PrEP use to family, friends and sexual partners
- Keeping their pills in a visible spot
- Understanding their own risk
- Believing in PrEP

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Barriers to adherence were as follows:

- Dislike of taking pills
- Self-perceived as having no risk
- Non-supportive friends and family
- No privacy
- Fear of long-term impact and side effects
- Sickness unrelated to PrEP use
- Intoxication
- Lack of 100% trust in the effectiveness of PrEP

People in the daily dosing arm found it easier to remember to take PrEP by linking it to a daily activity. People in the time driven and event driven arms liked the idea of taking fewer pills and taking PrEP related to sex acts. The event driven group also liked the idea of being able to exercise control over planning for sex.

The PrEP news continues to be very exciting. The more data we have, the better we understand feasibility issues and adherence patterns in MSM. We know that PrEP is highly effective in preventing HIV when people actually take their medication. We now have more information on what PrEP dosing strategies and interventions are the most effective. We also have a better understanding of PrEP adherence issues. Participant preference will probably be the best driver of adherence. It makes perfect sense that what works best for each individual will be the best way to prevent HIV infection for that individual.

We are left with the questions of whether different MSM communities will actually initiate PrEP and how PrEP will be used in real life situations, what support will be necessary to help people take their PrEP medications and how to overcome stigma related issues. Interventions, including PrEP information dissemination to the general community as well as targeted community education and adherence support are obviously paramount issues to be addressed in the African-American MSM community. ▼

For more PrEP information, please see the following links:

<http://www.cdc.gov/hiv/prevention/research/prep/>

<http://www.avac.org/event/croi-2015>

http://www.aidsactionbaltimore.org/?page_id=569

