

HPTN Community Working Group
2017 IAS Debrief

Drs. Mike Cohen and Wafaa El-Sadr provided a forum for the HPTN CWG to hear more about the HPTN activity at the International AIDS Society meeting in Paris. They invited comments and questions following their brief updates.

They framed the report back according to the HPTN mission:

- Integrated strategies that include a group of biological interventions
- PrEP

In terms of treatment as prevention, HPTN takes particular pride in the contribution of HPTN 052 that helped to endorse immediate and universal ART, and the 90-90-90 campaign. But 052 focused on heterosexual couples. Additional data was presented at IAS. These results suggest that the TaSP approach is working and that we are on the right track. In addition to the two studies highlighted below, there were several abstracts about detection and treatment of acute infection to improve immune function and reduce latent cell infection.

The Australian experience with MSM

Bavinton et al in a study led by Andrew Grulich. Enrollment in an observational study of MSM in Australia, Thailand and Brazil (opposites attract study of discordant MSM couples). A small number of couple years (210) but 16, 000 CAI. No linked transmission events were observed.

Swaziland Success

The realization of treatment as prevention was measured in a surveillance study reported by Nkambule from ICAP. 10,934 people studied, 3000 HIV positive individuals which is a prevalence of 27%. But among HIV positive people, the viral load suppression attributed to ART was >70% and HIV incidence was reduced in half from a study in 2011.

Biological Prevention Strategies. ART PrEP was a dominant theme. The combination of TDF-FTC was studied in the Proud study. The Proud study (White et al) in the UK compared early vs deferred antiviral with a LARGE (>90% difference) in HIV incidence ascribed to PrEP. Access to PrEP in the deferred group led to the anticipated decrease in HIV, even greater than before as the deferred group knew the idea worked. STD rates did not change implying continued risk. The group offered immediate ART had continued benefit of HV prevention.

Antoni provided follow up on the IPERGAY study. IPERGAY was an randomized control trial of on demand PrEP. In the follow up, even men who used pills less frequently each month compared to those who used pills on demand, experienced benefit.

STIs. STIs are attracting greater interest in the HIV field again because they:

- i) Do not overwhelm TDF FTC
- ii) Continue at a high rate, and are likely increased by prep
- iii) Are not effected by BC
- iv) Facilitate transmission as well established

New PrEP Agents. The HPTN is charged with studying new PrEP agents like cabotegravir. Cabotegravir is a new integrase inhibitor that is injectable. It is intended to be used for treatment and prevention. Dr.

Raphael Landovitz, chair of HPTN 077, reported on 199 Men and women who took a 600 mg single injection every 8 weeks. Results showed that cabotegravir is well tolerated and leads to drug level anticipated to prevent HIV infection. The study was done primarily to better understand the pharmacology in women. This dose will be used in a randomized control trial to prevent HIV acquisition in women in sub-Saharan Africa (HPTN 084). HPTN 084 study has been approved by all regulatory agencies.

What about “the tail”. The study design of the RCTs includes a prevention package after the last injection. This package includes TDF-FTC. This might be especially important if HIV is acquired while cabotegravir levels are dwindling,

Markowitz presented the ability of a new drug EFDA to prevent. Weekly ral MK 5891 was compared to placebo in macaques challenged with SHIV over 12 weeks. All placebo animals became infected compared to 0 who received MK 5891.

Topical microbicide agents. Dr. Zeda Rosenberg, developer of dapivirine rings at IPM, presented combined analysis of two trial of the rings already published. Overall reduction of HIV acquisition was 27%. As noted in earlier reports, older women (>21 years) had a greater degree of protection than younger women, perhaps as much as 40-50% protection in this group. A recent concern is that the bacteria that live in the vagina could compromise the benefits of topical antiretrovirals through metabolism. A publication in Science Magazine and an abstract presented at IAS reported that tenofovir is susceptible to metabolism by vaginal bacteria, implying that such metabolism could compromise benefit. Dr. Sharon Hillier examined dapivirine in genital and blood plasma concentrations and saw no effect of flora that causes BV concluding that metabolism of drug reported that this drug, dapivirine, is not susceptible to metabolism.

Broadly neutralizing antibodies (BnABS). There were several presentations related to the biology of BnABS. Dr. Nyaradzo Mgodzi reported on the AMP study in a satellite session. HPTN 081/085 is a placebo controlled trial to determine if an infusion of a broad neutralizing antibody, VRC01, prevents HIV acquisition. More than 1500 men and 1000 women have been enrolled in the study to date. As with other monoclonal antibodies, all adverse reactions require a great deal of attention, and is a central feature of the study.

Integrated Approaches. Treatment as Prevention, TasP, works but has not been shown yet at a population level such as a country or a city, meaning we do not yet know what the impact would be using ART for prevention and controlling the epidemic for an entire population.

PHIA surveys. ICAP has supported ongoing surveys known as Population Based HIV Impact Assessments (PHIA) done surveys in 4-5 countries to date, with plans to do extend into another 10 or more countries. Results from Swaziland’s survey from a period of a five-year period were presented. During this period, the country scaled scaled-up testing and other prevention methods and were able to decrease new infections and double viral suppression at population level. Gaps in these measures were still identified. They included issues around how to reach men for testing and treatment as well as how to reach younger people.

HPTN 071: The PopART Study. PopART is a very large scale study of 1.2 million people in communities within Zambia and South Africa. The study design is one of combination prevention centered on finding everyone who is HIV-positive, getting them promptly on treatment and keeping them on

treatment. It includes also a package of other prevention methods such as counseling, voluntary male circumcision for HIV negative men, condoms, assistance with the navigation of services, and linkage to care. The trial is telling important things about how to try to reach populations that need to be reached if we're trying to have a public health impact and control HIV epidemic.

- *Adolescents.* The PopART team developed a sub component of the study for adolescents called "PopART for Youth" or the PARTY study. In this study the team developed and used screening tools that asked four basic questions to identify adolescents at risk for HIV. If yes was answered to one or more of the questions, the youth was enrolled into the study. The questions asked of
 - recent hospitalizations
 - any skin problems
 - any poor health in the last 3 months
 - the death of one or both natural parents.

The study team asked these questions to more than 18000 youth between 10-14 years old. Approximately 2000 youth were screened with a high HIV prevalence of 2.4 found. The study found that the screening tool was effective in identifying a subset of youth who agreed to be tested and had high risk of being HIV-positive which is encouraging because this group needs to be engaged.

- *Reaching Men.* The PopART team looked at 4 communities in Zambia where the study is being done. They offered adults the choice of taking an HIV self-test or doing a traditional rapid test (finger prick). The team found that with the self-test more men were able to get tested versus with traditional rapid test. This information is helpful in reaching men which is challenging population. The team learned that HIV self-testing was preferred because it offered privacy, a feeling of ownership, and can be done in the privacy of homes with no interaction with health facilities, clinics, or health care provider. The PopART team is also looking to learn how to find as many people as possible. It has been found that there is better uptake and more successful visits with men when outreach is done in the late afternoon or on Saturdays.

HPTN 075 – MSM in Sub-Saharan Africa. There has been lots of work done on MSM in the US, Latin America, and elsewhere in terms of assessing risk of HIV infection. However, few studies have focused on MSM in Africa. HPTN 075 is a vanguard preparatory study to see if it is not only feasible to engage, enroll, recruit, and follow MSM in African countries but whether it can be done safely without risk of stigma, violence, and discrimination. The study was successful in fully enrolling 599 MSM from 3 African countries - Kenya, Malawi, South Africa. It found that 30% of the MSM tested (about 1/3 of participants) were HIV positive. This shows that these men have not benefited from a lot of our interventions to prevent HIV. Of those found to be HIV-positive, 2/3 were unaware of their HIV infection. Study results showed that HIV is a major challenge for MSM in the region who are often unaware of their HIV status and who do not get tested frequently enough. But 075 also showed that it is feasible to enroll and retain such men in research. This opens opportunity to develop studies to recruit MSM safely for other prevention studies in region.

HPTN 074- - People Who Inject Drugs, PWID. Early data was presented from HPTN 074 – a study of people who inject drugs in the Ukraine, Vietnam, and Indonesia. The study was designed to recruit PWID and their primary partner. It was found that drug use and injection practice differed substantially from country to country. In Vietnam heroine was almost exclusively the injection drug of use while in Indonesia many reported using both heroine and other opioids. However, in the Ukraine there were higher reports of a lot of homemade opioids and amphetamines. Risk of injection drug users also varied

substantially by country. In the Ukraine, about 40% of negative partners reported using needles after someone else had used it which is a high risk injection. Approximately 33% reported high risk injection in the Ukraine. Injection practices appeared safer in Vietnam where only 18% reported high risk injection. This early data may help us to design clearer prevention intervention in this population in these countries tailored towards identified risk behaviors from this study.

HPTN 073 – Black Men who have Sex with Men. HPTN 073 recruited BMSM from three cities in the US. The study enrolled 225 HIV-negative black MSM of which about 80% accepted PrEP. When looking at data to see what are the characteristics of those most likely to initiate and start PrEP, those were employed or reported having enough money for rent and food were more likely to start PrEP. High adherence was also associated with being employed and having higher education. This tells us if we are to try to overcome barriers to PrEP initiation and adherence with BMSM in the US, we will have to look at both behavioral and structural issues that stand in the way to taking PrEP. This includes overcoming disadvantages to education.

Questions

Q1. Please provide more information from the opening plenary regarding “differentiated service delivery”.

Dr. El-Sadr presented during the opening plenary largely focusing on how to tailor services for specific populations or “differentiated service delivery” or DSD. There is a need to scale up treatment and prevention services very fast and at a population level in order to control the HIV epidemic. Some segments of the population need specific types of services and for this reason they are sometimes left behind. Therefore, unless we begin to think about how to tailor our services to them they will continue to be left behind.

For examples, there is recognition that youth and young people will need tailored services. They need specific ways to reach and engage them. Generally key populations will have their own specific needs as well. These include PWID, MSM, and sex workers. They have special needs because of the stigma they face, discrimination, and bad treatment they receive sometimes from healthcare providers who are insensitive to their needs. There are various models of DSD that place the needs of people living with HIV (PLHIV) at its core. These models tailor delivery methods around the needs and preferences of specific groups or populations.

One model of DSD that has been used in several sub-Saharan African countries is Community ART Groups (CAGs). CAGs are formed groups of PLHIV who live near each other. Essentially one person from the group goes to the clinic and picks up the medication for themselves and all other members of the group then comes back and distributes it to the other members. Then three months later another member will go to the clinic and pick up medicine for the group. These are new novel ideas trying to push pass doing things simply out of convenience for the health services but trying to think about how to do things in ways that are more convenient for the recipients of the service.

Q2: What are the names of any topical HIV prevention agents either available or being studied?

Antiretroviral drugs currently in development are:

Systemic:

- Pills - The only approved pill for HIV prevention is branded as Truvada which is emtricitabine and tenofovir disoproxil fumarate (TDF+FTC). This drug is approved for both the treatment and prevention of HIV. The same company who manufactures Truvada is also studying a new drug, F/TAF, which is a variation of tenofovir that is very much like Truvada. This drug is currently being tested in a clinical trial.
- Injections - The only one injection drug being developed and explored as an injectable is cabotegravir. It is within a class of drugs called integrase inhibitors. It is a milled nano-suspension that lasts a long time.
- Implant - There is no implant at this time, however, there are some drugs being considered for placement in an implant. Those include cabotegravir, T/TAF, MK5891 (Merck) that is an NRTI classed drug that has become attractive because it is very potent and lasts a very long time.

Topical

- Gel - Tenofovir was explored but not approved for this purpose
- Vaginal Ring - Dapivirine is the only drug that has gone forward to date in a vaginal ring. The manufacturers of dapivirine are currently seeking approval for the ring now.

Q3: Please restate the difference between active immunity and passive immunity.

Active Immunity is what we have all benefited from in 20th and 21st century. It is the discovery that we can take something in the arm that's called an antigen and the cells in the body (especially b-cells) see the foreign antigen and can react to it, and make antibodies. A good antigen can make antibodies at a high enough level that infections can be prevented for many years. The science of vaccinations: measles, mumps, rubella, polio – all of these are antigens that are put in the muscles, stimulating active immunity where cells of the bodies are committed for long periods of time to making these antibodies to help protect us from infection. Sometimes these concentrations wane so we receive boosters as with the three injections needed for Hepatitis B. The boosters remind the b-cells that they have to make the antibodies. Not all vaccines work 100% - some work 60% or 50%. In the HIV field, the ultimate goal is to make a vaccine that simulates active immunity to HIV. This has not been accomplished yet.

Passive immunity is another idea that if we think we know of an antibody that can prevent HIV infection why don't we prove the antibody can prevent HIV infection. We don't know how to make a vaccine but we know how to make the antibody. people are now making the antibodies in test tubes. We infuse the antibody by giving it into the tissue through subcutaneous injections. It only lasts for a few weeks but if you keep getting the infusions or subcutaneous injections every few weeks, it might be able to stimulate protection. If you see protection, #1 it would prove that antibodies can work. It would also stimulate the idea on how you might make a vaccine and this passive immunity might become a product. We've learned in doing these experiments how to make antibodies last six months or maybe even a year.

Q: With Truvada being approved for PrEP and you have different agents and approaches to see if we can find other ways to protect people from HIV infection, how can we really know if the science is proven if individuals are on PrEP.

Clinical trials are designed following one of two basic strategies - direct comparisons and placebo-controlled. Both are imperfect.

Strategy 1: Direct Comparison. An example of a direct comparison study is if you wanted to compare Truvada, which has already been found safe and effective for HIV prevention, against something else. In the case of HPTN 083 and HPTN 084, Truvada is being compared to cabotegravir injections. This study design is called “double-blind, double dummy”. This means that a person who is getting Truvada pills and an injection of saline (without knowing that they’re actually getting a Truvada pill) is being compared to someone getting an active injection of cabotegravir and placebo pill (without knowing that they’re getting an active injection). In this example there is a *direct comparison* between Truvada pill and injectable cabotegravir. The direct comparison model allows you to see if the injection has an advantage because you can see if people will or will not take pills.

- A comparison that is done to show that there is no difference between the two drugs is called a *non-inferiority* study. HPTN 083 is a non-inferiority study where we are looking to show that cabotegravir works just as well as Truvada in MSM and TGW.
- A comparison that is done to show that the new drug has an advantage over the existing drug is called a *superiority* study. HPTN 084 is a superiority study where we are arguing that injectable cabotegravir is superior, or more advantageous, to Truvada in women in sub-Saharan Africa.

Strategy 2: Placebo-Controlled. Direct comparisons become a problem when you have something, such as a new drug or prevention method, and have no idea if it works. In this setting you’d want to test a placebo versus the new method or active agent such as the VRC01 antibody which is being tested in HPTN 081/085 – The AMP Study. In these studies, a placebo is being compared to the active antibody.

A prevention package is offered to all participants of HIV prevention studies. Comprehensive prevention packages of evidence-based HIV-related recommendations will include things such as counseling on safer sex and condom use and the distribution of condoms. PrEP is not included in the prevention packages for direct comparison studies such as HPTN 083 and HPTN 084. However, PrEP is generally included in the prevention packages for placebo-controlled trials like the AMP study. This means that access to PrEP is available to those interested in taking PrEP while participating in the study.

The comparison must still be between the active agent and the placebo. PrEP is in background so when the setup the study, you also setup yourself up to measure how much PrEP people are using. Therefore, the analysis plan also includes PrEP. When you do your analysis plan you say “if for whatever reason 100% of people want to use PrEP, the experiment can no longer be done and you stop the experiment. so it is stopped. Mostly you’re looking at people who don’t to use PrEP or might want to use PrEP. Make it available and then measure if they’re using it or not when you analyze results. And when you measure it, you measure it in the blood because not everyone who says they’re taking prep is taking it and some people might get PrEP from other place. So nowadays in the background you have a biological measurement of Truvada in the blood for the analysis.

Q: Can you please provide an update on HPTN 084

- Approved by FDA and MCC of south Africa
- Funding has been secured
- Product is being prepared for shipment
- Sites have been selected
- Community stakeholder consultation planned for this week in Cape Town, South Africa (10-11 August 2017)
- Study specific training for sites will take place in October
- Study launch expected in the last quarter of 2017

Q: Can you provide any additional information on how the new drug that's being developed for an implant with greater potency and longer acting effects might be used for treatment.

This new drug will definitely be used for treatment. The challenge for treatment is to pair it with another product. Merck is looking for a partner whether it is a pill once a week or an implant. Right now the pill that Merck has lasts a week at very low dose. But they need a partner drug.

The prevention program would be in parallel to the treatment program. The prevention program could also be once a week prevention pill but in general decision-makers have been more excited about an implant. Merck has an implant development program in-house since this is what they do also for contraception/birth control. They could put two drugs in an implant and have a 2-drug implant prevention program at some point. But there is not an identified drug pairing at this time.

Melissa Turner thanked Drs. Cohen and Wafaa and all HPTN Community Working Group members for their participation on the call.