What means 'PrEP' and the chance for a substitute for an AIDS vaccine

A long-lasting injectable might improve pre-exposure prophylaxis for HIV infection

Some decades ago, advisors of graduate students, enrolled in master- and doctorate programs for public health had a difficult time. Students jumped on thesis topics about AIDS. Not all heterosexually orientated university staff enjoyed reading through details about the sexual behavior of those, being at risk to be infected with HIV. Somehow, the interest in AIDS among students seemed to have vanished. The headlines, including the word AIDS, on thesis manuscripts, became rare and were substituted by the term 'MSM". One had to learn that this means 'men having sex with men'.

From MSM and PrEP to those burdened "disproportionately"

Now, also MSM theses topics are infrequent. An interest in an additional related issue seems to be even less in focus. That is, that men having sex with men, also might have sex with females, including their wives. Somehow, it is worrying, that a 'quick and dirty' PubMed search, using the phrase 'bisexual MSM and wives' resulted in only eight hits. Five papers were listed from China, two from India, and one each for Pakistan and Peru (11 June 2020). The nowadays ongoing interest in what is called 'PrEP', might not only help the group of MSM but also females having sex with bisexual men. PrEP stands for the promising attempt of 'pre-exposure prophylaxis'. PrEP, therefore, might be of benefit, not only to MSM and the wives of bisexual men but generally for "populations that bear a disproportionate burden" of HIV infection (1).

Is HIV transmission interrupted by ART? – the 'HPTN 052' investigation

How to fight AIDS by PrEP has a history going along for some time (2). After antiviral therapy (ART), became common in the treatment of HIV infection, the first of such an agent was 'azidothymidine', the idea was favored, to protect people from HIV transmission by ART as well. After years of negotiations and planning the NIAID HIV Prevention Trial Network could be established. The network was supported by the National Institute of Allergy and Infectious Diseases /National Institute of Health (NIAID/NIH) in cooperation with a number of other initiatives and pharmaceutical companies. Finally, the efforts resulted in the HIV Prevention Trials Network (HPTN) 052. All in all, 13 sites in countries in Africa, Asia, and the American continent participated. The study allocated randomly 'serodiscordant' couples into two study arms. Serodiscordant means, that while one partner already was under treatment because of an HIV infection, the other one was HIV negative. One group consisted out of pairs, with one partner being treated **early** in the infection. The other group was couples of which one partner was under a **delayed** therapeutically scheme. Almost all couples (96%) were heterosexual. To define an 'early' and a 'delayed' arm of the trial, the conventual CD4 cell count was used. For the 'early' arm ART was offered at a CD4 cell count 'higher than when ART was recommended by the WHO for that particular country'. Those on the 'delayed' arm consisted out of couples where the HIV positive partner's CD4 cell count 'fell to the general standard of care', which finally was decided for the final trial 'to or below' 250 cells/mm^3. The trial was conducted for 42 months with an initial number of 893 partners in the 'early-' and 882 in the 'late' infected group.

The conclusion from 'HPTN 052'

After considering the 'drop-outs' for each group and those cases, in which transition took place with other partners than the original ones enrolled in the study, only one transmission took place for a pair in the 'early' therapy group, while 27 transmissions occurred in the 'delayed' ART group (3). The hazard ratio of the incidence rate of the 28 infected partners was 0.9 per 100 person-years (95% CI, 0.6-1.3) against the early therapy group with 0.04 (95% CI, 0.01 to 0.27). It was concluded, that 'HPTN 052 provides unambiguous proof that ART can stop the transmission of HIV'.

PrEP by 'Truvada' not fully satisfying

Presently the drug of choice for PrEP seems to be 'Truvada' (4). This drug has been tested in additional PrEP studies, conducted in the African countries of Kenya and Uganda by the epidemiologists Jared Beaton. The drug is a combination of the tenofovir disoproxil fumarate antiviral remedy and the nucleoside reverse transcriptase inhibitor 'emtricitabine' (FTC/TDF). The drug has to be taken daily, goes along with a number of side effects, and requires additional safer sex behavior. The medicine doesn't protect from other sexually transmitted diseases and might not work in individuals with low weight and being undernourished. Those taking the drug should be HIV negative and should know, that the drug **doesn't treat** HIV infection. Serious side effects could be experienced from individuals with kidney and bone problems, and in particular, hepatitis B infection could become worse.

PrEP is available and encouraged in Thailand. It is claimed that taking the pills every day a week will protect someone to 99% but the protection might decline to 76% with only 2 pills a week. The drug is not cheap and failure of protection often is due to not taking the pills regularly. Obviously, the use of the drug Truvada is problematic and cannot substitute for a vaccine. So far, despite serious attempts, to develop a vaccine for HIV was not successful. However, it seems, that a long-acting drug could be a substitute for a short-term AIDS vaccine (5).

A step forward – ViiV Healthcare and the HIV Prevention Trials Network

Such a drug might be 'cabotegravir' (6). The preparation is an 'integrase strand transfer inhibitor'. This kind of antiretroviral drug blocks the HIV coded enzyme 'integrase', by which the virus integrates its genetic information into the host cell DNA. The remedy is not yet approved for the treatment or prevention of HIV anywhere. Nevertheless, it seems to be promising as medication against HIV infection, and cabotegravir was tested as an HIV pre-exposure prophylaxis against the more conventional Truvada medication. Results of an interim analysis of a IIb/III double-blind was made public on the 18th of May 2020 by ViiV Healthcare. ViiV is a complex conglomeration of pharmaceutical companies collaborating with an even more complex international working network of groups, known as HPTN, as mentioned above. Under the label of HPTN around 50 trials, completed or ongoing, have been conducted on sites within 19 countries. The trial reviewed here is labeled under HPTN 083. Supposedly, AIDS, with an estimated 1.7 million people newly diagnosed each year, will still be around, when the world has recovered from the present coronavirus pandemic. Those, who initiated, financed, supported, and conducted the trial about HIV prevention, wanted the results of this study not been submerged

under the ‘tsunami’ of Covid-19 news. Obviously, they felt, they could not wait with their achievements being published as a conventional publication in a high-ranking journal.

The set-up HPTN 083

In fact, the results of the trial HPTN 083 are remarkable. The trial started in December 2016 and enrolled about 4.600 men of 40 sites in countries of North-and South America, Asia, and Africa. Two-thirds of the participants were under 30 years of age and 12% belonged to the group of transgender women. The organizers claim that the study enrolled adequately those, who are especially affected by HIV, namely black MSM in the US, young MSM globally, and transgender women. All those enrolled in the study were HIV negative. The study was a randomized blinded trial, consisting of two arms. The ones in the cabotegravir arm (named CAB LA) got an intramuscular injection and a placebo pill every two months. The Truvada group (labeled FTC/TDF) was under a daily pill, a combination of 200 mg emtricitabine and 300 mg tenofovir. Individuals in this group also got a placebo injection. Adherence to the oral treatment of FTC/TDF was tested by a random subset sampling and tenofovir (>0.31 ng/ml) was found in 87% of the samples, indicating that adherence was good. Within the Cab LA group 80% complained about pain or tenderness at the injection site, but only 31% of the FTC/TDF groups grumbled about the injection. Throughout the trial 2% of the CAB La group actually discontinued to take part in the trial but none of the FTC/TDF group dropped out because of intolerance to the regime.

Result of HPTN 083 and benefits for the participants

Throughout the observation time 50 participants acquired HIV. Out of those 12 participants belonged to the CAB LA group and 38 to the FTC/TDF arm. To express the result in technical terms of statistics, the CAB LA group experienced an incidence of HIV infection of 0.38% (95% CI, 0.2-0.66), and the FTC/TDF group an incidence of 1.21% (95% CI, 0.86-1.66). The conclusion is that an injection of cabotegravir every two months is to 69% (95% CI, 41-84) more effective to prevent an HIV infection than a daily pill of Truvada.

Based on the findings, the independent Data and Safety Monitoring Board (DSMB) proposed to discontinue the trial. To those in the FTC/TDF group, the CAB LA regiment will be offered up to the originally planned duration of the blind trial, while those already under the cabotegravir medication will continue to receive it. Those, who decided not to get an injection every two months, will be offered to have one daily pill of FTC/TDF instead.

Finally, one through about women

Fortunately, the initiators of the MSM trial seemed also to have thought about women. While the project for MSM are sponsored by the NIAID/NIH, the ‘sister’ project HTPN 084 is cofounded by NIAID, ViiV Health Care and the Bill & Melinda Gates Foundation. The project started in November 2017 and enrolled about 3.000 sexually active females in seven African countries. The outlay of HPTN 084 also is a phase III double-blind safety and efficacy study, aimed to investigate the long-acting injectable cabotegravir against the daily FTC/TDF tablet. Hopefully, also the results of this endeavor will be as positive as the one for the MSM groups.

Conclusion of a principal investigator

Prof. Dr. Myron S. Cohen from the University of North Carolina at Chapel Hill and Co-Principal Investigator of the HPTN have the vision, that if the presently available daily oral tablets could be substituted by the long acting injection of cabotegravir and approved HIV transmission could be reduced considerably. The frequency of dosing reduced from 365 days to six times a year could be a game-changer for HIV prevention.

Literature

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