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Antiretrovirals and HIV Prevention: New insights, challenges, and new directions

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The past two years have seen remarkable progress in the development of understanding of how antiretroviral drugs might be used to enhance HIV prevention. At the 18th International AIDS Conference in Vienna, Austria in 2010, data presented from the CAPRISA 004 study demonstrated the first proof of concept in humans that antiretrovirals could protect HIV uninfected people from infection (1). Their study showed that a peri-coitally administered gel could decrease the likelihood of HIV infection by close to 40% in women in high-prevalence communities in KwaZulu-Natal, South Africa. This important observation was followed within a few months by the first report of the use of oral medication for prevention in the iPREX study (2). This multi-national trial followed almost 2,500 men who have sex with men and demonstrated a 44% decrease in the rate of HIV acquisition in men who took oral Tenofovir-Emtricitabine (FTC) compared to those assigned to the placebo. Over the subsequent year, new data that emerged from HPTN052, which suggested that early initiation of antiretroviral therapy in HIV infected individuals in serodiscordant relationships decreased HIV transmission by a remarkable 96% (3). But, in the course of the past 2 years, there have also been some surprises. A study of sexually active women in sub-Saharan Africa, the FEMPrEP study failed to show efficacy of oral Tenofovir-FTC and a large study comparing pills and gels (4). Another study, the VOICE trial (MTN 003), discontinued two of the active study arms, one evaluating oral Tenofovir alone versus placebo medication, and the other evaluating daily Tenofovir gel use (5). However, not all of the more recent news has been negative, given that the Partner's PrEP study, the largest PrEP study to date, showed that oral Tenofovir-FTC used daily protected men and women who were in heterosexual discordant relationships, and a study of young heterosexuals in Botswana administered by the U.S. Centers for Disease Control and Prevention also demonstrated protection for men and women (6). So, what do all of these contradictory results mean? It is incontrovertible, based on multiple different studies of oral and topical

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medication in diverse populations, including heterosexual men and women and homosexual men, that antiretrovirals can be protective, but it is also clear that there may be many other mitigating circumstances that may attenuate the efficacy of antiretroviral chemoprophylaxis, highlighting the need for further study.

In the current issue of *Current Opinions in HIV and AIDS*, there are several excellent articles that carefully review these recent data in detail and advance the current understanding of the field of antiretrovirals for HIV prevention. The papers review the basic pharmacology of these medications, as well as their specific applications for unique populations, including men who have sex with men, and heterosexual men and women, particularly discordant couples. Several of the articles summarize the state-of-the-art and ongoing trials, and several others thoughtfully discuss the next steps in the field of antiretroviral chemoprophylaxis. This may include new delivery mechanisms beyond pills and gels, such as intravaginal rings and long-lasting injectable medications.

One of the major themes to emerge from the earlier studies was the recognition that using antiretrovirals for primary prevention is highly dependent on medication adherence, given that first trials presumed that the medication needed to be taken daily. In the study that had the greatest success rates, the Partner's PrEP study, adherence rates were exceedingly high whereas in the FEMPrEP study, which was the first study to report the lack of efficacy of oral medication, adherence rates were extremely low. There are several clues from some of the existing data about levels of adherence that should be maintained in order to have a maximally protective effect (7). It was also clear from the CAPRISA 004 study that adherence to gel use may wane over time. In CAPRISA 004 the protective rate was at 50% at one year, but at two and a half years, the specified study end point, the adherence rate was down to 39% (1). Thus, a whole new area of research is needed to focus on the ways in which adherence can be optimized. The current state of thinking regarding strategies to enhance adherence is reviewed by Dr. Rivet Amico in this monograph. However, there are suggestions that other factors may be involved in affecting PrEP efficacy besides adherence. It is clear from the pharmacology that tissue levels in cervicovaginal secretions and mucosal samples in women after oral use of Tenofovir are only about 1% of those achieved in rectal secretions (7). Thus, at least for oral medication, individuals who engage in anal sex may have relatively increased protection from HIV exposure after using oral PrEP compared to women who will need protective drug levels that permeate their cervicovaginal mucosa. Another major question is why Tenofovir gel was unsuccessful in protecting women in the second study, the VOICE trial, when it was clearly successful in the CAPRISA 004 study. The difference between CAPRISA 004 and VOICE was that VOICE asked the women to apply gel on a daily basis whereas CAPRISA 004 only involved pericoital dosing. It is possible that the daily application of the gel could cause untoward effects in the genital mucosa, compared to less frequent dosing, and this hypothesis deserves further study. One possibility could be that Tenofovir or the excipients carrying the compound caused a local tissue inflammation bringing cells that might permeate the mucosa and be targets for HIV acquisition. The other possibility is that because Tenofovir inhibits the enzyme reverse transcriptase, that it might be interfering with the cellular metabolism for some of the musocal cells, particularly when high concentrations were applied on a daily basis, and this might make those cells more susceptible to HIV (8). More intensive studies are needed to

disentangle the reasons for the different results in the different trials and these studies may help inform the optimal way to dose these medications, i.e. oral versus topical (or as a slow release ring or as an injection), and the optimal dosing frequencies.

There are several major new studies underway to address some of the questions raised by the first generation of PrEP studies. Studies of intermittent PrEP use are being conducted, including Project ADAPT (HPTN 067), which is enrolling men who have sex with men in Bangkok, Thailand, and Harlem, New York, and at-risk women in Cape Town, South Africa. This study will examine whether at-risk individuals are more likely to benefit and adhere to pericoital use of intermittent PrEP or whether fixed, but less frequent intervals than daily PrEP, is the optimal way to offer intermittent PrEP. An earlier study conducted by IAVI, found that the problem with pericoitally administered medication was that many individuals in their sample of East African men who have sex with men and female sex workers tended to miss postcoital doses (9). Missing a postcoital dose could be quite serious, particularly for individuals who do not engage intercourse with regular frequency since that may mean that they have low tissue levels at the time that they are exposed to the virus. In addition to thinking that intermittent PrEP may be useful because it may conform more reasonably to people's patterns of behavior, and potentially because it may offer less likelihood of toxicity and would invariably entail lower costs, other researchers are wondering whether other antiretroviral agents might be better suited to be used for PrEP. Thus, new studies are underway looking at the CCR5-Blocker, Maraviroc, as PrEP. The first study of oral Maraviroc for PrEP is getting underway (HPTN 069), which will enroll at-risk men who have sex with men and at-risk women in 12 sites throughout the U.S. At the same time, new formulations of antiretroviral medications are also under study. Maraviroc is being studied as a microbicidal gel and also in a ring format. The ring has an advantage of only needing to be inserted once a month. A large efficacy trial of Dapirvirine, a non-nucleotide reverse transcriptase drug, is getting underway in several countries in the sub-Saharan Africa at the present time. Additionally, because of concerns about medication adherence, studies are underway to evaluate injectable formulations which might only need to be administered once a month or even quarterly.

So, given the diverse findings in the first set of PrEP studies and unequivocally strong finding of decrease in HIV transmission when antiretroviral medication was administered early in HPTN 052, is there a role for PrEP in the future for HIV prevention? The answer is unequivocally yes because it is clear that one single approach for prevention will not result in the necessary changes to arrest the epidemic. It is worth noting that in HPTN 052 more than one quarter of the HIV transmissions that occurred were unlinked, that is to say that although the individuals entered the study as committed couples, at least a quarter of the people who became HIV infected were infected by an outside partner. Moreover, relying on treatment as prevention is not a realistic strategy in the short run given that the majority of people living with HIV across the globe are unaware of their infection. Clearly, massive efforts of scaling up HIV testing are necessary before treatment as prevention can gain sufficient traction. In addition, given that many individuals at risk for HIV may not know their partner's status, such as men who have sex with men and sex workers, enabling them to protect themselves with the use of either oral or topical or other modes of chemoprophylaxis makes perfect sense. Additionally, several research groups have conducted mathematical

models both in the U.S as well as in South Africa and have found that the combination of antiretroviral medication used as early treatment for infected people plus PrEP for subsets of individuals who are very high risk, may result in more rapid attenuation of the global epidemic.

With more than 2.5 million new HIV infections per year globally, including more than 50,000 new infections in the United States, clearly approaches that avail themselves of the best new science are necessary (10,11). The challenge of the global community will be to have the political will to be able to support these efforts. At the present time, there are more than 8 million patients on antiretroviral therapy across the globe. There is a goal to achieve a level of 15 million people on antiretroviral therapy by 2015. This is a laudable goal, but still means that more than half the people living with HIV across the globe will not be on medication. Therefore, in the short run careful use of antiretrovirals primary for prevention in the form of oral PrEP or topical microbicides may be the best way to keep the numbers of new infections in check. It is important to understand that the development of antiretrovirals for prevention is currently a work in progress but over the past two years the proof of the concept that this approach can be beneficial has been clearly demonstrated. Now the onus on the research community and on public health and institutional funders is to apply the best knowledge that we currently have to stop the epidemic as quickly as possible where feasible and to continue an accelerated pace of research in order to better refine the optimal use of these agents in the most discrete and selective circumstances.

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