Antiretroviral prophylaxis for HIV prevention reaches a key milestone

Salim S Abdool Karim, and Quarraisha Abdool Karim

On May 10, 2012, a US Food and Drug Administration (FDA) advisory committee voted in support of the use of tenofovir-emtricitabine for HIV prevention. [1] If the FDA, which is scheduled to make its decision by June 15, adopts the committee's recommendations, tenofovir-emtricitabine will become the first antiretroviral drug to be approved as pre-exposure prophylaxis (PrEP) for the prevention of HIV, paving the way for implementation.

PrEP has a unique advantage in young women in southern Africa, who bear a disproportionate burden of the HIV epidemic. In much of this region, young women are often unable to convince their male partners to use condoms, remain faithful, or have an HIV test. To rely on her HIV-positive discordant male partner to come forward to test, to agree to take antiretroviral therapy (ART), and to take his ART with high adherence, all for her protection, puts a woman's risk of acquiring HIV back in the hands of men, thereby disempowering women and undermining their efforts to control their risk of HIV.

However, there are several criticisms and concerns about PrEP. First, that data on the effectiveness of PrEP, especially in women, are inconsistent. This concern is based on the results of two PrEP studies—the FEM-PrEP [2] and VOICE [3] [4] trials—which were stopped, at least partly, earlier than planned when they did not show efficacy. To some extent, this concern has been allayed by recent data from the FEM-PrEP trial [5] which show that adherence to daily tenofovir-emtricitabine in the trial was too low allow assessment of efficacy. Data to explain the VOICE trial, which still has an ongoing tenofovir-emtricitabine group, are not expected until 2013.

Second, some suggest that antiretroviral drugs should be provided to HIV-negative people only when all eligible HIV-positive patients are receiving ART. Although it is a legitimate concern that eligible HIV-positive patients should be prioritised for ART for their own health and to save their lives, it is spurious to trade off treatment and prevention as if these drugs are being taken away from sick and dying patients to be given to healthy people. Treatment and prevention strategies are a continuum in their use of antiretroviral drugs—both are needed in conjunction with each other to ensure ART provision is sustainable in the long term and to realise the quest to end the HIV epidemic.

Third, there is a fear that PrEP will lead to worsening of the HIV epidemic, since PrEP users might reduce their use of higher-efficacy HIV prevention strategies such as condoms. Behavioural disinhibition, which was not noted in either the CAPRISA 004 [6] or iPrEx trials, [7] is a potential concern when implementing any new suboptimum HIV prevention strategy, and is not specific to PrEP. This challenge can be mitigated through the counselling of people being started on PrEP. Indeed, PrEP is most appropriate for the target populations where condom use is low or non-existent.

Fourth, could PrEP undermine future AIDS treatment by causing drug resistance? The risk of drug resistance from PrEP is very different from that noted when, for example, nevirapine is given to HIV-positive pregnant women, since those taking PrEP generally do not have circulating virus which can become drug-resistant. However, the possibility of resistance is present in instances where PrEP is taken for several weeks inadvertently by those with unidentified HIV infection. The main issue in resistance is whether this will compromise their

antiretroviral treatment options in several years' time when they might require ART. At present, there are no data to answer this question.

Finally, some claim that PrEP is unaffordable. Concern about the high cost of PrEP in the developing world (and, to some extent, even in the developed world) remains a legitimate one, given the lack of capacity in developing country health services. However, costs are not static and the new PrEP indication might lead to a lower cost for tenofovir-emtricitabine owing to economies of scale. Similar cost and affordability arguments were made about a decade ago when the provision of ART was being considered in the developing world. Health systems, even those under duress, evolve. Innovative ways are being found to deal with the need to reduce costs—eg, task shifting in ART services.

Many of the concerns being raised will need additional research to obviate them or to reduce their effect. Research is needed to identify additional drugs (beyond nucleoside reverse transcriptase inhibitors), additional formulations (eg, rings, gels, injectables), and alternative dosing strategies (coital, intermittent, once a month) for PrEP to have an even bigger effect with greater safety, less risk of resistance, higher adherence, and greater efficacy. Once PrEP becomes part of the HIV armamentarium, research will probably see this prevention technique advance rapidly with new formulations, and improved efficacy and safety. The strongest impetus for further research and rapid innovation in PrEP would be demand from patients and field implementation experience.

Despite its limitations, PrEP has, in conjunction with ART for prevention, created new-found optimism in HIV prevention. PrEP increases options for HIV prevention, especially for specific high-risk populations. Mathematical models have illustrated PrEP's potential effect on the epidemic trajectory. PrEP has been found to be cost-effective [8] in a South African setting. By enhancing HIV prevention, PrEP affects the long-term sustainability of AIDS treatment programmes. Can we afford not to implement it?

We were the co-principal investigators of the CAPRISA 004 trial of tenofovir gel. QAK is co-principal investigator of the HIV Prevention Trials Network, which is undertaking the HPTN 052 trial of treatment for prevention. SSAK is an executive committee member of the Microbicide Trials Network, which is undertaking the VOICE trial of oral and topical PrEP.

Centre for the AIDS Programme of Research in South Africa (CAPRISA), University of KwaZulu-Natal, Durban, KwaZulu-Natal 4013, South Africa (SSAK); and Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA (QAK)

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