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EDITORIALS

# HIV pre-exposure prophylaxis

## A once daily pill reduces risk in some groups but implementation will be challenging

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On 16 July 2012, the US Food and Drug Administration (FDA) approved a fixed dose combination of tenofovir disoproxil fumarate and emtricitabine (TDF-FTC; Truvada) as a once daily pill for prevention of HIV infection in at risk adults.[1] Approval of this combination for pre-exposure prophylaxis is one of several reasons why some HIV experts believe "the end of AIDS" is in sight.[2] But is such optimism justified?

The excitement about this treatment is understandable given that the HIV epidemic in the United States persists,[1] mainly among men who have sex with men and African-Americans. Condoms are effective at preventing HIV,[3] but their use is inconsistent.[1] Identifying and treating every infected person to achieve viral suppression could reduce transmission (so called treatment as prevention),[4] but such treatment expansion is still a long way off. Therefore, pre-exposure prophylaxis could, in theory, produce population level reductions in HIV transmission.

The efficacy of TDF-FTC for pre-exposure prophylaxis was demonstrated in two large randomised double blind placebo controlled trials, which were the basis for its approval by the FDA. The multinational Pre-exposure Prophylaxis Initiative trial, which looked at 2499 HIV negative men or transgender women who have sex with men who reported high risk behaviour, found a 44% reduction in incidence (95% confidence interval 15% to 63%; P=0.005).[5] A pre-exposure prophylaxis trial in Kenya and Uganda of 4758 HIV serodiscordant heterosexual couples found a 75% reduction in HIV infection (55% to 87%; P<0.001).[6] In both trials, efficacy was strongly correlated with adherence.

The FDA also noted, however, that pre-exposure prophylaxis was not beneficial in all trials. One trial of oral daily TDF-FTC in high risk women was stopped early for futility.[7] In a second trial, also in women, which had five arms (daily tenofovir vaginal gel, daily oral TDF, and daily oral TDF-FTC compared with respective gel and oral placebos), the oral TDF and TDF gel arms were stopped because no protection against HIV was seen.[8] These outcomes may have been related to poor adherence.[1] Pre-exposure prophylaxis works by supplying a therapeutic level of antiretroviral drugs in the bloodstream before exposure to the virus, so it is crucial that adequate levels of drug are present in the system.

The FDA determined that TDF-FTC had an acceptable risk-benefit ratio. No new side effects were identified across the clinical trials. Nonetheless, a recent study with in-depth interviews on health providers' views about implementing this prevention strategy found widespread concern about the use of a potentially toxic drug in otherwise healthy people.[9]

FDA approval included a risk management plan for training prescribers. It also included outreach to educate uninfected people considering prophylaxis about the risk of developing drug resistant variants that could complicate treatment if they became infected while taking prophylaxis. Potential patients need to have a negative HIV-1 antibody test before starting prophylaxis. The FDA recommends monitoring visits every three months to assess physical status, testing for HIV to confirm that the patient has remained uninfected, and checking for drug side effects. These visits would also include counselling on the importance of adherence and of continuing other preventive practices, such as condom use.

Who would benefit most from pre-exposure prophylaxis? On the basis of data reviewed by the FDA, serodiscordant couples and high risk men who have sex with men would benefit the most. However, US providers who see large numbers of men who have sex with men do not agree on the most appropriate patients for prophylaxis, and clear practice guidance on screening for risk needs to be developed.[9] Furthermore, these providers report very low demand from their patients, so if implemented community education campaigns would need to be developed to promote this approach.

TDF-FTC is expensive, with cost estimates in the US market of more than $1000 (£640; €810) for a one month prescription.[10] Insurance providers may be motivated to cover such treatment because of the high lifetime cost associated with HIV infection. But it is unclear how such costs would be covered in publicly financed programmes. In the US, programmes have been established to assist people with low incomes with HIV related services, including coverage for antiretroviral drugs. However, the law authorising this programme is clear that services can be

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provided only to people infected with HIV. No parallel programme currently exists for uninfected people.

Healthy young adults do not typically see a provider four times a year, and this level of attention for prevention services is not usually provided. Furthermore, public health systems typically see adult patients in drop-in clinics, such as sexually transmitted disease clinics, on a one time basis, and they do not regularly monitor patients over time. Providers do not believe that the current models of care are well suited to prescribing pre-exposure prophylaxis.[9]

Large scale implementation of pre-exposure prophylaxis therefore faces formidable challenges. Several demonstration projects have just begun in the US that will assess the barriers to its implementation in real life situations and that will also improve our knowledge of the costs and cost effectiveness. Amidst debates about how best to allocate HIV prevention resources, such knowledge will also help in assessing the comparative value of pre-exposure prophylaxis against treatment as prevention.

While there has been much discussion about the possibility of an AIDS-free generation and about the important scientific breakthroughs in HIV prevention, the goal of these strategies is largely containment. There is still no effective vaccine against, and still no cure for, HIV. Pre-exposure prophylaxis adds another potentially valuable tool to our growing list of containment strategies, but by itself it is unlikely to signal the end of AIDS.

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