EDITORIALS

Preventing HIV among Women — A Step Forward, but Much Farther to Go

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The 900,000 new HIV infections among women globally in 2015 attest to the urgent need for the dissemination of effective new HIV-prevention products for women. Most women are infected with HIV by means of sexual activity with men. Therefore, the treatment of persons with HIV is one of the most effective strategies for the prevention of new cases of HIV infection among women. However, few countries have attained the level of antiretroviral coverage in the population that is required to eliminate transmission, and women need prevention methods that they can control themselves. Long-acting products that decrease the burden of adherence are especially needed. This issue of the *Journal* reports the results of two trials that move HIV prevention a step closer.

Baeten et al.[1] and Nel et al.[2] conducted randomized, double-blind, placebo-controlled trials of a vaginal ring containing the antiretroviral drug dapivirine for the prevention of HIV infection in women between 18 and 45 years of age. These two well-designed and well-executed studies — conducted in eastern and southern Africa, where the incidence of HIV infection is high — were preceded by preclinical explant studies and were coordinated in timing and design. The trial results were consistent; both trials showed moderate efficacy overall (27% lower incidence of HIV infection in the dapivirine group than in the placebo group in the trial by Baeten et al. and 31% lower incidence in the trial by Nel et al.), with differences in protection according to age. Among women older than 21 years of age, protection was higher (56% lower incidence of HIV infection in the trial by Baeten et al. and 37% in the trial by Nel et al.). But disappointingly, the ring did not protect women 21 years of age or younger, the age group at highest risk for HIV infection (–27% in the trial by Baeten et al. and 15% in the trial by Nel et al.). Analyses by Baeten et al. suggest that lower adherence to ring use among younger women attenuated the efficacy, although the potential contribution of biologic factors is being investigated.

These two trials highlight major current challenges in the prevention of HIV infection in women, which in some respects has lagged behind prevention in men. Among men who have sex with men, 44% efficacy of tenofovir–emtricitabine as preexposure prophylaxis for HIV prevention was observed in a randomized, double-blind, placebo-controlled trial,[3] with some subsequent studies in Europe and the United States suggesting higher protection estimates in real-world settings.[4-6]

These results contrast sharply with those observed in women — especially young women — for whom the efficacy of tenofovir-based preexposure prophylaxis has been inconsistent and difficult to translate into effectiveness. Vaginal tenofovir gel decreased the incidence of HIV infection among women by 39% in the initial study[7] but provided no protection in two subsequent larger trials in which participants' adherence was lower.[8,9] Oral tenofovir–emtricitabine, when used as preexposure prophylaxis, was 66% effective in protecting women in serodiscordant partnerships from HIV infection[10] but did not protect young, predominantly unmarried, women in two other studies in which adherence was lower.[8,11]

The disparate results between men and women with regard to the efficacy of tenofovir–emtricitabine appear to result in part from lower concentrations of tenofovir in the female genital tract than in rectal tissue and higher levels of competing endogenous nucleotides in cervical tissue than in rectal tissue.[12] Most women with HIV infection were infected by means of vaginal intercourse, whereas the dominant route of transmission among men who have sex with men is anal sex, but the use of tenofovir to prevent vaginal acquisition of HIV requires greater adherence than does protection against rectal acquisition.[12]

In addition to some adherence issues in younger women, a vaginal ring presents other challenges. Although the antiviral agent in a ring should be associated with adequate concentrations in genital-tract tissues, it is unlikely to provide sufficient drug in the rectal tissue to protect women from acquiring HIV by means of anal sex, which is increasingly prevalent.[13] A total of 2% of the participants in one of the vaginal ring studies reported having had anal sex within the previous 3 months.[1]

Providers and women must ensure that the HIV interventions that women adopt match their sexual behaviors and needs. Different women — and women at different life stages — will require different types of HIV prevention. Ideally, a variety of prevention products that simplify adherence will be available: diverse methods with different durations of action, including multipurpose products with and without contraception and protection against other sexually transmitted infections.

Most studies of HIV prevention involving women have been conducted in African countries in which a higher incidence of HIV infection enables the conduct of randomized, controlled trials. The varied results of efficacy studies show the importance of adherence and the need to assess effectiveness in diverse populations; what works in one setting could fail elsewhere, and conversely, a product that fails because of lower adherence in one population could succeed in another. The need for such effectiveness studies is particularly acute in the United States, where despite the relatively low overall incidence, marked racial disparities in the rates of HIV infection persist among women. Although the diagnosis rates among black women in the United States are more than 17 times as high as those among white women, few estimates of the effectiveness of biologic HIV interventions among black women in the United States exist to support evidence-based guidelines for them.

The past few years have yielded substantial progress in strategies for the prevention of HIV infection. Nevertheless, considerable work will be required to achieve safe, effective, affordable HIV prevention for all women at risk.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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DOI: 10.1056/NEJMe1613661