Enhancing HIV Prevention with Injectable Preexposure Prophylaxis

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A worldwide goal set by the United Nations in 2016 was to end AIDS as a public health threat by 2030. A key component of the worldwide strategy to achieve this goal is the scale-up of antiretroviral treatment (ART), with viral suppression targets of 73% by 2020 and 86% by 2025.[1] Although good progress has been made in reducing the incidence of HIV infection with high ART coverage, this approach has not been sufficient to lower the number of new infections in order to achieve the United Nations' goal.[2] The use of ART both as treatment for persons with HIV infection and as preexposure prophylaxis (PrEP) for those at risk for becoming infected with HIV has become the one–two combination approach to slowing the spread of the virus in populations and countries in which transmission has remained stubbornly high. However, PrEP has fallen short of expectations, primarily because of suboptimal uptake and adherence among at-risk persons.[3]

In this issue of the *Journal*, Landovitz and colleagues[4] report the results of a noninferiority trial (HPTN 083) of PrEP with cabotegravir, an integrase strand-transfer inhibitor (INSTI) that was administered every 2 months as an intramuscular gluteal injection. Long-acting injectable cabotegravir was found to be superior to daily oral tenofovir disoproxil fumarate–emtricitabine (TDF–FTC) in preventing HIV infection among men who have sex with men (MSM) and among transgender women who have sex with men. Specifically, the risk of HIV infection was lower by 66% in the cabotegravir group than in the TDF–FTC group. In the TDF–FTC group, tenofovir–diphosphate concentrations that were indicative of good adherence to the tablet regimen were present in 72.3% of the participants, which suggests that the greater efficacy of injectable cabotegravir may not be a result of better adherence alone.

Injectable cabotegravir provides a new option for MSM and transgender women who have sex with men who are starting PrEP, and it is likely to increase PrEP uptake, as is seen in the case of contraception uptake when new contraceptive choices become available. Injectable cabotegravir is well suited to persons who are unable to adhere to a daily tablet regimen. Adherence has been a major drawback of oral PrEP. Adherence is also a concern with injectable cabotegravir owing to the potential for drug resistance when breakthrough HIV infection occurs during the long period of diminishing drug concentrations after the last injection, although in the trial, no resistance was detected in the 4 cases of HIV infection that occurred during the "tail" phase. The importance of good adherence to the tablet regimen during the oral-tablet lead-in phase and to the injections given every 2 months is highlighted by the observation that 4 of the 13 HIV infections in the cabotegravir group that met the criteria for the primary end point occurred in participants who had received their cabotegravir injections on time. With the recent Food and Drug Administration approval of the combination of injectable cabotegravir and injectable rilpivirine for the treatment of HIV infection,[5] it is possible that treatment-related, INSTI-resistant HIV infection could become more common in the future and bears close monitoring. However, this concern is lessened, given that, thus far, data are lacking to indicate that the use of tenofovir-containing regimens for both treatment and PrEP leads to a meaningful reduction in the efficacy of oral PrEP.[6]

Several new classes of antiretroviral drugs that are delivered through long-acting, slow-release vehicles in a variety of formulations (e.g., once-monthly islatravir tablets, six once-monthly lenacapavir injections, and annual tenofovir–alafenamide or islatravir implants) are currently being assessed as new PrEP options for MSM and transgender women who have sex with men.[7] Furthermore, monoclonal antibodies with broad neutralization capabilities are being evaluated in various combinations, building on the Antibody Mediated Prevention trials of a broadly neutralizing antibody (VRC01),[8] as biologic agents for long-acting injectable PrEP.

PrEP uptake is constrained by the challenge that many of the persons at risk for becoming infected with HIV do not recognize or accept that they are at high risk. In addition, persons need to be aware of, and to accept, the fact that PrEP is efficacious, and they need to have self-efficacy (belief in one's ability to meet challenges and achieve goals) to take PrEP in order to derive its benefits in mitigating their perceived HIV risk.[9] Hence, increasing PrEP coverage by means of individual persons seeking PrEP may need more than additional PrEP options. Greater consideration is being given to alternative approaches, wherein providers actively promote and provide longer-acting PrEP to high-risk persons at locations where they are likely to congregate instead of simply waiting for persons to seek PrEP. Implementation studies will become increasingly important as the array of longer-acting PrEP options — especially those requiring administration every 6 months or annually — become available.

PrEP coverage needs to increase substantially to achieve the worldwide goal for reducing HIV infection. As an initial step in this direction, real-world implementation studies of injectable cabotegravir could explore multiple approaches to increase PrEP coverage, especially if the companion efficacy trial (HPTN 084) of injectable cabotegravir that is currently under way in women in Africa[10] shows similar promising results. Expanding PrEP options with longer-acting formulations such as injectable cabotegravir is a step in the right direction on the path to ending AIDS as a public health threat.

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

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