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Perspective

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Free the PrEP — Over-the-Counter Access to HIV Preexposure Prophylaxis

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On July 13, 2023 — after a years-long campaign to "free the Pill" — the Food and Drug Administration (FDA) approved the first over-the-counter (OTC) oral contraceptive pill.

There is another medication whose availability on pharmacy shelves we believe could promote access and autonomy in the domain of sexual health: preexposure prophylaxis (PrEP) for HIV.

Like oral contraception, PrEP is highly effective at preventing an undesired sexual health outcome. Also like oral contraception, it works only if it's accessible, and there are substantial barriers to access. Many people are reluctant to ask clinicians for PrEP for fear of being judged for their sexual or substance-use behaviors, such as having condomless sex, or because of homophobia, transphobia, or racism in health care. An additional barrier is the requirement that people undergo frequent laboratory monitoring during PrEP use, which can be particularly inconvenient or infeasible for people who are employed, in school, caregivers, or struggling to meet their basic needs and those who live far from medical facilities. Although insurance plans and patient-assistance programs offer access to PrEP medications at low or no cost for most people, the complexity involved in navigating these programs can deter people from using PrEP, and financing mechanisms don't consistently cover associated provider fees or laboratory costs. Policies allowing pharmacists to independently prescribe PrEP have been an important step toward streamlining access, but implementation has been limited.[1]

The result of these barriers is that only 30% of the 1.2 million people in the United States who are likely to benefit from PrEP received a prescription in 2021, according to the Centers for Disease Control and Prevention (CDC). Meanwhile, more than 30,000 new HIV infections are diagnosed in the United States each year, with stark racial and ethnic inequities in HIV incidence and PrEP use.

Several key barriers to PrEP access could be alleviated by making PrEP available over the counter. People would no longer need to disclose information about their behaviors to clinicians, which could facilitate access for all people, but particularly for populations that face stigma in health care settings, such as Black and Latino men who have sex with

men. Adolescents and young adults, who have low rates of PrEP use, may prefer OTC PrEP if they are covered by their parents' insurance plan and concerned about inadvertent disclosure of prescription PrEP use. For people facing challenges related to the complexity of PrEP financing or care, the convenience of OTC PrEP could facilitate both initiation and sustained use; studies have found that rates of continued use of oral contraception among people using OTC pills are equivalent to or higher than rates among those using pills obtained with a prescription.[2] The juxtaposition of PrEP on shelves with other sexual health products, which will soon include oral contraception, could help normalize its use. Thoughtful marketing could increase demand and use in priority groups, including in populations — such as Black cisgender women — that have tended to perceive PrEP as being exclusively for men who have sex with men.[3]

Of currently available oral and injectable PrEP formulations, the logical initial choice for OTC access would be a daily fixed-dose combination tablet containing tenofovir disoproxil fumarate and emtricitabine (TDF–FTC). This formulation is approved for use in all populations at risk for HIV, including people of all genders, and for all modes of HIV exposure (i.e., sexual contact and injection-drug use) and is the only PrEP formulation for which a generic option is available.

Although TDF–FTC for PrEP is well tolerated, there would be safety considerations related to OTC use. TDF–FTC for PrEP has been associated with decreased bone mineral density and renal function and isn't recommended for people with osteoporosis or an estimated creatinine clearance of less than 60 ml per minute. TDF–FTC has antiviral activity against hepatitis B, and discontinuation can cause clinical relapse. For HIV treatment, TDF–FTC is insufficient to suppress viral replication, and use by people with undiagnosed HIV can select for resistance-associated mutations. FDA-approved labeling therefore advises testing for renal disease, hepatitis B, and HIV — and consideration of bone mineral density assessment in people with a history of pathologic fractures or risk factors for osteoporosis — before initiation of TDF–FTC for PrEP, as well as quarterly HIV testing and renal-function testing as clinically appropriate during use. Labeling also instructs clinicians to counsel patients on periodic screening for bacterial sexually transmitted infections (STIs), which are common among PrEP users.

OTC status for oral contraceptives was approved with the understanding that the small potential increase in risk associated with making the medication available without a prescription will most likely be outweighed by the benefits — and we believe the same conclusion could be reached for TDF–FTC for PrEP. Most people at heightened risk for HIV are in an age group in which osteoporosis and renal disease are uncommon; moreover, decreases in bone mineral density and renal function associated with TDF–FTC for PrEP are generally mild and reversible, and TDF–FTC for PrEP hasn't been associated with a significantly increased risk of fractures or serious renal events in clinical trials.[4] Hepatitis B prevalence is low in the United States, even in populations at risk for HIV, and serious hepatic inflammation or acute liver failure after discontinuing antiviral treatment is rare in the absence of cirrhosis. As in the case of widely used OTC pain medications that can affect the kidneys or liver, such as ibuprofen and acetaminophen, labels for OTC PrEP could warn people with potential contraindications to consult a clinician before use.

OTC HIV tests, which have been available for years in the United States, could be bundled with OTC PrEP; an example would be a 3-month PrEP package containing 90 pills and an HIV test. Although HIV self-tests designed for home use are less sensitive than laboratory-based tests, the CDC considers them an option for people using PrEP and recently launched a program to mail 1 million free self-tests to people who request them online. Even if people with undiagnosed HIV used TDF–FTC for PrEP and acquired drug-resistance mutations, first-line HIV treatment regimens would still probably lead to viral suppression. The World Health Organization strongly encourages but doesn't require hepatitis B testing, considers renal-function testing optional for people younger than 50 years of age without kidney-related conditions, and supports HIV self-testing before use of TDF–FTC for PrEP (in addition to supporting HIV self-testing during ongoing use); U.S. guidelines could adopt similarly simplified approaches for implementing OTC PrEP.

Additional research is needed before a manufacturer could pursue regulatory approval for OTC PrEP. Surveys and qualitative as-

sessments could evaluate whether potential PrEP users, particularly those from underserved populations, would be interested in this option. Modeling studies could project the public health effects of OTC availability so that the potential benefits associated with increased PrEP access could be weighed against the potential risks associated with reduced monitoring. Strategies for minimizing potential risks, such as development and FDA approval of more sensitive HIV self-tests and hepatitis B self-tests, could be pursued. Finally, self-selection and label-comprehension studies would be needed to evaluate whether people would use PrEP safely and effectively without a clinician's supervision, including whether they would seek medical care if they have contraindications to OTC use or need testing for STIs.

An audio interview with Douglas Krakower is available at NEJM.org

OTC availability of PrEP wouldn't be a panacea. Even without the costs of provider visits and laboratory monitoring, generic TDF–FTC may remain unaffordable for some people, particularly with the additional cost of an HIV self-test. Legislation was recently introduced to require insurers to fully cover the cost of OTC oral contraceptive pills when they become available. Similarly, policies requiring insurance coverage for OTC PrEP and HIV self-tests would be critical to keeping PrEP affordable. A national PrEP program has been proposed to support PrEP care for people who are uninsured,[5] and inclusion of OTC medications in such a program could help ensure broad and equitable access.

It has taken 63 years since initial approval to free the Pill from prescription-only status. We can't wait that long for PrEP: the federal Ending the HIV Epidemic in the U.S. initiative aims to reduce national HIV incidence by 90% by 2030. Building on lessons learned from contraception, we believe it's incumbent on the HIV-prevention community — including health professionals, advocates, and manufacturers — to lay the groundwork for a collaborative movement to "free the PrEP."

Disclosure forms provided by the authors are available at NEJM.org.

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Preparing Physicians for the Clinical Algorithm Era

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Clinical decision support (CDS) systems provide information or data, usually at the point of care, to guide clinical decision making and help improve health care delivery. As the use of these systems has grown since their introduction in the 1970s, the scope of their clinical applications has changed. Whereas initially, CDS primarily automated the provision of "facts" (e.g., drug-interaction checkers), many current CDS systems algorithmically make predictions under conditions of clinical uncertainty. Algorithmic CDS assumes many forms, from a simple regression-derived risk calculator to a more complex system based on machine learning or artificial intelligence that operates in the electronic health record.

The way in which physicians interpret and act on algorithmic CDS predictions can substantially affect patient care. For exam-