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Perspective

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PrEParing to End the HIV Epidemic — California's Route as a Road Map for the United States

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More than 1.1 million U.S. adults are currently living with HIV, and 38,739 Americans were newly infected with the virus in 2017. Yet ending the U.S. epidemic — once unimaginable — has become a realistic endeavor. On February 5, 2019, the Trump administration announced the ambitious goal of reducing new HIV infections by at least 90% by 2030. Key components of this effort include improving rates of viral suppression among people living with HIV, thereby preventing further transmission, and increasing use of preexposure prophylaxis (PrEP) for people at heightened risk of acquiring HIV infection.[1]

PrEP, which contains two antiretrovirals in a single daily pill, has been shown to reduce the rate of new HIV infections by at least 86%.[2] However, only about 10% of the potentially 1.2 million U.S. adults who could benefit from PrEP are currently receiving it.[1] Some of the lowest rates of PrEP use are found among men who have sex with men and are young, are members of racial or ethnic minority groups, or live in the South or Southeast, despite a clustering of new infections in these communities.

Why is PrEP uptake so low? There are several contributing factors, including stigma, distrust of the medical system, lack of awareness among patients and clinicians, and limited access due to cost.[3] Patients are often reluctant to speak with their primary care providers about their sexual activity or risky behavior, fearing that disclosing such information will lead to bias in their care. Physicians themselves may be unfamiliar with the correct use of PrEP.[3] And PrEP costs nearly $22,000 a year, with no generic formulations currently available. Given these costs, payers often impose onerous preauthorization requirements, so providers who want to prescribe PrEP face a large administrative burden when initiating therapy or refilling a prescription. A recent survey of primary care and HIV-treatment providers identified preauthorization as the most common barrier to prescribing PrEP.

Policymakers are exploring ways to address these barriers and increase PrEP uptake, including supporting the use of new care delivery models to expand access. In September 2019, the California State Senate and Assembly both voted unanimously to approve a bold if controversial bill (CA SB 159) that could serve as a road map for policy interventions to increase PrEP use in the United States (it has provisions related to postexposure prophylaxis as well). SB 159 allows California pharma-

cists to furnish a 30-to-60-day supply of PrEP, in keeping with federal clinical guidelines, without a prescription from a physician; requires pharmacists to complete a training program approved by the state board of pharmacy in order to be certified to furnish these drugs; requires insurance companies to pay for at least one formulation of PrEP without prior authorization; and adds PrEP to the pharmacist services covered by the Medi-Cal program. The legislation was cosponsored by the San Francisco AIDS Foundation, the Los Angeles LGBT Center, and the California Pharmacists Association, among others, but was opposed by the California Medical Association and some health plans, including Kaiser Permanente.

The San Francisco AIDS Foundation argued that pharmacist-led PrEP delivery would enable people to learn about and to access PrEP in nontraditional settings, citing the importance of involving pharmacists as highly trusted health care professionals. The California Medical Association, for its part, expressed concerns about lack of physician oversight of PrEP initiation, arguing that a physician–patient relationship is necessary for discussing the sensitive topics associated with HIV risk and for ensuring proper monitoring for potential side effects. The bill's sponsors cited the training requirements for pharmacists included in the bill as a safeguard.

There is evidence that pharmacists can safely dispense PrEP. The California legislation built on the experience with pharmacist-led HIV prevention in Seattle, as well as local policies that have expanded access to contraceptives and naloxone in California. In Seattle, a community pharmacy initiative, One Step PrEP, allows pharmacists to initiate and manage PrEP under a collaborative-practice agreement with a local primary care clinic.[4] Of 714 patients evaluated at this pharmacy between March 2015 and February 2018, a total of 695 (97%) initiated PrEP, and 513 of those (74%) received their medication on the day of their initial appointment. Over 3 years, 81% remained available for follow-up. Among patients who had two or more visits, 90% were adherent to PrEP, and there were no HIV seroconversions.[4] This model is now being replicated in other community pharmacies around the country, including pharmacies in Omaha, Nebraska, and in San Francisco.

There are other precedents for expanding access to medications by allowing pharmacists to dispense them without patient-specific prescriptions, including policies regarding naloxone, contraceptives, and nicotine-replacement therapy. Pharmacists can now administer influenza, pneumococcal, and zoster vaccines in all 50 states, and studies suggest that these delivery models have increased vaccine uptake. Pharmacist-led community-based interventions have also been effective and safe in the long-term control of other chronic conditions, such as hypertension and heart failure.[5] The success of all these initiatives should give us confidence that pharmacists can safely and effectively deliver PrEP.

On October 7, 2019, California Governor Gavin Newsom signed SB 159 into law. We believe that of its various components, the removal of prior-authorization requirements has the greatest potential for long-term benefit. The law should also help reduce stigma by making PrEP easily available at pharmacies — a component of the health care system that is more accessible and more anonymous than doctor's offices. However, patients initiating PrEP will still need a physician's prescription to refill the medication after the first 60 days, since the law allows pharmacists to dispense no more than one 60-day supply every 2 years. For some, this restriction may lead to discontinuation of therapy at 60 days, but once they are taking PrEP, patients may feel more confident about approaching their physicians for a refill. Concerns about the lack of side-effect monitoring during this initial period may be overstated, since drug-related adverse events are exceedingly rare among people with normal renal function at baseline. The rarity of acute adverse reactions to either of the currently available formulations of PrEP suggests that the net public health benefit of expanded access is likely to be substantial.

Nevertheless, the law has two shortcomings that deserve attention as other states consider adapting the California approach. First, it does not address the issue of out-of-pocket costs: eliminating stigma and preauthorization requirements will be inadequate if high out-of-pocket costs keep PrEP unaffordable. In this respect, New York's PrEP Assistance Program could serve as a model for states seeking to lower financial barriers to PrEP, since it covers support services such as testing, counseling, and follow-up and connects patients to the manufacturer's patient assistance program. Another approach that the World Health Organization endorses is an event-driven protocol for PrEP, which involves dosing PrEP around each coital act rather than as a daily pill. This approach can reduce the pill burden and cost of PrEP

for some people, but its implementation in the United States will require careful selection, counseling, and monitoring of patients.

Second, the California law does not provide resources for monitoring and evaluation of this expanded access. It will be critical to understand which communities are being reached by the expansion, rates of adverse events, and adherence to therapy beyond 60 days. California can still address these issues as the law is implemented, and policymakers in other states can be more proactive in both reducing the cost burden and monitoring the impact closely.

An audio interview with Dr. Kazi is available at NEJM.org

For the first time since the onset of the HIV epidemic, an end to its spread is now within sight. Health care providers, public health officials, and policymakers are increasingly recognizing that broader access to and use of PrEP is critical to achieving that goal, and pharmacist-led care delivery models can help. Though the California law is imperfect, it's an important step forward and could provide a road map for the rest of the country. By rethinking our approach to the distribution and financing of PrEP, we can make crucial progress toward our goal of zero new HIV infections in the United States — an accomplishment that was unimaginable just a generation ago.

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Where Were the Women? Gender Parity in Clinical Trials

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In 2017, a total of 19% of all new HIV infections in the United States and nearly half of infections globally were in cisgender (nontransgender) women. Women of childbearing potential shoulder a disproportionate burden, which raises further concerns about perinatal transmission of the virus. Preexposure prophylaxis — pharmacologic prevention of HIV acquisition with coformulated tenofovir disoproxil fumarate and emtricitabine (F/TDF) — has been shown to be effective in women, was approved by the Food and Drug Administration (FDA) in 2012 for women and men, and is a cornerstone of the national strategy for Ending the HIV Epidemic.

Coformulated tenofovir alafenamide and emtricitabine (F/TAF) is a sister prodrug of F/TDF that has the potential to cause less loss of bone mineral density and fewer renal toxic effects than F/TDF. A new drug application for F/TAF for the treatment of HIV infection in men and women was submitted to the FDA in April 2015 and approved in April 2016. The FDA reviewed a substantial amount of safety and efficacy data for F/TAF, as it does for all new medications, and confirmed that the supporting studies met its established criteria for statistical rigor, pharmacologic standards, and inclusion of diverse populations.

Two months after its approval for treatment, F/TAF's manufacturer, Gilead Sciences, moved forward with an effort to expand the drug's indications to include prevention of HIV infection. To do so, they collaborated with researchers, community members, and the FDA to develop a new preexposure prophylaxis trial protocol — the DISCOVER trial — and to work toward a supplemental new drug application for F/TAF. Designed as a noninferiority trial, DISCOVER compared F/TDF with F/TAF in more than 5000 men who have sex with men and 74 transgender women who have sex with men to evaluate the efficacy and safety of F/TAF when used for prevention. The trial specifically excluded cisgen-