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EDITORIAL COMMENTARY

Has Pre-exposure Prophylaxis Made a Difference at a Population Level? Jury Is Still Out

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(See the Major Article by Smith et al on pages 3144–51.)

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Once-daily preexposure prophylaxis (PrEP) is up to 99% effective in reducing the risk of human immunodeficiency virus (HIV) acquisition [1–5]. Although PrEP has been approved by the US Food and Drug Administration since 2012, for those watching stagnant HIV incidence statistics, PrEP uptake has been frustratingly slow. Two recent developments cemented PrEP as a prevention priority. First, PrEP received a grade A recommendation from the US Preventive Services Task Force for people at high risk of HIV acquisition [6]. Second, the federal government highlighted PrEP implementation as 1 of the 4 strategic pillars of its the Ending the HIV Epidemic initiative, which aims to reduce HIV incidence in the United States by 90% by 2030 [7]. Mathematical models have suggested that scaling up PrEP in priority populations could have a substantial impact on the trajectory of the HIV epidemic [8, 9]; however, empirical data that link expanded PrEP coverage to reductions in HIV incidence at a population level remain elusive.

In this issue of *Clinical Infectious Diseases*, Smith et al [10] seek to answer an ambitious, important, but not-so-straightforward question: Has PrEP scale-up made a difference? And if so, what is the relationship between PrEP coverage and HIV diagnosis rates in the United States? Using an ecologic approach, the authors estimated the association between increases in PrEP coverage and the annual percentage change in HIV diagnosis rates (as a proxy for HIV incidence) at the state and national level. To do so, they used the most reliable data available from the Centers for Disease Control and Prevention (CDC), including nationwide surveillance statistics on HIV diagnoses and viral suppression and state-by-state estimates of the number of people with a PrEP indication [11]. The study also used a national database of pharmacy fills for PrEP, initially Gilead-purchased and now publicly available [12].

The authors found that an increase in PrEP coverage of 1 per 100 people was associated with a 1.1% decrease in HIV diagnoses per 100 000 people in the following year, reaching a 1.3% decrease after adjusting for viral suppression rates. Notably, one might expect to observe a strong relationship between viral suppression rates and HIV diagnosis rates [13], but the authors observed no association between these 2 variables. Although they report an increase in the rates of viral suppression from 40% in 2012 to 49% in 2015 (no data were available in 2016), the authors posit that these changes may have been too small to affect rates of HIV diagnosis.

We reiterate the authors' critical point that this ecologic study investigated an association rather than a causal relationship. Although the authors adjusted for viral suppression rates in an attempt to isolate the causal effect of PrEP, adjusted results are difficult to interpret in the absence of a well-specified causal question [14]. Assessing the causal impact of increases in PrEP uptake on HIV incidence at a population level requires an analytic approach that accounts for key time-varying confounders—such as HIV testing—that are themselves affected by past PrEP use [15]. Moreover, viral suppression is likely to modify the relationship between PrEP coverage and HIV diagnosis rates: in a scenario where 100% of a subpopulation is virologically suppressed, PrEP would have no impact on new HIV diagnoses.

We also highlight the challenge of missing data, which is likely to vary by state. The authors suggest, unreferenced, that their medication database includes 82% of US PrEP prescriptions. However, data are excluded from closed healthcare systems, such as Kaiser Permanente and the Veterans Health Administration. While missing data are unlikely to undermine estimates of PrEP coverage in states where such healthcare systems provide few PrEP prescriptions, we would expect substantial underestimation of PrEP coverage in states such as California, where Kaiser Permanente has over 30% of the health insurance market share [16]. During

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this study's period of 2012–2016, Kaiser Permanente provided PrEP to approximately 7500 people in California, reaching about 20 000 people through 2019 (J. Volk and W. Towner, personal communication, 18 December 2019). Although these limitations of the available data may preclude valid comparisons between jurisdictions, analyses such as those presented by Smith et al could be useful for tracking progress toward Ending the HIV Epidemic goals within jurisdictions over time [17].

Are the findings from this study good news or bad news? Although statistically significant, the observed level of change in new HIV diagnoses may not be reason to celebrate, even if the association was presumed causal. The authors' outcome of interest was the estimated annual percentage change (EAPC) in HIV diagnosis rates per 100 000 population. Because this is a relative measure, the absolute change in the number of HIV diagnoses will vary by state, with smaller absolute changes in states with low HIV diagnosis rates. As such, with an EAPC of 1.1% in Georgia, which has an HIV diagnosis rate of 30 per 100 000, for every additional 1 per 100 eligible people on PrEP we would expect an absolute reduction of only 0.3 HIV diagnoses per 100 000. In Ohio, which has an HIV diagnosis rate of 10 per 100 000, the absolute reduction would be even smaller, at 0.1 HIV diagnoses per 100 000.

The authors argue that this small but statistically significant association between PrEP coverage and HIV diagnosis rates "supports bringing PrEP use to scale in the US." At an annual cost of $24 000 for PrEP, the substantial societal costs to achieve such a modest effect could easily lead to the opposite conclusion—that this country simply cannot afford national scale-up of PrEP for such a small impact. We also urge readers, when reflecting on this study's conclusions, to consider the disclosures of the authors, some of whom stand to benefit financially from PrEP scale-up.

Further complicating the interpretation of this study's findings is the reliance on change in HIV diagnosis rates as the measure of PrEP program performance. A guideline-concordant PrEP intervention consists of more than just medications. It also comprises services—notably frequent HIV testing—that could pull HIV diagnosis rates in different directions. Increasing PrEP coverage could reduce new HIV transmissions and increase linkage of partners with HIV to antiretroviral therapy, thereby decreasing HIV diagnosis rates. At the same time, increasing PrEP coverage could increase the frequency of HIV testing, among both PrEP users and their partners, thereby increasing HIV diagnosis rates. With the outcome of interest potentially responding in opposite directions to different facets of the same PrEP campaign, it is difficult to draw policy conclusions from the authors' results—even if we were willing to make the leap of faith that the observed association is causal and to accept that the small reductions in reported HIV diagnosis rates are epidemiologically meaningful.

PrEP is making a difference in the lives of people at risk for HIV infection and their partners. However, when extended to the population level, the impact of PrEP needs to be measured with rigorous statistical methods for causal inference and using a variety of metrics, with attention to the ways these measures may interact and what magnitude of change we consider meaningful. Further, we must not discount the importance of frequent HIV screening among people at risk on rates of HIV diagnosis. In the meantime, while PrEP remains an essential component of our HIV prevention strategy, the jury is still out on its population-level impact.

Notes

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