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Author manuscript

*Ann Epidemiol.* Author manuscript; available in PMC 2019 March 14.

Published in final edited form as:

*Ann Epidemiol.* 2018 December ; 28(12): 830–832. doi:10.1016/j.annepidem.2018.08.005.

## Progress and pitfalls in measuring HIV preexposure prophylaxis coverage in the United States

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Once-daily emtricitabine/tenofovir for HIV preexposure prophylaxis (PrEP) has emerged as a primary tool for HIV prevention. PrEP has been shown to be highly effective in clinical trials<sup>1–5</sup> and demonstration projects,<sup>6,7</sup> and HIV incidence has been low among PrEP users in clinical practice.<sup>8,9</sup> Scale-up of PrEP could substantially reduce HIV incidence at the population level if coverage in high-risk individuals is sufficient.<sup>10</sup> As efforts to scale up PrEP are underway at the local, state, and national levels,<sup>11–15</sup> it is critical to develop rigorous metrics for monitoring success, including measures of PrEP coverage in at-risk populations.

In this issue of *Annals of Epidemiology*, four studies lay the foundation for such metrics. Two studies conduct trend (Sullivan et al.<sup>16</sup>) and cross-sectional (Siegler et al.<sup>17</sup>) analyses of novel measures of PrEP coverage, specifically the prevalence of PrEP use and the ratio of PrEP users to the number of new HIV diagnoses (“PrEP-to-need ratio”). These studies identify populations with slower increases in PrEP use over time, and with lower levels of PrEP use relative to need, including individuals in the south, women, and those at extremes of age. Siegler et al. evaluate PrEP access using the location of PrEP-providing clinics, finding a lower density of PrEP clinics in the south and in counties with higher proportions of the population living in poverty, uninsured, or of racial/ethnic minority groups.<sup>18</sup> Finally, Smith et al. develop estimates of the number of adults with indications for PrEP by race/ethnicity, HIV-transmission risk group, and state, suggesting that these estimates could serve as denominators for estimates of PrEP coverage.<sup>19</sup>

Taken together, these four studies rise to the challenge of developing metrics for PrEP coverage in the United States, with estimates of PrEP use and access as numerators and estimates of PrEP need as denominators. Here, we discuss what these new metrics do and do not measure, their utility for informing policy, and paths forward for future measure development.

### Numerators for PrEP coverage: measures of PrEP use and access

The numerators for metrics of PrEP coverage, including the PrEP prevalence and PrEP-to-need ratio estimates in Sullivan et al. and Siegler et al., are estimates of *PrEP use* derived from a national prescription database obtained from Source Healthcare Analytics, LLC by

Gilead Sciences, Inc., and recently made public through [AIDSVU.org](https://www.aidsvu.org). Drug exposure periods were identified for each individual, and the authors state that prescription data were linked to a healthcare claims database to identify those that were likely for a PrEP indication. The two manuscripts report different period prevalence measures – one for quarters, and one for annual prevalence. Quarterly period prevalence presents a snapshot view of PrEP coverage, corresponds to the quarterly clinical PrEP prescription cycle, and is expected to be lower than annual prevalence. Annual period prevalence provides a more inclusive view of levels of potential PrEP protection over time and is well-suited to monitoring longer-term trends in PrEP usage.

The PrEP prescription data source is impressively large, but has several notable limitations and needs further elucidation. First, the authors suggest that the data represent more than 80% of all commercial prescriptions, but this is based on an analysis that used a different dataset that remains unpublished.<sup>20</sup> Second, although the data are referred to as filled prescriptions in Sullivan et al., the data are variably described as prescription fills, prescriptions, and pharmacy data from both pharmacies and other settings, including hospitals, outpatient facilities, and physician practices in both relevant publications.<sup>16,17</sup> Prescriptions would be a strong indicator of successful linkage to PrEP care, but recent studies of the PrEP continuum have illuminated that there are drop-offs along the pathway to true PrEP use, with cost reported as a common barrier to filling prescriptions for PrEP.<sup>21,22</sup> Filled prescriptions are a more proximal indicator of actual usage, and care should be taken by investigators to choose the most specific indicators available for their PrEP construct of interest. Third, of the drug exposure periods identified, 28% did not have sufficient data to determine whether the prescription was for PrEP. If these data were missing at random, estimates of PrEP use would be underestimated but comparisons by region or other characteristics would remain unbiased. As the authors acknowledge, an additional source of missingness is prescriptions from closed healthcare systems, which are excluded from the dataset. For example, Kaiser Permanente Northern California has 4.1 million members, corresponding to one-third of insured individuals in the surrounding population.<sup>23</sup> Sullivan et al. found that the prevalence of PrEP use was substantially lower in the western region of the U.S. compared with the northeast, but these results may have differed if the data had included prescriptions from the approximately 5,000 PrEP users in Kaiser Permanente Northern California.<sup>8</sup> Non-commercial prescription or pharmacy fill data could potentially be added through collaborations with researchers at closed healthcare systems, such as Kaiser Permanente and the Veterans Administration, or weights could be developed to account for the population that is covered by these systems and thus missing from commercial prescription data.<sup>24</sup> Finally, PrEP discontinuation is common, with one study finding that 44% of initiators discontinued within one year.<sup>25,26</sup> Prescription renewals or repeat pharmacy fills could be used to derive measures of duration of use, such as the mean percentage of days covered by PrEP in a given time period,<sup>25-28</sup> but this aspect of the data has yet to be described.

In addition to estimates of PrEP use, Siegler et al. use a database they developed to evaluate *PrEP access* by the number of PrEP-providing clinics in a given area with respect to various denominators, including the general population, PrEP-eligible men who have sex with men (MSM), and new HIV diagnoses. This is a novel approach, and this publicly available

database may itself help facilitate access to PrEP by helping health authorities, policymakers, and advocates understand which areas are relatively underserved. One might expect the areas identified as having low PrEP access to be more rural, with limited access to all types of healthcare. However, some results in Siegler et al. are surprising, with more rural states such as Maine, Vermont, and Idaho having the highest number of PrEP clinics per eligible MSM and per new HIV diagnoses. Further characterization of the approach used by Siegler et al. is needed to determine whether these results reflect the numeric instability of surveillance- and model-based estimates from jurisdictions with low population density. In addition, clinic size is not considered in this analysis, with some larger, urban clinics serving hundreds or even thousands of PrEP users;<sup>29</sup> future metrics of PrEP access might benefit from incorporating measures of clinic capacity.

## Denominators for PrEP coverage: measures of PrEP need

Critical to setting priorities and benchmarking progress for PrEP coverage is the availability of ‘denominators’ that reflect PrEP need in populations. Compared with the use of antiretroviral therapy for HIV treatment, for which the target population is easily defined and static over time within persons, HIV risk and the related construct of PrEP indication are fluid, time-dependent processes that are complex functions of both behaviors and epidemic characteristics.<sup>30,31</sup> We see multiple approaches to addressing this challenge in Siegler et al. and Smith et al.

Smith et al. present a state-level extension of their national methodology<sup>32</sup> for estimating the percent of persons indicated for PrEP by transmission risk group, deriving indication numbers for heterosexuals and persons who inject drugs by relating the number of HIV diagnoses for these groups to those among MSM. As this method is applied to smaller geographic units, care must be taken to evaluate the extent to which this approach accounts for local HIV epidemic variations that may alter the PrEP indication findings. For example, above-average population densities of MSM or concentrations of HIV diagnoses in MSM, relative to other risk groups in a jurisdiction, may result in a lower number with PrEP indications in the non-MSM groups because of the largely independent MSM epidemics. Local divergences from the national percent of MSM indicated for PrEP (i.e., 24.7%), itself calculated as the union of qualifying risk behaviors and HIV prevalence,<sup>32</sup> may further skew estimates.

The PrEP-to-need ratio, developed in Siegler et al. and applied in both that paper and Sullivan et al., tackles the denominator question by comparing PrEP use to “need,” as measured by new HIV diagnoses, in a given population. Setting aside challenges in numerator completeness that complicate comparisons of the PrEP-to-need ratio across populations, this ratio offers an alternative approach to a true coverage fraction, which might be computed by dividing PrEP usage numerators from Siegler et al. or Sullivan et al. by the numbers indicated for PrEP in Smith et al. It is appealing to have multiple measures of PrEP coverage for triangulation of a fluid construct. However, because the proportions diagnosed with HIV infection and indicated for PrEP differ so vastly between populations (e.g., between males and females, principally because one group contains MSM), there is a need

to characterize the validity of the PrEP-to-need ratio for comparing between subgroups.<sup>33</sup> In doing so, there may emerge different target values for each subgroup.

The denominator approaches in Smith et al., and in Siegler et al. and Sullivan et al., both rely on new HIV diagnoses as a measure of HIV risk, and thus share several assumptions. First, new HIV diagnoses reflect true incidence but also delays and successes in HIV testing, which are known to be differential by the risk and biological sex subgroups under study.<sup>34</sup> Care and further characterization are therefore warranted for both metrics. Second, by using HIV infections to infer the future HIV risk of different individuals, neither denominator includes those represented in the numerator, such that these approaches are susceptible to ecological fallacy. In particular, HIV-uninfected individuals in need of PrEP may not be well-reflected by their demographic and geographic peers living with HIV infection.

## Translation to policy

How can we translate these epidemiologic measures to PrEP-related policies, most rudimentarily, “how much PrEP do we need for a given community?” Principles of the number needed to treat dictate that more PrEP coverage will be required to avert HIV infections in low-incidence groups compared with high-incidence ones, an important consideration when comparing PrEP need between heterosexuals and MSM, or females and males.<sup>10,35</sup> Lack of efficiency demands that we try harder as a public health community to bring PrEP to those in need in these lower-incidence groups.

A related concept is the ability to identify those in need of PrEP. Knowing the number of MSM who need PrEP in a jurisdiction is more actionable than knowing the equivalent number of heterosexuals for two reasons. First, a substantially higher fraction of MSM are indicated for PrEP compared with heterosexuals (24.7% vs. 0.4% indicated nationally, per Smith et al.<sup>32</sup>). Second, HIV risk assessment tools are more readily available for MSM than for heterosexuals, for whom substantial overreach of PrEP programs may be necessary to ensure adequate coverage.<sup>36,37</sup> This further inflates the number needed to treat in groups that are both low-incidence and difficult to identify, rendering the numbers with PrEP need for heterosexuals less directly applicable to policy.

## Paths forward

Taken together, these four studies highlight paths forward for future research, with the goal of rigorously measuring the success of PrEP scale-up in at-risk populations. First, work is needed to further refine the metrics developed in these studies, and to understand to what extent they are valid measures of PrEP coverage, access, and need in a population. Second, work is needed to understand whether these metrics can be used for comparisons between populations, or over time within a population. Third, the development of targets for these metrics for different populations of interest could help guide policy and provide benchmarks for success. Finally, given the national target of a 25% reduction in new HIV diagnoses by 2020,<sup>11</sup> we must work toward rigorous measurement of not just PrEP coverage but also population-level impact on the HIV epidemic.

## Acknowledgments

This work was supported in part by the National Institute of Allergy and Infectious Diseases (K01 AI122853 to JLM), CDC National Center for HIV, Viral Hepatitis, STDs, and TB Prevention Epidemic and Economic Modeling Agreement (NEEMA) (U38 PS004646–01 to ESR), and National Institute on Drug Abuse (R01 DA038196 to ESR).

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