

Were we prepared for PrEP? Five years of implementation

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Although the overall incidence of HIV infections in the United States has decreased in recent years, certain populations remain particularly vulnerable, including racial/ethnic minorities, adolescents/young adults, and people in the southern United States [1]. The Centers for Disease Control and Prevention (CDC) stated strategy to combat new infections includes a combination of ‘cost-effective, scalable interventions based on current science’ [2]. In July 2012, the US Food and Drug Administration approved daily oral combination tenofovir/emtricitabine (Truvada) for preexposure prophylaxis (PrEP) in at-risk uninfected adults, with subsequent endorsement as blanket policy by the CDC in May 2014 [3].

These decisions occurred despite calls for more deliberate consideration based on concerns raised by some experts, including AIDS Healthcare Foundation, the largest global nonprofit provider of HIV prevention services, testing, and medical care. Although AIDS Healthcare Foundation was/is painted as ardently anti-PrEP [4], this is an inaccurate oversimplification of its voiced concerns that PrEP would be difficult to implement because of healthcare barriers, have limited efficacy because of poor adherence, and increase risky sexual behaviors and transmission of other sexually transmitted infections.

What do the first 5 years of Truvada PrEP reveal regarding these issues? The data are incomplete and subject to caveats and biases, but suggest that this approach has not had the positive impact anticipated by the CDC.

Implementation has been poor, particularly among the most vulnerable populations in the United States. Although the CDC estimated that PrEP was indicated for about 1.2 million persons in 2015 [5], there are currently only about 125 000 active prescriptions for Truvada as PrEP in the United States [6]. While this number is rising rapidly, it is concerning that penetration to the populations at greatest risk remains particularly poor [7]. African-Americans and Latinos account for about 45 and 24%, respectively of new diagnoses in the United States, but account for only about 10 and 12% of prescriptions. Similarly, about 8% of prescriptions go to adolescents/young adults, who account for about 20% of new diagnoses. Finally, about 50% of new infections are in the United States South, which comprises only about 30% of PrEP prescriptions. As a result, PrEP is considered even by its proponents to be a ‘boutique intervention’ that currently lacks the public health impact to protect populations at greatest risk for HIV acquisition [8].

Adherence to PrEP may be a major barrier to its utility even when available. There is no doubt that PrEP is highly effective when taken correctly, but adherence is a critical determinant of efficacy. Even under the idealized conditions of the initial clinical trials cited by the CDC in support of its PrEP policy, which had careful screening of participants, extensive counseling, and regular clinical visits, adherence rates were remarkably poor in several studies. Since then, it has been noted that more recent trials, termed, ‘open label extensions,’ and ‘demonstration

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projects' show higher adherence than the earlier trials [9], but these more recent data still share all the potential biases of participant selection, extensive counseling, close clinical follow-up that do not occur in a busy clinical practice, and behavior change that could occur as a result of giving informed consent to participate, which likely favor overestimation of adherence. True real-world data on adherence are scant; the only comprehensive dataset comes from a recent report of an insured population over 3 years [10]. The adherence rate was more than 90%, but observed only 850 person-years of PrEP in 972 persons and noted a discontinuation rate of 22.5% over this short time period. Thus, it remains uncertain that adherence is sustainable over time. It has been suggested that 'on-demand' Truvada as PrEP could reduce the barrier to adherence, but even this approach requires about a week of daily dosing to achieve therapeutic levels, followed by recommended 4 weeks after the last exposure [11]. Finally, a related concern is that breakthrough infections because of incomplete adherence could elicit drug resistance because of subtherapeutic drug levels of only two active drugs concurrent with infection; data to address this point are unavailable to date.

Increased risky sexual exposure (risk compensation) remains a significant concern for offsetting the potential benefit of PrEP. It is difficult to assess this issue accurately and the published data are contradictory, but overall the major concern that PrEP would increase risky sexual exposures and reduce condom usage

appears substantiated [12]. The above-mentioned real-world report documented rapidly rising rates of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* after starting Truvada as PrEP, with 35% of persons having at least one STI after a year, half of whom had multiple STIs [10]. In support, another study noted an association between therapeutic levels of tenofovir and lack of condom use during sex, although STI rates were too high at baseline (almost one per person-year) to note any change [13], which is a confounding factor in many reports finding no increase in STIs with PrEP. Although these impacts are difficult to quantify and thus debatable, anecdotally there has been a potentially damaging culture change in some demographic groups (Fig. 1) in the setting of historically low condom usage [12,14]. Even strong proponents of PrEP have noted in studies of persons who are extensively counseled regarding risk that 'PrEP allow(s) a relaxing of the (risk mitigation) rules' in some [15].

Eradicating HIV transmission is a goal shared by us all. PrEP clearly has a role in selected populations; the question is not whether PrEP has any role in HIV prevention, but rather whether it has met the CDC's expectation to be cost-effective and scalable. These first 5 years since Food and Drug Administration approval of Truvada as PrEP validated some of the initial concerns raised, and indicate that far more progress is needed before pharmacologic prevention of HIV infection is broadly successful without significant downsides.



Fig. 1. PrEP advertisement, Melbourne, Australia. From: <http://www.pinknews.co.uk/2015/09/18/shock-poster-campaign-tells-gays-to-f-raw-prep-works/>.

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Conflicts of interest

There are no conflicts of interest.

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