Published in final edited form as:

Curr Opin HIV AIDS. 2016 January ; 11(1): 67–73. doi:10.1097/COH.0000000000000222.

The PrEP revolution: from clinical trials to routine practice: Implementation “view from the US

Richard Elion, MD, ABFP and

Associate Clinical Professor of Medicine, George Washington University School of Medicine

Megan Coleman, FNP, MSN

Whitman Walker Health, Washington DC

Abstract

Purpose of review—To describe the use of Tenofovir/Emtricitabine (Truvada) as prevention for exposure to HIV (PrEP) infection in the US. The use of PrEP and the challenges of implementation are very instructive as other countries adopt this intervention and it becomes a fundamental part of worldwide efforts for HIV prevention and much can be learned from the first three years in the US.

Recent findings—Randomized trials and demonstration projects have shown the benefits of PrEP for men and women who are at risk for HIV. Numerous studies have showed that the level of prevention is excellent when the drug is taken at least four times weekly, once adequate levels are obtained. However, adherence remains a critical issue as well as tailoring delivery models for specific populations. Six recent studies are discussed which support excellent efficacy and significantly support PrEP as a means of prevention. These projects have shown high acceptance of PrEP with excellent adherence by individuals demonstrated by those at risk remaining free of HIV over extended periods of time.

Summary—The US faces three significant challenges in scaling up PrEP. The first challenge in implementation in the US has is to get individuals to recognize the actual risks that their behaviors represent and to engage with providers to address these issues. The second challenge is getting a population of providers to recognize the exact same issues and offer PrEP in a compassionate, non judgmental fashion. The third challenge is identifying the set of providers and locations to scale up the response in a timely, cost effective fashion.

Keywords

PrEP in US; Adherence with PrEP; Community issue and PrEP adoption

Corresponding Author: Richard Elion MD, 1640 Rhode Island Avenue suite 800, Washington DC 20036, rickelion@gmail.com.

Conflicts of Interest: Richard Elion MD is on the speakers bureau of Bristol Myers Squibb, Gilead, Janssen, Merck, and VIV. He is also on the advisory boards of Gilead, Janssen, and VIV and has received research funds from BMS, Gilead, Janssen, Merck and VIV while at Whitman Walker Health. He has no stock ownership in any of these companies.

Megan Coleman, FNP has no conflicts of interest to disclose.

Introduction

Pre-exposure prophylaxis for HIV is the use of drugs, typically antiretrovirals, by uninfected individuals to prevent them from acquiring HIV infection. Currently Truvada is the only FDA approved medicine and the US has been the only country where this preventive strategy has been approved, though there are active regulatory submissions in other countries. We discuss the uptake of and issues for implementation in the US, with extensive documentation of the challenges of integrating this approach into the US health care system from the provider and community perspectives.

PrEP utilization in the US

The United States is the only country to have approved daily use of FTC/TDF (Truvada) as an effective and safe biomedical option for HIV prevention (1). The US Food and Drug Administration's (FDA) 2012 ruling came on the heels of findings of several seminal studies on HIV prevention, whose results showed that PrEP reduced HIV by as much as 90% for those with excellent adherence (2-7). Based on these findings, the CDC, WHO and IAS-USA issued guidance on the use of tenofovir and Truvada for HIV prevention, and recommended PrEP use as part of prevention strategies in multiple high-risk populations (8-10).

The utilization of PrEP has been sluggish in the US since the FDA ruling in 2012. Gilead's analysis of 55% of all retail US pharmacies demonstrated approximately 8512 individuals utilizing this strategy from 2012-3/2015, with an increasing pace of growth over the last 12 months (Gilead communication). It is difficult to estimate the size of the population that would be appropriate for PrEP, but clearly the current usage patterns are only reaching a minority of those who might benefit. Grant estimated that 11.2% of MSM in SF in 2014 were currently on PrEP and approximately 32% had ever tried PrEP (11).

Estimates of the pool of individuals appropriate for PrEP include all sexually active individuals who meet the CDC defined definition of risk. Lieb and colleagues estimate that overall MSM rates in the US were 7.4% of the total population equating to 7.4 million men in this at risk population alone (12). MSM represent approximately 65% of new infections of HIV (13) and CDC estimated in a meta-analysis that as of 2012 (14) approximately 6.9% of men had sexual contact with another man ever, and approximately 3% in the last twelve months. This would project to approximately 200,000 MSM who might qualify for the risk pool of men who would have at least two unprotected encounters in the last six months

The current utilization of approximately 9,000 is modest compared to the size of the potential of MSM, and heterosexual men and women with behaviors that are considered high risk according to the CDC. There are approximately 50,000 new HIV infections yearly, so at a minimum, this utilization is impacting a fraction of those at risk. Many at risk individuals don't consider themselves at risk, and so don't seek care; while others are not engaged in health care or relationships with providers, so have no context to engage in this method of prevention. (7-8;15-16).

There has been an increase of 1% to 3% of MSM who are using PrEP from 2011-2014 based on a large online network of MSM. (Gilead communication) This low utilization was due to a variety of factors including only 25% familiarity with PrEP, although many more expressed interest in initiating PrEP. More recent surveys of MSM have shown higher levels of awareness of PrEP upwards of 60% (17) Recent data in Boston demonstrated increased interest and (18,19,20) an increase in utilization of PrEP despite a sluggish start. Mayer reported a nearly 5-fold increase in new users of PrEP at the Fenway community health center from 2012-2014.

Key Issues in Adoption of PrEP for providers

Risk Compensation and Toxicity

Providers, both specialists and primary care have expressed reservations about offering PrEP. Their concerns have focused on risk compensation, toxicities, and increased costs. (21-23). Multiple studies have now documented that there has been no increase in rate of sexually transmitted infections and the use of condoms has been fairly constant during the study period.(3,6,24) There is an association of greater adherence in men who have higher risk sexual contact, rather than an increase in risky behaviors across the demographic. These concerns about risk compensation mirror the concerns around oral contraceptives, and though there were some early increases in rates of gonorrhea, there has never been a definitive link between the pill and increased rates of STI's. (25)

The toxicities associated with Truvada have been mostly short term side effects such as nausea (most prominent in the first month), headaches and weight loss. (2,3,7,10) Longer term side effects such as decline in renal function and loss of bone density have been seen in longer term use in HIV positive patients, and will be evaluated over time in PrEP (26-28) These longer term side effects may be ameliorated as new options for prevention are available, such as cabotegravir (an injectable medicine) (29,30) and Tenofovir alafenamide (precursor to Tenofovir) which appears to not have much of the overlapping toxicities of Truvada.(31,32)

Costs

The cost of the medications has been a consistent issue of concern for both providers and community members; however most health plans have covered this on label indication. Individual insurance plans and multiple tiered co-pays have made PrEP less feasible in cost constrained settings though Gilead (the manufacturer of Truvada) has expanded their patient assistance program to help with these co-pays. In states that have not expanded to Medicaid as part of the Affordable Care Act, many have been left out leaving those at highest risk for HIV acquisition with limited availability of PrEP access. Additionally, utilization of assistance programs and navigation through insurance benefits and claims requires some health care system knowledge, and many individuals will need help with this.

The cost-effectiveness of PrEP has been addressed in a review in this series and documented as beneficial in high-incidence populations (33-35). However there is a real issue of direct costs for patients who purchase the medication due to the co-pays for purchase of the prescriptions as well as the labs needed to monitor the safety of Truvada. These co-pays are

only partially covered by patient assistance programs and still may result in monthly costs that vary widely for patients based on their particular insurance coverage. These combined costs of co-pays for labs and medications could vary from 0 to as high as \$5000 annually. This is a definite barrier to the adoption of PrEP and remains a key challenge to optimal utilization.

Efficacy—The clinical efficacy of PrEP has been well documented in this journal and through numerous publications (2-7). The number of clients needed to treat (NNT) in both Ipergay and Proud study was less than 1 in 20(4,5) When compared with the NNT with statins to prevent a non-fatal heart attack (1 in 39) (36), this is clearly an important intervention to potentially decrease the rate of new HIV infections with costs benefits if used with the right population and monitored properly.

Delivery Models

There is a need to expand the pool of providers to offer PrEP beyond HIV specialists and integrate this approach into primary care (37-38). Providers are generally aware of the benefits of PrEP, but many would like more training before they begin dispensing medication (39). Blumenthal and colleagues' recent study found prior PrEP knowledge increased the likelihood of a provider to have prescribed PrEP (40). In 2013, the total Primary Care Providers in the US was estimated to be over 280,000 Physicians, Nurse Practitioners and Physician Assistants).(41) Primary Care Providers play a key role in keeping their patients healthy and are perfect locations in which to hold conversations on health promotion and disease prevention. Incorporating HIV prevention and discussions on sexual health will reach a larger population at risk for HIV infection that would not come in contact with a STD clinic or Infectious Disease Specialist. Increased provider training will be needed to facilitate discussion of the concepts of risk and sexuality with patients. (42) A well-known HIV provider stated that "People are more comfortable having sex, then talking about it". The conversation between a provider and patient about sex, and the attendant risks of different types of sex, is one seldom had.

A recent study found that MSM who were uncomfortable disclosing their sexuality with their providers were less likely to ever learn or use PrEP. This survey by Krakower and colleagues reported troubling findings: 42% of these men were not comfortable discussing male to male sex with their primary care provider, and of the 82% of the men who were comfortable discussing sex many did not feel comfortable discussing PrEP use and approximately three quarters did not think their provider would be willing to provide PrEP. The group of men who were uncomfortable discussing sex with their provider, were less likely to have discussed anal sex (89% vs 42% of those who were comfortable) and generally preferred to get PrEP from a provider other than their usual provider (81% vs 33% of those who were comfortable discussing these issues). (43)

A key factor in the development of PrEP will be access to services. Initial efforts after approval were split between primary care providers and research projects such as the PrEP demo project. This has begun to change as characterized in a recent paper by Volk et al. who described the integration of PrEP at the Kaiser Permanente Medical Center in San Francisco,

a health maintenance organization. They developed a specialized program with a multi disciplinary team that received 1045 referrals from July 2012 through February 2015, with a marked increase in the rate of referrals in the last year. These referrals generated over 650 individuals with a mean duration of 7.2 months of use (99% MSM). There were no new HIV infections in the cohort on PrEP despite high rates of STIs (50% with any STI after 12 months of use). 74% of the men had no increases in their number of sexual partners and 41% reported decreased condom use. (44)

The delivery model of PrEP is evolving. Integration of these services into primary care settings for individuals at risk has clearly begun as evidenced by data from Boston and Chicago and San Francisco. However there is a need to expand prevention services into the STD clinics as well, as this is a location where high risk behavior has brought one into a clinical environment. PrEP is beginning to integrate into the fabric of public health in various states, (45,46), and this integration may prove valuable to allow for greater access. A frequent clinical engagement point for many MSM at risk for HIV are STD programs, which many jurisdictions are beginning to use as starting points for PrEP initiation. Through increasing local PrEP awareness at the patient level (via social media or information campaigns) and engaging community stakeholders, STD clinics may represent a logical entry point and referral source for sexual wellness and HIV prevention programs. The challenge will be in continuing the necessary longitudinal care model for PrEP in a setting that has traditionally been focused on episodic care. Local health departments and recent CDC funding support may assist in this transition to longitudinal treatment and monitoring.

The Washington DC Department of Health is currently developing a PrEP program and other prevention services to be nested within their STD programs to expand outreach for prevention. The evolution of prevention services may stimulate creation of additional specialty PrEP programs as well, such as seen in SF. The development of this clinical model to deliver PrEP will be different in various communities and will be an area for likely future innovation.

However, after the publication of iPrEX in 2010, Krakower reported that as many as one quarter of providers in some settings continued to be unaware of CDC or FDA guidance on PrEP (47). Castel reports in a survey of providers two classes of providers, those with more experience and training who felt comfortable providing and those with less experience and training who were reluctant to provide PrEP (48). There remain serious operational issues, such as which providers will provide the care, and reimbursement.

Key Issues in Adoption of PrEP for Community

Recognizing risk

As mentioned previously, the population who could potentially benefit from PrEP is large; however enabling at-risk populations to recognize their personal risk and translate this into motivation to access PrEP is a key challenge. The community of men and women at risk for contracting HIV infection is quite heterogeneous. The MSM community has a higher risk profile than the heterosexual community as evidenced by the high proportion of new HIV positives who are MSM. Therefore outreach to populations at greatest risk must engage

MSM community and adolescent MSM who represent the age group (15-24 years old) at greatest risk (12). The key factors are recognizing risk both for the individual as well as the provider and then subsequent engagement to offer PrEP. Men and women at risk for HIV through sexual behavior are frequently unaware about their risk.(49,50) Kwakka's survey conducted at an STD clinic demonstrated that while 65.4% of the population were open to using PrEP, their estimation of self-risk when compared to the trained outside observer was widely differentiated (9.5% identified self-risk compared to 68.5% by outside observer). Even with an overall negative association between self-risk underestimation and openness to PrEP, receptiveness was high across all races and ethnicities among those who may be clinically eligible for prophylaxis: 69.8% of African Americans, 74.1% of Hispanics and 71.7% of Caucasians who were identified by testers as being at high or moderate risk were receptive (51). There is a distinction between the global understanding that people have of belonging to an at-risk population, and the actual understanding that they as individuals are at risk even when they partake in behaviors that place them at risk.

African American Men, (especially MSM) and women of color are disproportionately impacted by HIV (52,53). Ongoing studies such as HPTN 073, (225 Black MSM recruited in DC, Los Angeles and North Carolina) a demonstration project with a rich model of social support will provide vital information on PrEP uptake and use. African American men have been under-represented in previous PrEP studies and it is hoped these current studies and CDC planned activities will foster broader participation.

The use of PrEP in women is a critical issue as women represent 25% of new HIV infections in the US. (54). These women have unique risks compared to their male counterparts. Jennings and colleagues' analysis of over 1000 African American women in HPTN 064 identified many of the unique vulnerabilities that affect women. For example, knowledge of their partners serostatus, a key component of HIV prevention, is strongly related to financial security and that women with fewer economic resources are less likely to have power in a relationship to negotiate knowledge and protection against HIV.(55) PrEP for these women must combine more than just a pill, but a "behavioral, economic and empowerment approaches are likely to be more effective in addressing the multiplicity of vulnerabilities of this population.

Finally, there are few data regarding transgender people, as there has been insufficient clinical experience or participation in clinical trials to really describe the clinical effectiveness. Concerns were raised in the iPrEX OLE trial that drug levels for TDF/FTC were lower compared to MSM. (3) The rationale for this may simply be related to sub optimal adherence since there is no recognized drug interaction between exogenous hormones and TDF/FTC levels, however further study is exploring this possible connection.

Stigma around HIV continues even in the realm of new HIV prevention efforts. Opponents of PrEP have made arguments against it based on moral judgments about condom use rather than evidence from clinical trials. The use of a medication to prevent HIV has caused some to be labeled as immoral, promiscuous and "Truvada Whores". The AIDS Healthcare Foundation which is the largest provider in the US of HIV services has been openly critical of this approach, while running provocative advertisements proclaiming the death of

condom use as men flock to these pills without any behavioral conscience. This idea of risk compensation has not materialized based on data from numerous trials including iPrEX, PrEP Demo project among others (3,4,5,6). However it has touched a sensitive point of how we counsel men and women who continue to have risky sexual behavior that can expose them to HIV.

Consumer Engagement

Digital and social media campaigns and discussions may represent unique methods for disseminating information about PrEP and other methods of HIV prevention. Social media may be especially helpful in reaching young adults and adolescents who utilize this frequently and increasingly. (56) Online communication and education may allow for open and frank discussions about sexual risk and methods for prevention without the fear of self-disclosure and stigmatization.

Americans are researching on-line for health information in addition to visiting provider offices as reflected in 2013, 59% reported looking on-line for health information in the preceding year according to Pew Research Center's Internet & American Life Project. (57) Providing accurate and timely information about PrEP on-line can increase engagement with at-risk individuals, empower them to recognize the risk of their own behaviors and to discuss potential options with their providers as well as host on-line forums for discussions about PrEP access, availability, side effects and personal stories to support sustained use of PrEP.

Future challenges and directions

The recent release of six different studies demonstrating the effectiveness and potential of PrEP to impact the epidemic has created a critical momentum for both consumers and providers. (2-7)

Recent modeling work by Grant, show what the combined approach of PrEP and Treatment as Prevention can offer for communities when PrEP uptake increases from a third to 95% amongst those in need, and viral suppression increases from the current 62% to 90% (14).

Kelley and colleagues were not as optimistic as Grant, based on their analysis in Atlanta that due to various structural and societal obstacles it would be unlikely to achieve more than 44% coverage for MSM in Atlanta which could avoid 25% of new infections over a ten year period.(58) The estimate of 44% is optimistic, as current data show that only 15% of MSM who would be appropriate are accessing the medicine. Mayer et al. comments on the myriad of reasons contributing to these sobering data. The intersection of social constructs with less health access amongst African Americans, compounded in MSM population, stigmatization and finally the financial issues of inadequate insurance throughout much of the US impedes efficient and cost effective roll-out of PrEP.

Conclusion

We are at a crossroads regarding the provision of PrEP in the US. There has been enough data to satisfy skeptics that this intervention is effective when taken at least four times a

week with minimal toxicity, especially considering the age of clients and the intermittent nature of using this approach. The barriers to providing adequate prevention are operational and societal. These obstacles are not simple to overcome and will be a litmus test for our evolving health care system that will seek to find the sweet spot between decreasing the incidence of an infectious disease and the cost/benefits associated with the societal commitment to provide this for all appropriate populations. HIV is unique however, in that it is transmitted through sex, a topic still difficult for both providers and consumers to talk freely about.

Acknowledgments

We would like to thank the team of the PrEP demo project including Al Liu, Stephanie Cohen, Oliver Bacon, Michael Kolber and Suzanne Doblecki-Lewis, and the PrEP team at Whitman Walker Health including Justin Schmandt, Gwen Ledford, Anna Wimpelberg, and JJ Locquiao for their expert assistance in helping us to learn about PrEP, and finally all the participants in the studies for helping to educate us

Financial Support and Sponsorship: The PrEP demo project was supported by NIH extramural grant. We had no financial support for the writing of this paper.

References

1. US Food and Drug Administration. FDA approves first drug for reducing the risk of sexually acquired HIV infection. 2012. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312210.htm>
2. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. 2010; 363:2587–99. [PubMed: 21091279]
- 3**. Grant RM, Anderson PL, McMahan V, Liu A, Amico KR, Mehrotra M, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *Lancet Infect Dis*. 2014; 14:820–9. Outstanding (Excellent description of open label experience after IPREX was closed and allows close analysis of PK levels of drug associated with prevention.). [PubMed: 25065857]
4. McCormack, S.; Dunn, D. Pragmatic open-label randomised trial of preexposure prophylaxis: the PROUD STUDY; Conference on Retroviruses and Opportunistic Infections (CROI); 2015 February 23–26; Seattle, WA. 2015. Abstract 22LB
5. Molina, JM.; Capitant, C.; Spire, B. On demand PrEP with oral TDF-FTC in MSM: results of the ANRS Ipergay trial; Conference on Retroviruses and Opportunistic Infections (CROI); 2015 February 23–26; Seattle, WA. Abstract 23LB
- 6**. Liu, a, et al. Pre-exposure prophylaxis for Human Immunodeficiency Virus infection integrated with municipal- and community- based sexual health services. *JAMA internal medicine-in press*. 2015 Outstanding (Excellent work detailing issues of engagement, adherence and clinical experience in offering PrEP in US outpatient setting. This study will be the first demonstration project reported in US).
7. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med*. 2012; 367:399–410. [PubMed: 22784037]
8. HIV Prevention in clinical care settings; Recommendations of IAS. *JAMA*. 2014; 312(4):390–409. [PubMed: 25038358]
9. Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations. WHO; Jul. 2014
10. CDC Federal Guidelines US Public Health Service. Preexposure Prophylaxis for the Prevention of HIV Infection in the United States—2014: a clinical practice guide.

11. Grant, R., et al. CROI 15. Seattle: 2015. Scaleup of pre exposure prophylaxis in San Francisco to impact HIV incidence. Abs-25
12. Lieb S, Fallon SJ, Friedman SR, et al. Statewide estimation of racial/ethnic populations of men who have sex with men in the USA. Public Health Rep. 2011; 126:60–7. [PubMed: 21351396]
13. CDC. HIV Surveillance Supplemental Report. Dec.2012 17(4)
14. Purcell DW, Johnson CH, Lansky A, et al. Estimating the Population Size of Men Who Have Sex with Men in the United States to Obtain HIV and Syphilis Rates. The Open AIDS Journal. 2012; 6:98–107. [PubMed: 23049658]
15. Krakower DS, Mimiaga MJ, Rosenberger JG, Novak DS, Mitty JA, White JM, et al. Limited awareness and low immediate up- take of pre-exposure prophylaxis among men who have sex with men using an internet social networking site. PLoS One. 2012; 7(3):e33119. [PubMed: 22470438]
16. Mayer, KH.; Oldenburg, CE.; Novak, DS.; Krakower, DS.; Mimiaga, MJ. Differences in PrEP knowledge and use in US MSM users of a popular sexual networking site surveyed in August 2013 and January 2014; R4P Conference; 28–31 Oct 2014; Cape Town.
- 17*. Krakower, DS.; Oldenburg, CE.; Mimiaga, MJ., et al. Patient-provider communication about sexual behaviors and pre-exposure prophylaxis: results from a national online survey of men who have sex with men in the United States IAS 2015; 8th Conference on HIV Pathogenesis, Treatment and Prevention; July 19-22, 2015; Vancouver. Abstract TUPEC506. Outstanding (Helps with the understanding of the dynamics of the therapeutic relationship of provider and patient and the challenges of PrEP delivery
18. Mayer, KH.; Oldenburg, CE.; Novak, D.; Elsesser, S.; Krakower, DS.; Mimiaga, MJ. Early adopters: socio-demographic and behavioral correlates of chemoprophylaxis use in a recent national online sample of men who have sex with men in the US; Presented at the 21st Conference on Retroviruses and Opportunistic Infections; 3–6 Mar 2014; Boston. abstract no. 954
- 19*. Mayer, KH.; Levine, K.; Grasso, C.; Krakower, DS.; Mimiaga, M. Recent increases in PrEP utilization among men who have sex with men in a Boston community health center 2011 - 2014: transition from research to clinical practice; Conference on Retroviruses and Opportunistic Infections (CROI); 2015 February 23-26; Seattle, WA. Abstract Outstanding (Important description of increase of PrEP use at Fenway in Boston, supporting concept of increasing implementation over time)
20. Mayer, K. Significant Increases in HIV Pre-Exposure Prophylaxis (PrEP) Uptake in a Boston Community Health Center in 2014: Who are the recent users?; 8th IAS Conference; Vancouver. July 19-22, 2015; Brooks RA, Kaplan RL, Lieber E, Landovitz RJ, Lee SJ, Leibowitz AA. Motivators, concerns, and barriers to adoption of preexposure prophylaxis for HIV prevention among gay and bisexual men in HIV-serodiscordant male relationships. AIDS Care. 2011; 23(9): 1136–45. [PubMed: 21476147]
21. Krakower, D.; Oldenburg, CE.; Mitty, JA.; Wilson, I.; Kurth, A.; Maloney, K., et al. New England healthcare providers' perceptions, knowledge and practices regarding the use of antiretrovirals for prevention; 9th International Conference on HIV Treatment and Prevention Adherence; 2014 June 8-10; Miami, FL. Abstract 270
- 22*. Karris MY, Beekmann SE, Mehta SR, Anderson CM, Polgreen PM. Are we prepped for preexposure prophylaxis (PrEP)? Provider opinions on the real- world use of PrEP in the United States and Canada. Clin Infect Dis. 2014; 58:704–12. Special-Description of the attitudes of providers towards PrEP and the obstacles to provider adoption of PrEP. [PubMed: 24319083]
23. Tellalian D, Maznavi K, Bredeek UF, Hardy WD. Pre-exposure prophylaxis (PrEP) for HIV infection: results of a survey of HIV healthcare providers evaluating their knowledge, attitudes, and prescribing practices. AIDS Patient Care STDs. 2013; 27:553. [PubMed: 24053478]
24. Marcus JL, Glidden DV, Mayer KH, Liu AY, Buchbinder SP, et al. No Evidence of Sexual Risk Compensation in the iPrEx Trial of Daily Oral HIV Preexposure Prophylaxis. PLoS ONE. 2013; 8(12)
25. Myers JE, Sepkowitz KA. A pill for HIV prevention: déjà vu all over again? Clin Infect Dis. 2013; 56(11):1604–12. [PubMed: 23408681]

26. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med*. 2012; 367(5):423–34. [PubMed: 22784038]
27. Choopanya K, Martin M, Suntharasamai P, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (The Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2013; 381(9883):2083–90. [PubMed: 23769234]
28. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med*. 2012; 367(5):411–22. [PubMed: 22784040]
- 29*. Spreen W, Min S, Ford SL, et al. Pharmacokinetics, safety, and monotherapy antiviral activity of GSK1265744, an HIV integrase strand transfer inhibitor. *HIV Clin Trials*. 2013; 14(5):192–203. A potential new agent that could be used for PrEP with potentially bimonthly injections, addressing adherence issues in a unique fashion. [PubMed: 24144896]
30. Spreen, W.; Ford, S.; Chen, S., et al. Pharmacokinetics, safety and tolerability of the HIV integrase inhibitor S/GSK1265744 long acting parenteral nanosuspension following single dose administration to healthy adults; International AIDS Conference; Washington, DC. July 22-27, 2012; abstract TUPE040
31. Sax P, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. *Lancet*. Jun 27; 2015 385(9987):2606–2615. [PubMed: 25890673]
- 32**. Gunawardana M, et al. Pharmacokinetics of Long-Acting Tenofovir Alafenamide Subdermal Implant for HIV Prophylaxis. *Antimicrobial Agents and Chemotherapy* July. 2015; 59(7):3913–3919. Potentially important new drug for PrEP and unique model of delivery.
33. Cambiano, et al. What do we know about the cost-effectiveness of HIV Pre-Exposure Prophylaxis, and is it affordable?. Published in this issue.
34. Hellinger FJ. Assessing the cost effectiveness of pre-exposure prophylaxis for HIV prevention in the US. *Pharmacoeconomics*. 2013; 31(12):1091–104. [PubMed: 24271858]
35. Juusola JL, Brandeau ML, Long EF, Owens DK, Bendavid E. The cost-effectiveness of symptom-based and routine screening for acute HIV infection in men who have sex with men in the USA. *AIDS*. 2011; 25:1779–87. [PubMed: 21716076]
36. Thavendiranathan P. Primary prevention of cardiovascular disease with statin therapy. *Arch Int Med*. 2006; 166:2307–13. [PubMed: 17130382]
- 37**. Krakower D, Ware N, Mitty JA, Maloney K, Mayer KH. HIV providers; perceived barriers and facilitators to implementing pre-exposure prophylaxis in care settings: a qualitative study. *AIDS Behav*. 2014; 18:1712–21. Outstanding (Addresses the issues of providers who are contemplating delivery of PrEP through qualitative assessments, allowing insights into current adoption by providers). [PubMed: 24965676]
38. Krakower D, Mayer KH. Engaging healthcare providers to implement HIV pre-exposure prophylaxis. *Curr Opin HIV AIDS*. 2012; 7(6):593–9. [PubMed: 23032736]
39. Whiteside Y, Harris T, Scanlon C, et al. Self-perceived risk of HIV infection and attitudes about pre-exposure prophylaxis among sexually transmitted disease clinic attendees in South Carolina. *AIDS Patient Care STDS*. 2011 Jun; 25(6):365–70. [PubMed: 21470046]
40. Blumenthal J, Jain S, Krakower D, Sun X, Young J, Mayer K, Haubrich R. Knowledge is Power! Increased Provider Knowledge Scores Regarding Pre-exposure Prophylaxis (PrEP) are Associated with Higher Rates of PrEP Prescription and Future Intent to Prescribe PrEP. *AIDS Behav*. 2015 May; 19(5):802–10. [PubMed: 25616837]
41. Projecting the Supply and Demand for Primary Care Practitioners Through 2020. Nov. 2013 published <http://bhpr.hrsa.gov/healthworkforce/supplydemand/usworkforce/primarycare/>
42. Tripathi A, Ogbuanu C, Monger M, et al. Preexposure prophylaxis for HIV infection: Healthcare providers' knowledge, perception, and willingness to adopt future implementation in the southern US. *South Med J*. 2012; 105(4):199–206. [PubMed: 22475669]
- 43**. Krakower, DS.; Oldenburg, CE.; Mimiaga, MJ., et al. Patient-provider communication about sexual behaviors and pre-exposure prophylaxis: results from a national online survey of men who

have sex with men in the United States IAS 2015; 8th Conference on HIV Pathogenesis, Treatment and Prevention; July 19-22, 2015; Vancouver. Abstract TUPEC506. Outstanding (Helps with the understanding of the dynamics of the therapeutic relationship of provider and patient and the challenges of PrEP delivery

44. Volk J, Marcus J, Phengrasamy T, Bleckinger D, Phuong Nguyen D, Follansbee S, Bradley H. No New HIV Infections with Increasing Use of HIV Preexposure Prophylaxis in a Clinical Practice Setting. *Clinical Infectious Diseases*. 2015 Released ahead of publication 9/1/2015.
45. Massachusetts Department of Public Health. Frequently asked questions: pre-exposure prophylaxis (PrEP) for HIV infection Massachusetts Department of Public Health. 2013
46. Norton WE, Larson RS, Dearing JW. Primary care and public health partnerships for implementing pre-exposure prophylaxis. *Am J Prev Med*. 2013; 44(1 Suppl 2):S77–9. [PubMed: 23253766]
47. Krakower, D., et al. New England Healthcare Providers' Perceptions, Knowledge and Practices Regarding the Use of Antiretrovirals for Prevention; Paper presented at 9th International Conference on HIV Treatment and Prevention Adherence; June 8-10, 2014; Miami, Florida.
48. Castel A, et al. Understanding HIV Care Provider Attitudes Regarding Intentions to Prescribe PrEP. *JAMA*. 2015 in submission.
49. White JM, Mimiaga MJ, Krakower DS, et al. Evolution of Massachusetts physician attitudes, knowledge, and experience regarding the use of antiretrovirals for HIV prevention. *AIDS Patient Care STDS*. 2012; 26(7):395–405. [PubMed: 22694239]
50. Petroll AE, Mosack KE. Physician awareness of sexual orientation and preventive health recommendations to men who have sex with men. *Sex Transm Dis*. 2011; 38:63–7. [PubMed: 20706178]
- 51*. Kwakwa, H., et al. IAC. Melbourne, Australia: 2014. Underestimation of HIV risk associated with reduced openness to HIV pre-exposure prophylaxis among African Americans. TUPE090; Special (The concept of perceived risk is critical for PrEP, and especially so for African americans who make up a disproportionate share of HIV cases in US.)
52. Millett GA, Peterson JL, Flores SA, Hart TA, Jeffries WL, Wilson PA, et al. Comparisons of disparities and risks of HIV infection in black and other men who have sex with men in Canada, UK, and USA: a meta-analysis. *Lancet*. 2012; 380:341–8. [PubMed: 22819656]
53. Raymond HF, McFarland W. Racial mixing and HIV risk among men who have sex with men. *AIDS Behav*. 2009; 13:630–7. [PubMed: 19479369]
54. Aaron E, Cohan D. Pre-exposure prophylaxis for the prevention of HIV transmission to women. *AIDS*. 2013; 27(1):F1–5. [PubMed: 22914582]
- 55*. Jennings L. (2015-02). Prevalence and Correlates of Knowledge of Male Partner HIV Testing and Serostatus Among African-American Women Living in High Poverty, High HIV Prevalence Communities (HPTN 064). *AIDS and behavior*. 2015; 19(2):291–301. Special (Insights into knowledge and its relationship to risk and how this influences prevention in African American population.). [PubMed: 25160901]
56. Madden, M.; Lenhart, A.; Duggan, M.; Cortesi, S.; Gasser, U. Teens and Technology. 2013. Accessed from: <http://www.pewinternet.org/Reports/2013/Teens-and-Tech.aspx>
57. Pew Research Center's Internet & American Life Project. 2013. Accessed from: http://www.pewinternet.org/files/old-media/Files/Reports/PIP_HealthOnline.pdf
58. Kelley CF, Kahle E, Siegler A, et al. Applying a PrEP Continuum of Care for Men who Have Sex with Men in Atlanta, GA. *Clin Inf Dis*. 2015

Key Points

PrEP has been demonstrated to be effective in clinical demonstration projects in the US and over 80% of the patients took enough doses to be protected against HIV

The uptake of this prevention tool has been slow for the first two years and is beginning to increase due to greater provider comfort and patient demand for this approach.

The implementation of PrEP will not likely be the same for all populations at risk. Women, and adolescents will likely need different strategies of engagement and follow-up to ensure adequate adherence. African Americans have not been adequately represented in the demonstration projects in the US and may need specific strategies to optimally engage this community.

More work is needed to help both providers and patients discuss sexual risk and how to prioritize who is at greatest need for PrEP. There is still ambivalence and some stigmatization regarding asking and using this mode of prevention, and further education is still needed for both patients and providers.