Current Infectious Disease Reports (2019) 21: 28
https://doi.org/10.1007/s11908-019-0685-6

HIV/AIDS (C YOON, SECTION EDITOR)

Update on HIV Preexposure Prophylaxis: Effectiveness, Drug Resistance, and Risk Compensation

Victoria E. Powell[1] · Kevin M. Gibas[1] · Joshua DuBow[1] · Douglas S. Krakower[1,2,3]

Published online: 21 June 2019

Abstract

Purpose of Review In 2019, the US government launched an initiative to decrease new HIV infections by 90% over the next decade. Studies have demonstrated the efficacy of HIV preexposure prophylaxis (PrEP) for high-risk populations, and the United States Preventative Services Task Force has issued a grade A recommendation for PrEP, indicating substantial net benefit. However, questions have been raised about the effectiveness of PrEP in clinical settings and whether PrEP use might promote antiretroviral drug resistance and increased sexual risk behaviors, which could increase transmission of bacterial sexually transmitted infections. In this narrative review, we summarize recent evidence of the effectiveness of PrEP when provided in clinical and community settings, the emergence of antiretroviral drug resistance during PrEP use, and associations between PrEP use and increased sexual risk behaviors. We also review novel PrEP modalities that are being developed to optimize PrEP acceptability, adherence, and effectiveness.

Recent Findings Studies suggest that PrEP is effective when provided in clinical settings. However, PrEP uptake and impact have been limited in the USA thus far, and major disparities in access to PrEP exist. In addition, there is evidence that drug resistance can occur with PrEP use, particularly with inadvertent PrEP use during undiagnosed acute HIV infection. Risk compensation can also occur with PrEP use and has been associated with increased sexually transmitted infections. Promising new modalities for PrEP could expand options.

Summary PrEP has strong potential to decrease HIV incidence. However, disparities in access must be addressed to ensure equity and impact for PrEP. While drug resistance and risk compensation can occur with PrEP use, these are not valid reasons to withhold PrEP from patients given its substantial protective benefits.

Keywords HIV · Preexposure prophylaxis · Drug resistance · Risk compensation · Clinical effectiveness

Victoria E. Powell and Kevin M. Gibas contributed equally to this work.

This article is part of the Topical Collection on *HIV/AIDs*

✉ Douglas S. Krakower
dkrakowe@bidmc.harvard.edu

Victoria E. Powell
vpowell1@bidmc.harvard.edu

Kevin M. Gibas
kgibas@bidmc.harvard.edu

Joshua DuBow
jdubow@bidmc.harvard.edu

[1] Division of Infectious Diseases, Beth Israel Deaconess Medical Center, 110 Francis St. W/LMOB, Suite GB, Boston, MA 02215, USA

[2] The Fenway Institute, Fenway Health, Boston, MA, USA

[3] Department of Population Medicine, Harvard Medical School, Boston, MA, USA

Introduction

There are approximately 40,000 new HIV infections in the USA each year [1], indicating a need to implement effective HIV-prevention strategies. In early 2019, the US government launched the Ending the HIV Epidemic Initiative, with a goal of decreasing new HIV infections nationally by 75% in 5 years and by 90% in 10 years [2]. One of the main pillars of this initiative is to implement HIV preexposure prophylaxis (PrEP) more widely and more effectively. Over the past decade, studies have demonstrated the efficacy of tenofovir disoproxil fumarate with or without emtricitabine (TDF/FTC) as PrEP to decrease HIV transmission in multiple populations with disproportionately high rates of new HIV infections, including men who have sex with men (MSM) [3], transgender women [3], people who inject drugs (PWID) [4], heterosexual persons engaging in high-risk behaviors [5], and HIV-serodiscordant partnerships [6]. However, PrEP

uptake and impact remain low in the USA. The Centers for Disease Control and Prevention (CDC) estimates that 1.1 million people have indications for PrEP [7], but less than 10% of people with indications received prescriptions in 2016 [8]. In addition, concerns have been raised that PrEP could potentially promote HIV drug resistance or be associated with increased sexual risk-taking, which could increase the transmission of bacterial sexually transmitted infections (STIs).

In this review, we summarize recent evidence on the effectiveness of PrEP at decreasing HIV incidence, the potential for PrEP to increase antiretroviral drug resistance, and changes in sexual behaviors and bacterial STIs that might occur with PrEP use. We also review studies of novel PrEP regimens being developed and their potential future role in improving PrEP effectiveness and impact on the HIV epidemic.

PrEP Effectiveness at Decreasing HIV Incidence

Recent studies have examined the population-level effectiveness of daily oral PrEP with TDF/FTC when prescribed to early adopters in clinical settings. These studies have focused on daily TDF/FTC because it is the only regimen recommended by CDC [9] and having a formal indication for HIV prevention [10]. An observational study of patients initiating PrEP at an integrated health care system in Northern California was one of the first studies to provide evidence of substantial effectiveness for PrEP [11]. Among 972 patients (nearly all MSM) using PrEP for a total of 850 person-years, there were no HIV seroconversions during active PrEP use; 2 patients were diagnosed with HIV after discontinuing PrEP due to insurance barriers. Adherence as measured by pharmacy refill data was high in this cohort, suggesting that PrEP can have a strong impact on HIV incidence when taken consistently.

In a study of the first 50 patients prescribed PrEP at an infectious diseases clinic in Providence, RI, only one patient was diagnosed with HIV during study follow-up. The patient diagnosed with HIV had high adherence by self-report and by objective measures, including a dried blood spot test at diagnosis with a concentration of tenofovir consistent with daily dosing. This patient was found to have multiple viral mutations associated with resistance to TDF and FTC, suggesting that TDF/FTC may not have been able to avert infection by a drug-resistant strain of HIV in this case. Only 38% of PrEP patients in this study attended a 6-month follow-up visit, suggesting that retention in PrEP care may be challenging in some care settings, which could also compromise effectiveness [12].

An additional study at a community health center in Boston, Massachusetts, specializing in health care for sexual and gender minorities suggests that PrEP provision in primary care can decrease new HIV infections. Using data from 2012 to 2017, the study compared new HIV diagnoses among patients using PrEP with patients that had received two or more HIV tests and did not use PrEP. The proportion of PrEP users newly diagnosed with HIV (0.43%) was lower than the proportion for patients who did not use PrEP (1.34%) [13]. A majority of PrEP users who acquired HIV had discontinued PrEP at least 1 month prior to their HIV diagnosis. Reasons for discontinuation included insurance barriers, scheduling challenges, perceiving themselves to be at low risk for HIV infection, and PrEP-related stigma. These findings suggest that multifaceted strategies to prevent inappropriate discontinuations of PrEP and to reengage individuals in PrEP after discontinuations could improve the effectiveness of PrEP.

A study in Australia examined whether large-scale PrEP provision could impact HIV incidence at the community level. In the Expanded PrEP Implementation in Communities-New South Wales study, 3700 participants (nearly all MSM) across 21 clinics were provided with PrEP, and community-level changes in HIV incidence were tracked [14]. During 4100 person-years of follow-up, only 2 HIV infections were observed, with both occurring during non-adherence to PrEP. HIV diagnoses in MSM in New South Wales declined rapidly and by 25% from the 12 months before PrEP roll-out to the 12 months after, including decreases in recent HIV infections. Although the impact of secular trends unrelated to PrEP in reducing HIV incidence in New South Wales could not be fully excluded because of the non-randomized design, this study offers among the strongest evidence thus far that scaling up PrEP in communities can impact HIV incidence.

In these observational studies, nearly all patients using PrEP were MSM at risk for sexual transmission of HIV, so studies assessing the effectiveness of PrEP provision to cisgender or transgender women or PWID outside of clinical trials [4, 15, 16] are needed. This need is important for cisgender women because of earlier studies suggesting that these women might need to maintain higher levels of adherence than MSM to derive full protection from TDF/FTC, such as taking at least 6 daily doses per week (versus 4 or more doses per week for MSM) [17]. These gender differences may be due to differences in the pharmacokinetics of TDF/FTC for vaginal versus rectal exposure [18–21] or the possible influence of vaginal dysbiosis or inflammation on HIV susceptibility or antiretroviral drug efficacy [22–25]. A recent study found that feminizing hormone therapy might reduce the effectiveness of PrEP in rectal tissue for transgender women, suggesting that high adherence might also be needed for protection in this population [26]. Larger studies are needed to clarify the influence of hormone therapy on PrEP effectiveness.

Inequities in PrEP Uptake

Observational studies have provided evidence that PrEP can decrease new HIV infections in community settings, but important disparities in access to PrEP have emerged. A study that used national pharmacy prescribing data to characterize trends in PrEP prescribing found racial inequities in PrEP provision. Only 11% of people receiving PrEP in this database were Black and 13% were Hispanic/Latino, even though 43% of people newly infected with HIV in the USA are Black and 26% are Hispanic/Latino [1, 8]. Survey studies have corroborated inequities in PrEP use among Black and Hispanic/Latino MSM [27, 28]. Cisgender women and PWID have also had disproportionately low rates of PrEP use. Nearly one-fifth (19%) of new HIV infections in the USA occur among cisgender women [29], with higher rates among women of color, but only 5% of PrEP users have been women [8]. Transgender women and PWID have are at increased risk for HIV acquisition [30], but there are limited data on PrEP access in these groups, suggesting a need to expand efforts to ascertain trends in PrEP uptake for all priority populations.

Barriers to PrEP Use and Effectiveness

To eliminate disparities in access and effectiveness for PrEP, multiple barriers to PrEP initiation and persistence need to be addressed. Awareness of PrEP in priority populations is suboptimal, particularly among adolescents, MSM of color, transgender persons, those in rural areas, and PWID [31–35]. In a survey of patients recently infected with HIV in an integrated health system in Northern California, almost half of respondents were unaware of PrEP [36]. A study with MSM in New York City found that even among those individuals who were aware of PrEP, many had an incomplete understanding of what PrEP was, how it prevents HIV acquisition, and its potential side effects [37], suggesting a need for strategies to improve knowledge of PrEP in key populations. Strategies could include innovative uses of social media, culturally tailored public health campaigns, and tools to improve patient-provider communication about PrEP. Awareness and use of PrEP have been increasing in some urban, white, educated, and affluent MSM populations, so efforts to disseminate information about PrEP and improve access in underserved populations should be prioritized [38].

Low knowledge and experience with PrEP among healthcare providers represents an additional barrier to PrEP uptake. Many providers are not trained in PrEP and lack support to navigate financial, insurance, and other logistical barriers that can exist with PrEP [39–41]. Providers also do not routinely discuss sexual and substance use histories with patients, which may result in missed opportunities to identify potential candidates for PrEP [42, 43]. Moreover, providers lack consensus about whether PrEP provision is more appropriate in primary or specialty care settings, such as HIV or sexual health clinics, creating a "purview paradox" whereby providers may not perceive themselves as being responsible for offering PrEP [44–47]. Promising strategies to engage more providers in PrEP include academic detailing [48], electronic clinical decision support to help providers identify PrEP candidates more effectively [49, 50], and tools to facilitate patient-provider communication and informed decision-making about PrEP [51, 52].

Even when patients and providers are motivated to initiate PrEP, cost and insurance barriers are often significant barriers to PrEP use and continuation. PrEP-related care includes the cost of medications—over $10,000 annually for TDF/FTC—as well as providers' fees and laboratory monitoring costs, so insurance coverage is essential for most patients. Commercial and public insurance plans generally provide coverage for PrEP, but high deductibles and other out-of-pocket costs may be cost-prohibitive for many patients. At a community-based sexual health clinic in San Francisco, almost one-third of patients who did not start PrEP cited cost or insurance gaps as reasons for non-initiation [53]. Similarly, among patients recently diagnosed with HIV at a health system in Northern California, one-third of patients that had been aware of PrEP prior to their HIV diagnosis cited cost or insurance coverage as barriers to PrEP use [36]. Patient assistance programs from the manufacturer of TDF/FTC and from government programs in some states can help some patients to overcome financial barriers. However, additional financial assistance programs are needed, particularly for economically disadvantaged populations with high rates of underinsurance and low rates of PrEP use, such as rural communities of color in the Southern USA [54].

PrEP and Drug Resistance

As scale up of PrEP proceeds, a consideration is the possibility that wider PrEP use could promote antiretroviral drug resistance, which could impact the effectiveness of HIV treatment and PrEP in the community. Clinical scenarios in which resistance to TDF and/or FTC might develop in PrEP users include PrEP initiation with undiagnosed acute HIV; HIV acquisition during the period of suboptimal adherence to PrEP; and infection with viral strains resistant to TDF or FTC.

Randomized studies can shed light on the potential for antiretroviral drug resistance to emerge among individuals who are prescribed PrEP. In a recent review of 13 randomized PrEP studies [55], a minority (11%) of all participants with HIV seroconversions had undiagnosed acute HIV infection at study entry, while most (89%) study participants acquired HIV during study follow-up. Of participants with undiagnosed HIV at study enrollment, about one-fifth (21%) had

mutations that conferred resistance to FTC and almost all received FTC-containing PrEP, suggesting that drug selection pressure from FTC use during acute HIV promoted drug resistance. Only two (3%) participants with undiagnosed HIV at study entry had TDF resistance, both of whom received TDF-containing PrEP during acute HIV. The lower frequency of TDF resistance as compared with FTC resistance during acute HIV is likely because of a higher genetic barrier to resistance for TDF than for FTC. Drug resistance was less common among participants who acquired HIV after study entry, with only 3% of these participants having FTC resistance and < 1% having TDF resistance, possibly because many participants in these studies had low adherence to PrEP and insufficient drug levels to select for resistance mutations. Resistance data from these efficacy studies, including the findings from a meta-analysis of drug resistance in six of these studies [56], suggests that initiating PrEP during undiagnosed acute HIV represents a high-risk scenario for the selection of drug resistance, in particular for FTC, presumably because of the use of non-suppressive antiretroviral regimens during periods of high levels of viremia.

Studies of drug resistance during PrEP use in care settings are also important to consider, as patterns of adherence and persistence with PrEP might be different outside of randomized studies. In the study of 663 PrEP patients at a community health center in Boston, seven patients had HIV seroconversions [57]. Resistance mutations were detected in two patients who were thought to have initiated PrEP during undiagnosed acute HIV (resistance to FTC in one patient and resistance to FTC and TDF in the other patient) and in none of the patients who became infected after discontinuing PrEP. This study provides additional evidence that initiating PrEP during undiagnosed acute HIV poses the greatest risk for drug resistance and that acquiring HIV after discontinuing PrEP, when drug exposure is likely to be limited or absent, is less likely to result in drug resistance.

A larger observational study suggests that HIV acquisition among PrEP users in care settings could result in substantial rates of drug-resistant HIV. In a public health partner services program in New York City, among 3721 persons newly diagnosed with HIV, 95 (3%) had previously used PrEP [58]. FTC-resistance mutations were found in 26% of former PrEP users and only 2% of persons who had not used PrEP. Thus, surveillance for HIV drug resistance among PrEP users, such as through analyses of clinical HIV genotypes, will be needed as scale up of PrEP proceeds.

Another important question is whether PrEP will protect people who are exposed to drug-resistant strains of HIV. There have been at least six individuals who have acquired HIV despite consistent use of TDF/FTC PrEP as confirmed using objective adherence measures, such as drug levels in dried blood spots or segmental hair analyses. Five of these individuals had non-nucleoside reverse transcriptase inhibitor mutations that would not be a result of selection pressure from TDF or FTC, suggesting they were infected with multidrug-resistant HIV [59–63]; one of these patients had viral genetic studies demonstrating linked infection with a drug-resistant quasispecies from a partner with HIV viremia, which is consistent with the failure of TDF/FTC to avert infection [63]. An additional patient was infected with wild type HIV in the context of having an estimated 75 sexual partners monthly and bacterial STIs, raising the possibility that repeated exposure, coupled with potential rectal inflammation, may have allowed for HIV infection despite high PrEP adherence [64]. Thus, clinicians will need to counsel patients that adherence to PrEP provides excellent protection, but that infection is still possible with intensive exposure.

PrEP and Risk Compensation

Another consideration is that PrEP users might increase their HIV risk behaviors, such as condomless anal sex, because of the sense of protection the medication provides—a concept known as risk compensation. Increased risk behaviors could potentially increase the transmission of STIs, which are already increasing among MSM and other populations heavily affected by HIV [65]. In addition, providers' concerns about risk compensation may decrease their willingness to prescribe PrEP [66]. Concerns about risk compensation pre-date the use of PrEP and initially focused on HIV-infected patients using ART [67]. However, studies from early in the era of combination ART did not find evidence that HIV-infected patients increased their sexual risk behaviors with ART or that postexposure prophylaxis resulted in risk compensation among HIV-uninfected persons [68, 69]. Nonetheless, as the effectiveness of HIV treatment to prevent forward transmission, now popularly known as "Undetectable = Untransmittable" or "U=U," and the effectiveness of PrEP become widely known, there is a need revisit whether or not PrEP use is associated with risk compensation.

Studies of risk compensation during PrEP use have produced mixed results, with some finding no evidence of risk compensation and others finding increases in condomless anal sex and STIs among PrEP users. In an efficacy study of PrEP for MSM and transgender women, there was no association between participants' beliefs that they were receiving TDF/FTC and increased condomless receptive anal intercourse [70]. Notably, this study occurred before the effectiveness of PrEP was proven, so it is possible that individuals were less likely to engage in condomless intercourse when effectiveness was unknown. A review published in 2015 concluded that no risk compensation had been demonstrated in clinical trials prior to that year [71].

However, more recent data from open-label and observational studies of PrEP after its efficacy had been demonstrated

suggest that MSM are more likely to engage in condomless anal sex while using PrEP [72–75]. There is also evidence that MSM have a higher incidence of bacterial STIs after initiating PrEP [76], even when controlling for increased screening and diagnoses that accompany comprehensive PrEP care [77]. This effect appears to be stronger in later studies [78], which suggests that PrEP may be having a greater impact on STI diagnoses as awareness of its effectiveness is disseminated. MSM who use PrEP are also at increased risk of HCV acquisition, possibly because they are more willing to have sex with HIV-infected individuals, who are more likely to have HCV infection than other partners [79]. The role of PrEP in the ongoing STI epidemic among MSM is complex. Condom use has been decreasing among MSM since before the widespread use of PrEP [80] and thus cannot be solely attributed to risk compensation among PrEP users. Likewise, the increasing rate of bacterial STIs among MSM precedes the approval and widespread use of PrEP [54, 65]. While efforts to improve control of bacterial STIs are needed, clinicians should not withhold PrEP out of concerns for risk compensation given the high effectiveness of PrEP at preventing HIV infection.

New Modalities of PrEP

In addition to daily TDF/FTC for PrEP, new regimens and delivery methods are being explored to improve acceptability, adherence, and effectiveness. Studies in France and Canada have demonstrated that on-demand (peri-coital) oral PrEP (i.e., two tablets of TDF/FTC between 2 and 24 h before exposure and a daily tablet for 48 h after) is highly effective at decreasing HIV incidence among MSM [81, 82]. In France, many individuals have opted for on-demand PrEP instead of daily use in open-label studies comparing these dosing schedules [83, 84]. On-demand PrEP can be prescribed in an off-label manner in the USA and may be an attractive option for persons with intermittent HIV exposures. A recent study also demonstrated that daily oral PrEP with tenofovir alafenamide plus FTC was non-inferior to TDF/FTC in MSM and transgender women, and was less likely to impact renal and bone parameters, so this formulation could also be prescribed off-label for select patients at high risk for renal and bone harms [85].

Additional novel PrEP modalities that are being developed and are not yet available for prescribing include intravaginal rings, long-acting injectable agents and other extended-delivery systems (e.g., subcutaneous implants), and infusions of broadly neutralizing antibodies against HIV. An intravaginal ring that elutes dapivirine, a non-nucleoside reverse transcriptase inhibitor, was moderately effective at decreasing HIV incidence among African women [86, 87], with efficacy correlating with adherence, and this device is under review at the European Medicines Agency [88]. Studies are also evaluating the efficacy of bimonthly injections of cabotegravir, an integrase inhibitor, among MSM and transgender women and African women, in the hope that intermittent injections could improve PrEP effectiveness for persons who face adherence challenges with oral PrEP (NCT02720094, NCT03164564). Cabotegravir has an extremely long half-life, so it is possible that drug resistance might emerge among persons who discontinue injections and are exposed to HIV when they have sub-protective levels of drug. In addition, among six macaques given cabotegravir injections during acute retroviral infection, three developed mutations conferring cross-resistance to all licensed integrase inhibitors, underscoring that newer PrEP agents will also require rigorous exclusion of HIV infection before their use and monitoring for HIV drug resistance [89]. Intermittent infusions of broadly neutralizing antibodies could offer a preventive approach that would avoid the challenges of daily pill use and antiretroviral drug resistance, though the efficacy of this approach is still being tested (NCT02716675).

Conclusions

Daily oral TDF/FTC for PrEP is effective at decreasing HIV incidence, but PrEP uptake in the USA remains limited, particularly among underserved populations experiencing the highest rates of new HIV infections. Diverse patient, provider, and structural barriers to PrEP use exist and must be addressed for PrEP to achieve maximal impact on HIV incidence. Drug resistance during PrEP use seems to be most likely to occur when PrEP is initiated during undiagnosed HIV infection, so developing protocols that include rigorously excluding HIV infection prior to PrEP use will be important to minimize resistance. Finally, evidence suggests that some individuals are likely increasing sexual risk behaviors while using PrEP, suggesting a need for intensive efforts to diagnose and treat bacterial STIs among PrEP users. If the implementation of daily oral PrEP can be optimized, and if new modalities of PrEP become available and can help engage greater numbers of individuals in effective PrEP use, then PrEP has the potential to have a major impact on the HIV epidemic.

Funding Information This manuscript was made possible with help from the Harvard University Center for AIDS Research (CFAR), a National Institutes of Health–funded program (P30 AI060354).

Compliance with Ethical Standards

Conflict of Interest DK has participated in HIV-prevention research supported by a grant from Gilead Sciences to Fenway Health, has received honoraria from Medscape, MED-IQ, and DKBmed for developing continuing medical education content focused on HIV prevention, and has received royalties from UptoDate, Inc. for authoring medical

education content on HIV preexposure prophylaxis. VP, KG, and JD declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Centers for Disease Control and Prevention. HIV in the United States: at a glance. 2017. https://www.cdc.gov/hiv/statistics/overview/ataglance.html. Accessed May 20, 2019.
2. U.S. Department of Health & Human Services. Ending the HIV Epidemic. 2019. https://www.hiv.gov/federal-response/ending-the-hiv-epidemic/overview. Accessed May 20, 2019.
3. 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(27):2587–99.
4. Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, 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.
5. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med. 2012;367(5):423–34.
6. 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(5):399–410.
7. Smith DK, Van Handel M, Grey J. Estimates of adults with indications for HIV pre-exposure prophylaxis by jurisdiction, transmission risk group, and race/ethnicity, United States, 2015. Annals of Epidemiology. 2018;28(12):850–7. e9.
8. Huang Y-lA, Zhu W, Smith DK, Harris N, Hoover KW. HIV preexposure prophylaxis, by race and ethnicity—United States, 2014–2016. Morb Mortal Wkly Rep. 2018;67(41):1147–50.
9. Centers for Disease Control and Prevention. Preexposure prophylaxis for the prevention of HIV infection in the United States—2017 Update: a clinical practice guideline. **Atlanta: CDC.** 2018.
10. U.S. Department of Health and Human Services. FDA approves first drug for reducing the risk of sexually acquired HIV infection. 2012. https://aidsinfo.nih.gov/news/1254/fda-approves-first-drug-for-reducing-the-risk-of-sexually-acquired-hiv-infection. Accessed May 20, 2019.
11. Marcus JL, Hurley LB, Hare CB, Nguyen DP, Phengrasamy T, Silverberg MJ, et al. Preexposure prophylaxis for HIV prevention in a large integrated health care system: adherence, renal safety, and discontinuation. J Acquir Immune Defic Syndr (1999). 2016;73(5):540–6.
12. Montgomery MC, Oldenburg CE, Nunn AS, Mena L, Anderson P, Liegler T, et al. Adherence to pre-exposure prophylaxis for HIV prevention in a clinical setting. PLoS One. 2016;11(6):e0157742.
13. Mayer KH, Krakower D, Grasso C, Levine K, Powell V, Campbell J et al., editors. Decreased HIV incidence among PrEP users compared to non-users in a Boston community health center, 2012-2017. HIV research for prevention conference; 2018.
14. Grulich AE, Guy R, Amin J, Jin F, Selvey C, Holden J, et al. Population-level effectiveness of rapid, targeted, high-coverage roll-out of HIV pre-exposure prophylaxis in men who have sex with men: the EPIC-NSW prospective cohort study. The Lancet HIV. 2018;5(11):e629–37.
15. Deutsch MB, Glidden DV, Sevelius J, Keatley J, McMahan V, Guanira J, et al. HIV pre-exposure prophylaxis in transgender women: a subgroup analysis of the iPrEx trial. The Lancet HIV. 2015;2(12):e512–e9.
16. Hanscom B, Janes HE, Guarino PD, Huang Y, Brown ER, Chen YQ, et al. Preventing HIV-1 infection in women using oral pre-exposure prophylaxis: a meta-analysis of current evidence. J Acquir Immune Defic Syndr (1999). 2016;73(5):606–8.
17. Cottrell ML, Yang KH, Prince HM, Sykes C, White N, Malone S, et al. A translational pharmacology approach to predicting outcomes of preexposure prophylaxis against HIV in men and women using tenofovir disoproxil fumarate with or without emtricitabine. J Infect Dis. 2016;214(1):55–64.
18. Wahl A, Ho PT, Denton PW, Garrett KL, Hudgens MG, Swartz G, et al. Predicting HIV pre-exposure prophylaxis efficacy for women using a preclinical pharmacokinetic-pharmacodynamic in vivo model. Sci Rep. 2017;7:41098.
19. Patterson KB, Prince HA, Kraft E, Jenkins AJ, Shaheen NJ, Rooney JF, et al. Penetration of tenofovir and emtricitabine in mucosal tissues: implications for prevention of HIV-1 transmission. Sci Transl Med. 2011;3(112):112re4–4.
20. Seifert SM, Chen X, Meditz AL, Castillo-Mancilla JR, Gardner EM, Predhomme JA, et al. Intracellular tenofovir and emtricitabine anabolites in genital, rectal, and blood compartments from first dose to steady state. AIDS Res Hum Retrovir. 2016;32(10–11):981–91.
21. Louissaint NA, Cao Y-J, Skipper PL, Liberman RG, Tannenbaum SR, Nimmagadda S, et al. Single dose pharmacokinetics of oral tenofovir in plasma, peripheral blood mononuclear cells, colonic tissue, and vaginal tissue. AIDS Res Hum Retrovir. 2013;29(11):1443–50.
22. Velloza J, Heffron R. The vaginal microbiome and its potential to impact efficacy of HIV pre-exposure prophylaxis for women. Current HIV/AIDS Reports. 2017;14(5):153–60.
23. Heffron R, McClelland RS, Balkus JE, Celum C, Cohen CR, Mugo N, et al. Efficacy of oral pre-exposure prophylaxis (PrEP) for HIV among women with abnormal vaginal microbiota: a post-hoc analysis of the randomised, placebo-controlled Partners PrEP Study. The Lancet HIV. 2017;4(10):e449–e56.
24. Eastment MC, McClelland RS. Vaginal microbiota and susceptibility to HIV. AIDS (London, England). 2018;32(6):687–98.
25. McKinnon LR, Liebenberg LJ, Yende-Zuma N, Archary D, Ngcapu S, Sivro A, et al. Genital inflammation undermines the effectiveness of tenofovir gel in preventing HIV acquisition in women. Nat Med. 2018;24(4):491–6.
26. Cottrell ML, Prince H, Schauer AP, Sykes C, Maffuid K, Poliseno A et al. Decreased tenofovir diphosphate concentrations in a transgender female cohort: implications for HIV pre-exposure prophylaxis (PrEP). Clinical Infectious Diseases. 2019 [Accepted Manuscript].
27. Snowden JM, Chen Y-H, McFarland W, Raymond HF. Prevalence and characteristics of users of pre-exposure prophylaxis (PrEP) among men who have sex with men, San Francisco, 2014 in a cross-sectional survey: implications for disparities. Sex Transm Infect. 2017;93(1):52–5.
28. Hoots BE, Finlayson T, Nerlander L, Paz-Bailey G, Group NHBSS, Wortley P et al. Willingness to take, use of, and indications for pre-exposure prophylaxis among men who have sex with men—20 US cities, 2014. Clin Infect Dis 2016;63(5):672–677.
29. Centers for Disease Control and Prevention. HIV among women. 2017. https://www.cdc.gov/hiv/group/gender/women/index.html. Accessed May 20, 2019.
30. Centers for Disease Control and Prevention. HIV among people who inject drugs. 2016. https://www.cdc.gov/hiv/group/hiv-idu.html. Accessed May 20, 2019.
31. Arrington-Sanders R, Morgan A, Oidtman J, Qian I, Celentano D, Beyrer C. A medical care missed opportunity: preexposure

prophylaxis and young black men who have sex with men. J Adolesc Health. 2016;59(6):725–8.
32. Philbin MM, Parker CM, Parker RG, Wilson PA, Garcia J, Hirsch JS. The promise of pre-exposure prophylaxis for black men who have sex with men: an ecological approach to attitudes, beliefs, and barriers. AIDS Patient Care STDs. 2016;30(6):282–90.
33. Golub SA, Gamarel KE, Rendina HJ, Surace A, Lelutiu-Weinberger CL. From efficacy to effectiveness: facilitators and barriers to PrEP acceptability and motivations for adherence among MSM and transgender women in New York City. AIDS Patient Care STDs. 2013;27(4):248–54.
34. Hubach RD, Currin JM, Sanders CA, Durham AR, Kavanaugh KE, Wheeler DL, et al. Barriers to access and adoption of pre-exposure prophylaxis for the prevention of HIV among men who have sex with men (MSM) in a relatively rural state. AIDS Educ Prev. 2017;29(4):315–29.
35. Morgan J, Ferlatte O, Salway T, Wilton J, Hull M. Awareness of, interest in, and willingness to pay for HIV pre-exposure prophylaxis among Canadian gay, bisexual, and other men who have sex with men. Can J Public Health. 2018;109(5–6):791–9.
36. Marcus JL, Hurley LB, Dentoni-Lasofsky D, Ellis CG, Silverberg MJ, Slome S, et al. Barriers to preexposure prophylaxis use among individuals with recently acquired HIV infection in Northern California. AIDS Care. 2019;31(5):536–44.
37. Pérez-Figueroa RE, Kapadia F, Barton SC, Eddy JA, Halkitis PN. Acceptability of PrEP uptake among racially/ethnically diverse young men who have sex with men: the P18 study. AIDS Educ Prev. 2015;27(2):112–25.
38. Rana J, Wilton J, Fowler S, Hart TA, Bayoumi AM, Tan DH. Trends in the awareness, acceptability, and usage of HIV pre-exposure prophylaxis among at-risk men who have sex with men in Toronto. Can J Public Health. 2018;109:342–52.
39. Krakower DS, Mayer KH. The role of healthcare providers in the roll-out of PrEP. Curr Opin HIV AIDS. 2016;11(1):41–8.
40. Blumenthal J, Jain S, Krakower D, Sun X, Young J, Mayer K, et al. 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;19(5):802–10.
41. Wood BR, McMahan VM, Naismith K, Stockton JB, Delaney LA, Stekler JD. Knowledge, practices, and barriers to HIV preexposure prophylaxis prescribing among Washington state medical providers. Sex Transm Dis. 2018;45(7):452–8.
42. Petroll AE, Walsh JL, Owczarzak JL, McAuliffe TL, Bogart LM, Kelly JA. PrEP awareness, familiarity, comfort, and prescribing experience among US primary care providers and HIV specialists. AIDS Behav. 2017;21(5):1256–67.
43. Zablotska IB, O'Connor CC. Preexposure prophylaxis of HIV infection: the role of clinical practices in ending the HIV epidemic. Current HIV/AIDS Reports. 2017;14(6):201–10.
44. Patel RR, Chan PA, Harrison LC, Mayer KH, Nunn A, Mena LA, et al. Missed opportunities to prescribe HIV pre-exposure prophylaxis by primary care providers in Saint Louis, Missouri. LGBT health. 2018;5(4):250–6.
45. 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(9):1712–21.
46. Ojile N, Sweet D, Kallail KJ. A preliminary study of the attitudes and barriers of family physicians to prescribing HIV preexposure prophylaxis. Kans J Med. 2017;10(2):40–2.
47. Clement ME, Seidelman J, Wu J, Alexis K, McGee K, Okeke NL, et al. An educational initiative in response to identified PrEP prescribing needs among PCPs in the Southern US. AIDS Care. 2018;30(5):650–5.
48. Ard KL, Edelstein ZR, Bolduc P, Daskalakis D, Gandhi AD, Krakower DS, et al. Public health detailing for human immunodeficiency virus pre-exposure prophylaxis. Clin Infect Dis. 2018;68(5):860–4.
49. Krakower D, Gruber S, Hsu K, Menchaca J, Maro J, Kruskal B, et al. Development and validation of an automated HIV prediction algorithm to identify candidates for pre-exposure prophylaxis: a modelling study. The Lancet HIV. In press.
50. Marcus J, Hurley L, Krakower D, Alexeeff S, Silverberg M, Volk J. Use of electronic health record data and machine learning to identify candidates for HIV pre-exposure prophylaxis: a modelling study. The Lancet HIV. In press.
51. Krakower D, Powell VE, Maloney K, Wong JB, Wilson IB, Mayer K. Impact of a personalized clinical decision aid on informed decision-making about HIV preexposure prophylaxis among men who have sex with men. In: International conference on HIV treatment and prevention adherence; 2018.
52. Powell VE, Mayer K, MAloney KM, Wong JB, Wilson IB, Krakower DS. Impact of a clinical decision aid for prescribing HIV preexposure prophylaxis to men who have sex with men on primary care provider knowledge and intentions. In: International conference on HIV treatment and prevention adherence; 2018.
53. Hojilla JC, Vlahov D, Crouch P-C, Dawson-Rose C, Freeborn K, Carrico A. HIV pre-exposure prophylaxis (PrEP) uptake and retention among men who have sex with men in a community-based sexual health clinic. AIDS Behav. 2018;22(4):1096–9.
54. Siegler AJ, Mouhanna F, Giler RM, Weiss K, Pembleton E, Guest J, et al. The prevalence of pre-exposure prophylaxis use and the pre-exposure prophylaxis–to-need ratio in the fourth quarter of 2017, United States. Ann Epidemiol. 2018;28(12):841–9.
55. Gibas KM, van den Berg P, Powell VE, Krakower DS. Drug resistance during HIV pre-exposure prophylaxis. Drugs. 2019;79(6):609–19.
56. Fonner VA, Dalglish SL, Kennedy CE, Baggaley R, O'reilly KR, Koechlin FM, et al. Effectiveness and safety of oral HIV preexposure prophylaxis for all populations. AIDS (London, England). 2016;30(12):1973–83.
57. Krakower D, Maloney KM, Powell VE, Levine K, Grasso C, Melbourne K, et al. Patterns and clinical consequences of discontinuing HIV preexposure prophylaxis during primary care. J Int AIDS Soc. 2019;22(2):e25250.
58. Misra K, Huang J, Daskalakis DC, Udeagu C-C. Impact of PrEP on drug resistance and acute HIV infection. In: Conference on retroviruses and opportunistic infections. New York City; 2015-2017. p. 2019.
59. Knox DC, Anderson PL, Harrigan PR, Tan DH. Multidrug-resistant HIV-1 infection despite preexposure prophylaxis. N Engl J Med. 2017;376(5):501–2.
60. Colby DJ, Kroon E, Sacdalan C, Gandhi M, Grant RM, Phanuphak P, et al. Acquisition of multidrug-resistant human immunodeficiency virus type 1 infection in a patient taking preexposure prophylaxis. Clin Infect Dis. 2018;67(6):962–4.
61. Thaden JT, Gandhi M, Okochi H, Hurt CB, McKellar MS. Seroconversion on preexposure prophylaxis: a case report with segmental hair analysis for timed adherence determination. AIDS. 2018;32(9):F1–4.
62. Markowitz M, Grossman H, Anderson PL, Grant R, Gandhi M, Horng H, et al. Newly acquired infection with multidrug-resistant HIV-1 in a patient adherent to preexposure prophylaxis. J Acquir Immune Defic Syndr. 2017;76(4):e104–e6.
63. Cohen SE, Sachdev D, Lee SA, Scheer S, Bacon O, Chen M-J, et al. Acquisition of tenofovir-susceptible, emtricitabine-resistant HIV despite high adherence to daily pre-exposure prophylaxis: a case report. The Lancet HIV. 2019;6(1):e43–50.
64. Hoornenborg E, Prins M, Achterbergh RC, Woittiez LR, Cornelissen M, Jurriaans S, et al. Acquisition of wild-type HIV-1

infection in a patient on pre-exposure prophylaxis with high intracellular concentrations of tenofovir diphosphate: a case report. The Lancet HIV. 2017;4(11):e522–e8.
65. Braxton J, Davis DW, Emerson B, Flagg EW, Grey J, Grier L et al. Sexually transmitted disease surveillance 2017: Centers for Disease Control and Prevention. 2018.
66. Calabrese SK, Magnus M, Mayer KH, Krakower DS, Eldahan AI, Hawkins LAG, et al. "Support Your Client at the Space That They're in": HIV pre-exposure prophylaxis (PrEP) prescribers' perspectives on PrEP-related risk compensation. AIDS Patient Care STDs. 2017;31(4):196–204.
67. Cassell MM, Halperin DT, Shelton JD, Stanton D. Risk compensation: the Achilles' heel of innovations in HIV prevention? Br Med J. 2006;332(7541):605–7.
68. Crepaz N, Hart TA, Marks G. Highly active antiretroviral therapy and sexual risk behavior: a meta-analytic review. JAMA. 2004;292(2):224–36.
69. Martin JN, Roland ME, Neilands TB, Krone MR, Bamberger JD, Kohn RP, et al. Use of postexposure prophylaxis against HIV infection following sexual exposure does not lead to increases in high-risk behavior. AIDS. 2004;18(5):787–92.
70. Marcus JL, Glidden DV, Mayer KH, Liu AY, Buchbinder SP, Amico KR, et al. No evidence of sexual risk compensation in the iPrEx trial of daily oral HIV preexposure prophylaxis. PLoS One. 2013;8(12):e81997.
71. Doblecki-Lewis S, Cohen S, Liu A. Clinical treatment options infectious diseases: update on PrEP implementation, adherence, and advances in delivery. Current Treatment Options in Infectious Diseases. 2015;7(2):101–12.
72. Newcomb ME, Moran K, Feinstein BA, Forscher E, Mustanski B. Pre-exposure prophylaxis (PrEP) use and condomless anal sex: evidence of risk compensation in a cohort of young men who have sex with men. J Acquir Immune Defic Syndr. 2018;77(4):358–64.
73. Hoornenborg E, Coyer L, van Laarhoven A, Achterbergh R, de Vries H, Prins M, et al. Change in sexual risk behaviour after 6 months of pre-exposure prophylaxis use: results from the Amsterdam pre-exposure prophylaxis demonstration project. AIDS. 2018;32(11):1527–32.
74. Oldenburg CE, Nunn AS, Montgomery M, Almonte A, Mena L, Patel RR, et al. Behavioral changes following uptake of HIV preexposure prophylaxis among men who have sex with men in a clinical setting. AIDS Behav. 2018;22(4):1075–9.
75. Volk JE, Marcus JL, Phengrasamy T, Blechinger D, Nguyen DP, Follansbee S, et al. No new HIV infections with increasing use of HIV preexposure prophylaxis in a clinical practice setting. Clin Infect Dis. 2015;61(10):1601–3.
76. Nguyen V-K, Greenwald ZR, Trottier H, Cadieux M, Goyette A, Beauchemin M, et al. Incidence of sexually transmitted infections before and after preexposure prophylaxis for HIV. AIDS (London, England). 2018;32(4):523.
77. Traeger MW, Cornelisse VJ, Asselin J, Price B, Roth NJ, Willcox J, et al. Association of HIV preexposure prophylaxis with incidence of sexually transmitted infections among individuals at high risk of HIV infection. JAMA. 2019;321(14):1380–90.
78. Traeger MW, Schroeder SE, Wright EJ, Hellard ME, Cornelisse VJ, Doyle JS, et al. Effects of pre-exposure prophylaxis for the prevention of human immunodeficiency virus infection on sexual risk behavior in men who have sex with men: a systematic review and meta-analysis. Clin Infect Dis. 2018;67(5):676–86.
79. Price JC, McKinney JE, Crouch P-C, Dillon SM, Radix A, Stivala A, et al. Sexually acquired hepatitis C infection in HIV-uninfected men who have sex with men using preexposure prophylaxis against HIV. J Infect Dis. 2018;40:1–4.
80. Paz-Bailey G, Mendoza MC, Finlayson T, Wejnert C, Le B, Rose C, et al. Trends in condom use among MSM in the United States: the role of antiretroviral therapy and seroadaptive strategies. AIDS (London, England). 2016;30(12):1985–90.
81. Molina J-M, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. N Engl J Med. 2015;373(23):2237–46.
82. Molina J-M, Charreau I, Spire B, Cotte L, Chas J, Capitant C, et al. Efficacy, safety, and effect on sexual behaviour of on-demand pre-exposure prophylaxis for HIV in men who have sex with men: an observational cohort study. The Lancet HIV. 2017;4(9):e402–e10.
83. Molina J-M, Ghosn J, Béniguel L, Rojas-Castro D, Algarte-Genin M, Pialoux G et al., editors. Incidence of HIV-infection in the ANRS Prévenir study in Paris region with daily or on-demand PrEP with TDF/FTC. International AIDS Conference; 2018.
84. Reyniers T, Nöstlinger C, Laga M, De Baetselier I, Crucitti T, Wouters K, et al. Choosing between daily and event-driven pre-exposure prophylaxis: results of a Belgian PrEP demonstration project. J Acquir Immune Defic Syndr. 2018;79(2):186–94.
85. Hare CB, Coll J, Ruane P, Molina J-M, Mayer KH, Jessen H et al. The phase 3 DISCOVER study: daily F/TAF or F/TDF for HIV preexposure prophylaxis. Conference on retroviruses and opportunistic infections 2019.
86. Nel A, van Niekerk N, Kapiga S, Bekker L-G, Gama C, Gill K, et al. Safety and efficacy of a dapivirine vaginal ring for HIV prevention in women. N Engl J Med. 2016;375(22):2133–43.
87. Baeten JM, Palanee-Phillips T, Brown ER, Schwartz K, Soto-Torres LE, Govender V, et al. Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. N Engl J Med. 2016;375(22):2121–32.
88. International Partnership for Microbicides. IPM's application for dapivirine vaginal ring for reducing HIV risk in women now under review by European medicines agency. 2017.
89. Radzio-Basu J, Council O, Cong M-e, Ruone S, Newton A, Wei X, et al. Drug resistance emergence in macaques administered cabotegravir long-acting for pre-exposure prophylaxis during acute SHIV infection. Nat Commun. 2005;2019(10):1.