Preexposure Prophylaxis in Individuals at Risk for HIV Infection

BACKGROUND

Human immunodeficiency virus (HIV) is a retrovirus that attacks $CD4^+$ T cells, in addition to causing multiple additional immune-system derangements. In the absence of treatment, this results in the eventual collapse of the immune system and the onset of morbid and life-threatening opportunistic infections.[1] Treatment with antiretroviral therapy (ART), which targets these critical enzymes, can effectively manage infection in individuals with HIV.[1] Individuals with HIV infections who are treated with ART have near-normal life spans.[2]

Since its recognition in 1981,[3] HIV has become a global crisis. As of 2019, an estimated 38 million people are living with HIV.[4] The HIV virus is spread by sexual contact and can be found in semen, rectal secretions, and vaginal secretions. It is also spread via blood, such as in people who inject drugs using contaminated needles or in healthcare workplace exposures. Mother-to-child transmission of HIV can occur from breast milk.[5]

Numerous prevention strategies have emerged to reduce HIV transmission, including safe-sex practices, clean needle use for injectable drug users, and perinatal treatment of mothers with HIV infection.[6] Postexposure prophylaxis with ART has also been shown to be effective in preventing transmission.[2]

In addition to behavioral interventions, guidelines recommend treatment with ART as preexposure prophylaxis (PrEP) for individuals without HIV infection who are at high risk.[2] The first oral PrEP regimen was approved for use by the Food and Drug Administration (FDA) in 2012.[7] The use of PrEP increased by 56% annually from 2012 to 2017.[8] The US office of HIV/AIDS and Infectious Disease Policy considers PrEP access a key area of focus in HIV/AIDS prevention.[9] Access to PrEP, in addition to other interventions, has been associated with a reduction in new HIV cases.[10]

Treatment with PrEP is an effective method of HIV prevention. A meta-analysis of multiple studies comparing oral PrEP with placebo demonstrated a risk ratio of HIV infection of 0.30 (95% CI 0.21 to 0.45; $P < .001$).[11] There was no significant increase in adverse events, increase in incidence of drug-resistant HIV infection in previously uninfected individuals, increase in pregnancy-related adverse events, or change in hormonal contraceptive effectiveness.[11] Authors of this meta-analysis concluded that “PrEP . . . is effective in reducing risk of HIV infection among various populations. There is little evidence of risk compensation and adverse safety events.”[11]

As a result of treatment and prevention strategies, new HIV infections have declined by 23% from 2010 to 2019.[4] However, there is still spread of HIV, with 1.7 million new cases reported in 2019.[4] This suggests a large gap in knowledge and applications of HIV prevention strategies. The World Health Organization now recommends PrEP initiation in all at-risk populations.[12]

EDUCATIONAL ANALYSIS

Gap #1: Clinicians may be unaware of approved and upcoming PrEP treatment options and recommendations.

Learning Objective #1: Practitioners will be able to compare current and upcoming PrEP therapeutic options, treatment recommendations, and evidence supporting their effectiveness.

Clinicians may be unaware of the current approved PrEP therapy options or promising therapies currently in development.

<u>Testing Prior to Initiation of PrEP</u>

Prior to PrEP initiation, the International Antiviral Society recommends obtaining combined HIV antibody and antigen testing, serum creatinine level, hepatitis B surface antigen testing, hepatitis C testing

(hepatitis C immunoglobulin G antibody testing if the individual is not known to be positive previously or hepatitis C RNA level if the individual is known to be positive), hepatitis A immunoglobulin G antibody testing, *Neisseria gonorrhea* and *Chlamydia trachomatis* testing, and syphilis testing.[2] Repeat HIV testing is recommended at 1 month, followed by HIV testing every 3 months.[2] Creatinine level monitoring is also recommended every 3 months, and can be extended to every 3 to 6 months in individuals not at risk for kidney injury.[2]

Tenofovir disoproxil fumarate/emtricitabine

The combination of the nucleoside analog HIV-1 reverse transcriptase inhibitors tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC; derived from the chemical name 2'-deoxy-5-fluoro-3'-thiacytidine)[13] is currently the only FDA-approved medication for PrEP.[2,14] Recommended adult dosing of TDF/FTC for PrEP is 300 mg of TDF and 200 mg of FTC taken orally once daily.[2,14] Specifically in men who have sex with men, TDF/FTC can be administered in an on-demand manner. This is an off-label dosing of TDF/FTC. A double dose of TDF/FTC is taken 24 hours prior to high-risk activity followed by standard dosing for 2 days from the last high-risk exposure. This is also known as 2-1-1 dosing.[2]

Numerous clinical trials have demonstrated the effectiveness of TDF/FTC regimens. The Preexposure Prophylaxis Initiative (iPrEx) trial was a blinded randomized trial comparing TDF/FTC to placebo in 2499 individuals without HIV infection who were either men who have sex with men or transgender women who have sex with men. A 44% reduction in the incidence of HIV was noted in the TDF/FTC group compared with the placebo group (95% CI 15% to 63%; *P* = .005). Nausea was reported more often in the treatment group than the placebo group.[15] Similarly, the PROUD trial was an open open-label study of 544 men who have sex with men who were HIV-seronegative randomized to a group that received TDF/FTC immediately or to a group to receive TDF/FTC after a 1-year delay. An interim analysis demonstrated an 86% relative reduction in HIV infection in the immediate group compared with the delayed group (90% CI 64% to 96%; *P* <.001), after which participants in the delayed group were offered PrEP due to its effectiveness. Participants reported adverse events, including nausea, headache, and arthralgia, though no serious adverse events were reported.[16]This open-label study validated the real-world efficacy of PrEP.

To test the on-demand dosing strategy, a double-blind study of 414 men who had unprotected anal sex with men randomized to receive on-demand TDF/FTC or placebo demonstrated an 86% relative reduction in the incidence of HIV in the TDF/FTC group compared with the placebo group (95% CI 40% to 98%; *P* = .002). Participants reported more gastrointestinal adverse events in the TDF/FTC group, although rates of serious side effects were similar in both groups. This trial was also discontinued after an interim analysis showed effectiveness and demonstrated that on-demand therapy was a valid alternative to standard daily dosing.[17]

The use of TDF requires renal dosing adjustments and has been associated with reduced renal function.[1] The use of TDF has also been associated with reduced bone density, which may lead to increased fracture risk.[13] The use of FTC also requires renal dosing, and its most common reported side effect is skin discoloration.[1]

Cabotegravir

Although not yet FDA approved, cabotegravir is a promising PrEP medication currently in development. Cabotegravir, an integrase inhibitor like the currently used ART therapy dolutegravir, is a long-acting injectable therapy currently undergoing clinical trials that may make adherence easier.[19]

Clinical trials investigating cabotegravir are underway. Clinical trial HPTN 083 is a double-blind randomized trial of 4566 cisgender and transgender men who have sex with men randomized to either placebo injection every 8 weeks and oral TDF/FTC or cabotegravir injection every 8 weeks and placebo TDF/FTC pills. An interim analysis of this study demonstrated an incidence of HIV infection of 0.41% (95% CI 0.22% to 0.69%) in participants in the cabotegravir group compared with 1.22% (95% CI 0.87% to 1.67%) in those in the TDF/FTC group This suggested that, while both CAB and TDF/FTC were safe

and effective, CAB had higher efficacy in preventing HIV infection. [20] Injection site reactions, fever, and hypertension were more common in the cabotegravir group, while nausea was more common in the TDF/FTC group.[20] Clinical trial HPTN 084 is a similar trial of 3223 cisgender women; an interim analysis of this trial demonstrated that cabotegravir was 89% (95% CI 68% to 96%) more effective than TDF/FTC in preventing HIV transmission.[19] Similarly, injection site reactions were more common in the cabotegravir group, and gastrointestinal symptoms were more common in the TDF/FTC group.[19] These interim analyses suggest cabotegravir may be a highly effective PrEP option.[19]

Further research is needed on the safety of cabotegravir in pregnant women, and FDA approval is still needed.[19] However, the International Antiviral Society is recommending cabotegravir use for PrEP pending FDA approval.[2]

Dapivirine Vaginal Ring

Dapivirine, a non-nucleoside HIV-1 reverse transcriptase inhibitor, formulated in a vaginal ring is another treatment option under development.[21] A randomized double-blind study of 2629 women comparing use of a monthly dapivirine vaginal ring with a placebo vaginal ring demonstrated that women in the dapivirine vaginal ring group had a 27% (95% CI 1% to 46%; *P* = .046) lower incidence of HIV infection compared with those in the placebo group.[21] Efficacy was highly associated with adherence; a subgroup analysis of highly compliant participants revealed a 37% (95% CI 12% to 56%; *P* = .007) reduction in the incidence of HIV in the dapivirine group compared with the placebo group.[21] Adverse events were similar in both groups.[21]

The dapivirine vaginal ring is not currently a recommended method of PrEP by the International Antiviral Society or the Centers for Disease Control and Prevention.[2,22] There is an ongoing phase 3 trial ongoing to evaluate this method of PrEP.[23]

In summary, TDF/FTC is the only FDA-approved medication for PrEP at this time, with promising results demonstrating the effectiveness of cabotegravir and ongoing research regarding the dapivirine vaginal ring.

Gap#2: Clinicians may not recognize populations who may benefit from PrEP.

Gap#2: Clinicians will be able to classify populations at high-risk for HIV infection and the evidence supporting PrEP use in these populations.

Several specific populations have been studied for PrEP effectiveness.

Men who Have Sex With Men

Men who have sex with men are the most studied population for PrEP effectiveness, with many trials demonstrating the efficacy of PrEP in this population.[15-17] However, differences in PrEP effectiveness have been noted between gay men and transgender women who have sex with men when evaluated as subgroups. A subgroup analysis of the iPrEx trial evaluating transgender women compared with gay men found significant differences between these two groups. When evaluating transgender women alone, there was no difference between HIV incidence in the TDF/FTC group compared with the placebo group (hazard ratio 1.1; 95% CI 0.5 to 2.7; *P* = .77) despite the efficacy demonstrated in the total population.[23] This implies that the majority of benefit was seen in cisgender men. Transgender women reported higher rates of high-risk sexual behaviors, including transactional intercourse, unprotected receptive anal sex, and high numbers of sexual partners.[23] Further, the adherence to the study medication in transgender women was low.[23] Authors of this subgroup analysis suggested that “studies of PrEP use in TGW [transgender women] populations should be designed and tailored specifically for this population, rather than adapted from or subsumed into studies of MSM [men who have sex with men].”[23] These findings suggest that, while gay men and transgender women represent high-risk groups, transgender women are particularly vulnerable and represent a group that may strongly benefit from PrEP use. Clinicians need

education regarding PrEP use and patient counseling to overcome barriers to PrEP use among transgender women.

Serodiscordant Heterosexual Couples

Heterosexual couples with one partner who is HIV positive and one partner who is HIV negative benefit from PrEP. A randomized trial in which 4747 individuals without HIV infection who have a partner with HIV infection were randomized 1:1:1 to receive TDF/FTC, TDF alone, or placebo, respectively. Participants in the TDF/FTC group had a 75% (95% CI 55% to 87%; $P < .001$) reduction in HIV incidence compared with those in the placebo group, and those in the TDF group had a 67% (95% CI 44% to 81%; $P < .001$) reduction in the incidence of HIV compared with those in the placebo group.[24] There was no difference in HIV incidence seen in participants between the TDF/FTC and TDF groups.[24] PrEP can be effective in preventing transmission of HIV in serodiscordant couples.

Heterosexual Women

Women are a population that requires further study regarding PrEP use. Concentrations of TDF/FTC do not reach as high of levels in the female lower genital tract than in the colon or rectum.[25] Studies of heterosexual women at risk for HIV have not had positive results. A study in Africa randomizing 2210 women who were HIV negative failed to demonstrate a significant reduction in HIV infections in the PrEP group compared with the control group.[26] This study found increased adverse events, including hepatic and renal abnormalities, and was discontinued early due to lack of effectiveness. Adherence to the study medication was very low, which may explain the lack of efficacy.[26] Similarly, a study of 5029 women in Africa randomized to TDF alone, TDF/FTC, or placebo also failed to demonstrate a reduction in HIV incidence.[27] Adherence to the study medication was also low in this trial.[27] Adverse events, specifically elevated creatinine levels, were reported more often in the TDF/FTC group than in the placebo group.[27] These results “reaffirm the need for effective and acceptable prevention interventions for women at high risk for sexual acquisition of HIV-1.”[27] Both studies were conducted in Africa, and generalizability of the lack of effectiveness to other populations may be limited.

People who Inject Drugs

People who inject drugs benefit from PrEP use. In a randomized double-blind study of individuals who had injected drugs within the last year prior to enrollment, 2413 participants were randomized to receive TDF or placebo. There was a 48.9% (95% CI 9.6% to 72.2%; $P = .01$) reduction in HIV incidence in the TDF group compared with the placebo group.[28] Nausea was more common in the TDF group, though there was no difference in serious adverse events between the two groups.[28] This study supports the effectiveness of PrEP in people who inject drugs.

In summary, men who have sex with men, serodiscordant heterosexual couples, and people who inject drugs are populations in which PrEP use has strong evidence for effectiveness. Studies of heterosexual women at high risk for HIV infection have not shown significant results; however, this may be related to low adherence in these trials. The World Health Organization guidelines recommend offering PrEP to all at-risk populations.[12]

Gap #3: Clinicians may not recognize underutilization of PrEP and factors leading to treatment failure.

Learning Objective #3: Clinicians will assess gaps in the use of PrEP in at-risk populations as well as specific factors associated with PrEP failure.

Surveys have demonstrated increasing awareness of PrEP among clinicians, from 24% of respondents reporting awareness of PrEP in 2009 to 66% in 2016. Nevertheless, this suggests 1 in 3 clinicians may not be aware of PrEP.[29] Clinicians with low PrEP knowledge are less likely to prescribe PrEP; lack of understanding regarding eligible individuals, side effects, and adherence represents a barrier to PrEP prescription.[30] Additional barriers to PrEP prescription include cost concerns, interpersonal stigma, and

concerns about behavioral consequences.[31] Many individuals seeking PrEP from their primary care provider did not receive a prescription because it was perceived as specialty care; however, widespread use of PrEP may require increased prescription from primary care providers.[32] These represent barriers that require specific education among health care providers to increase PrEP administration.

There are large gaps in the percentage of individuals in various at-risk populations who are aware of PrEP and willing to take PrEP compared with the percentage of those who actually take PrEP. Survey data have demonstrated that only 22% of men who have sex with men in China were aware of PrEP, even though 75.6% stated they would probably or definitely take PrEP.[33] Similarly, only 29% of men who have sex with men surveyed in Nigeria had used PrEP, despite 80.1% being willing to use PrEP,[34] and only 8.2% of transgender women in Florida used PrEP, with 65.5% being aware of PrEP.[35] In the US, only 4% of men who have sex with men were taking PrEP, even though 50% were aware of PrEP.[36] These surveys from multiple locations suggest that there are many populations in which PrEP use could be increased substantially.

Lack of adherence to PrEP regimens is associated with lack of effectiveness. In a meta-analysis of multiple oral PrEP trials, studies with high adherence had a risk ratio of HIV infection of 0.30 (95% CI 0.21 to 0.45; $P < .001$) in the PrEP group compared with the placebo group, while studies with low adherence did not demonstrate a significant reduction in HIV infections.[11] PrEP adherence is highly associated with reduced HIV incidence. Clinicians require additional education regarding patient counseling for PrEP adherence.

In summary, many members of at-risk populations are unaware of PrEP and its benefits, and few of those who are aware of PrEP and willing to take PrEP are actually using it. High adherence is critical for PrEP effectiveness. There is a need to increase awareness of the benefits of PrEP in both clinicians and at-risk individuals.

SUGGESTED FACULTY LIST

1. Jared M. Baeten, MD, PhD, Vice Dean of the School of Public Health and Professor of Global Health, Medicine, and Epidemiology, University of Washington, Seattle, Washington

2. Antonio E. Urbina, MD, Medical Director, Mt. Sinai Institute for Advanced Medicine, New York, New York

3. Richard A. Elion, MD, Clinical Professor of Medicine, George Washington University School of Medicine, Washington, DC

4. Jonathan S. Appelbaum, MD, Florida State University College of Medicine, Tallahassee, Florida

5. Geeta Gupta, MD, Clinical Professor of Infectious Diseases, University of California, Irvine, California

CONCLUSION

PrEP is a safe and effective method of reducing HIV infection in individuals who are HIV negative. The use of TDF/FTC daily or on-demand is currently approved by the FDA for HIV prevention in high-risk individuals. Promising results were seen with long-acting injectable cabotegravir, which is currently awaiting FDA approval. There are still significant gaps in both clinician knowledge of PrEP and awareness and use of PrEP among at-risk populations. Men who have sex with men, people who inject drugs, and serodiscordant heterosexual couples are among the populations who may benefit from PrEP.

REFERENCES

1. Pau AK, George JM. Antiretroviral therapy: current drugs. *Infect Dis Clin North Am*. 2014;28(3):371-402. doi:10.1016/j.idc.2014.06.001

2. Saag MS, Gandhi RT, Hoy JF, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2020 recommendations of the International Antiviral Society-USA Panel. *JAMA*. 2020;324(16):1651-1669. doi:10.1001/jama.2020.17025

3. De Cock KM, Jaffe HW, Curran JW. The evolving epidemiology of HIV/AIDS. *AIDS*. 2012;26(10):1205-1213. doi:10.1097/QAD.0b013e328354622a

4. Global HIV & AIDS statistics — 2020 fact sheet. Joint United Nations Programme on HIV and AIDS. Accessed December 17, 2020. https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf

5. Ways HIV can be transmitted. Centers for Disease Control and Prevention. Updated November 3, 2020. Accessed December 19, 2020. https://www.cdc.gov/hiv/basics/hiv-transmission/ways-people-get-hiv.html

6. HIV prevention. Centers for Disease Control and Prevention. Updated October 22, 2020. Accessed December 19, 2020. https://www.cdc.gov/hiv/basics/prevention.html

7. FDA In Brief: FDA continues to encourage ongoing education about the benefits and risks associated with PrEP, including additional steps to help reduce the risk of getting HIV. US Food and Drug Administration. July 1, 2019. Accessed December 17, 2020. https://www.fda.gov/news-events/fda-brief/fda-brief-fda-continues-encourage-ongoing-education-about-benefits-and-risks-associated-prep#:~:text=In%202012%2C%20the%20FDA%20approved,35%20kilograms%20(77%20pounds)

8. Sullivan PS, Giler RM, Mouhanna F, et al. Trends in the use of oral emtricitabine/tenofovir disoproxil fumarate for pre-exposure prophylaxis against HIV infection, United States, 2012-2017. *Ann Epidemiol*. 2018;28(12):833-840. doi:10.1016/j.annepidem.2018.06.009

9. National HIV/AIDS Strategy for the United States: Updated to 2020. Office of National AIDS Policy. July 30, 2015. Updated January 31, 2017. Accessed December 17, 2020. https://www.hiv.gov/federal-response/national-hiv-aids-strategy/nhas-update

10. Brown AE, Mohammed H, Ogaz D, et al. Fall in new HIV diagnoses among men who have sex with men (MSM) at selected London sexual health clinics since early 2015: testing or treatment or pre-exposure prophylaxis (PrEP)? *Euro Surveill*. 2017;22(25):30553. doi:10.2807/1560-7917.ES.2017.22.25.30553

11. Fonner VA, Dalglish SL, Kennedy CE, et al. Effectiveness and safety of oral HIV preexposure prophylaxis for all populations. *AIDS*. 2016;30(12):1973-1983. doi:10.1097/QAD.0000000000001145

12. World Health Organization. *Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV*. World Health Organization; 2015. Accessed December 19, 2020.

13. Liotta DC, Schinazi RF, Choi W, inventors; Emory University, assignee; Method for the synthesis, compositions and use of 2'-deoxy-5-fluoro-3'-thiacytidine and related compounds. US patent 5 210 085. February 22, 1991.

14. Truvada package insert. US Food and Drug Administration. Updated June, 2020. Accessed December 19, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021752s061lbl.pdf

15. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. 2010;363(27):2587-2599. doi:10.1056/NEJMoa1011205

16. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet*. 2016;387(10013):53-60. doi:10.1016/S0140-6736(15)00056-2

17. Molina JM, Capitant C, Spire B, et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 Infection. *N Engl J Med*. 2015;373(23):2237-2246. doi:10.1056/NEJMoa1506273

18. Huang JS, Hughes MD, Riddler SA, Haubrich RH; Aids Clinical Trials Group A5142 Study Team. Bone mineral density effects of randomized regimen and nucleoside reverse transcriptase inhibitor selection from ACTG A5142. *HIV Clin Trials*. 2013;14(5):224-234. doi:10.1310/hct1405-224

19. Trial results reveal that long-acting injectable cabotegravir as PrEP is highly effective in preventing HIV acquisition in women. World Health Organization. November 9, 2020. Accessed December 19, 2020. https://www.who.int/news/item/09-11-2020-trial-results-reveal-that-long-acting-injectable-cabotegravir-as-prep-is-highly-effective-in-preventing-hiv-acquisition-in-women

20. Landovitz RJ, Donnell D, Clement M, et al. HPTN 083 interim results: pre-exposure prophylaxis containing long-acting injectable cabotegravir is safe and highly effective for cisgender men and transgender women who have sex with men. Abstract presented at: 23rd International AIDS Conference (AIDS 2020: Virtual); July 8, 2020

21. Baeten JM, Palanee-Phillips T, Brown ER, et al. Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. *N Engl J Med*. 2016;375(22):2121-2132. doi:10.1056/NEJMoa1506110

22. About PrEP. Centers for Disease Control and Prevention. Updated November 3, 2020. Accessed December 19, 2020. https://www.cdc.gov/hiv/basics/prep/about-prep.html

23. Deutsch MB, Glidden DV, Sevelius J, et al. HIV pre-exposure prophylaxis in transgender women: a subgroup analysis of the iPrEx trial. *Lancet HIV*. 2015;2(12):e512-e519. doi:10.1016/S2352-3018(15)00206-4

24. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med*. 2012;367(5):399-410. doi:10.1056/NEJMoa1108524

25. Cottrell ML, Yang KH, Prince HM, 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. doi:10.1093/infdis/jiw077

26. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med*. 2012;367(5):411-422. doi:10.1056/NEJMoa1202614

27. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *N Engl J Med*. 2015;372(6):509-518. doi:10.1056/NEJMoa1402269

28. 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):2083-2090. doi:10.1016/S0140-6736(13)61127-7

29. Smith DK, Mendoza MC, Stryker JE, Rose CE. PrEP awareness and attitudes in a national survey of primary care clinicians in the United States, 2009-2015. *PLoS One*. 2016;11(6):e0156592. doi:10.1371/journal.pone.0156592

30. Agovi AM, Anikpo I, Cvitanovich MJ, Craten KJ, Asuelime EO, Ojha RP. Knowledge needs for implementing HIV pre-exposure prophylaxis among primary care providers in a safety-net health system. *Prev Med Rep*. 2020;20:101266. Published 2020 Nov 28. doi:10.1016/j.pmedr.2020.101266

31. Pleuhs B, Quinn KG, Walsh JL, Petroll AE, John SA. Health Care Provider Barriers to HIV Pre-Exposure Prophylaxis in the United States: A Systematic Review. *AIDS Patient Care STDS*. 2020;34(3):111-123. doi:10.1089/apc.2019.0189

32. Patel RR, Chan PA, Harrison LC, et al. Missed Opportunities to Prescribe HIV Pre-Exposure Prophylaxis by Primary Care Providers in Saint Louis, Missouri. *LGBT Health*. 2018;5(4):250-256. doi:10.1089/lgbt.2017.0101

33. Han J, Bouey JZ, Wang L, et al. PrEP uptake preferences among men who have sex with men in China: results from a National Internet Survey. *J Int AIDS Soc*. 2019;22(2):e25242. doi:10.1002/jia2.25242

34. Ogunbajo A, Iwuagwu S, Williams R, Biello K, Mimiaga MJ. Awareness, willingness to use, and history of HIV PrEP use among gay, bisexual, and other men who have sex with men in Nigeria. *PLoS One*. 2019;14(12):e0226384. doi:10.1371/journal.pone.0226384

35. Holder CL, Perez-Gilbe HR, Fajardo FJ, Garcia S, Cyrus E. Disparities of HIV risk and PrEP use among transgender women of color in South Florida. *J Natl Med Assoc*. 2019;111(6):625-632. doi:10.1016/j.jnma.2019.08.001

36. Hoots BE, Finlayson T, Nerlander L, Paz-Bailey G. National HIV Behavioral Surveillance Study Group. 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. doi:10.1093/cid/ciw367