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HIV Pre-Exposure Prophylaxis: Efficacy and Safety of Approved Therapeutic Regimens and Promising Drugs

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Abstract

Background: Pre-Exposure Prophylaxis (PrEP) has emerged as a strategy for the prevention of HIV infection by antiretroviral drug use in seronegative individuals with continuous exposure to the virus. PrEP was approved in 2012 in the United States of America, by combining tenofovir disoproxil fumarate with emtricitabine (TDF/FTC). PrEP is based on TDF 300mg/FTC 200mg daily oral use, proposed to prevent infection in HIV-seronegative individuals with high risk of acquiring HIV.

Methods: A review was performed of major clinical trials and observational studies evaluating the efficacy of this approved treatment and others underway that propose new treatments and different routes of administration with the aim of improving the effectiveness of prophylaxis. In addition, protocols approved in some countries and those that are still under evaluation to be applied are presented.

Results and Conclusion: PrEP with TDF/FTC is effective and safe. However, the efficacy of other regimens is still being evaluated in clinical trials, preventing its recommendation.

Keywords:* *Pre-Exposure prophylaxis; HIV; Clinical trial; Clinical protocols; Clinical efficacy and safety

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1. Introduction

Significant advances in antiretroviral therapy (ART) in recent years have improved the life expectancy of seropositive patients, however, the transmission of human immunodeficiency virus (HIV) remains common, with almost 2 million new diagnoses worldwide [1,2]. Public health strategies to prevent HIV infection include educational campaigns promoting safe sex and the use of antiretroviral drugs, which quantitatively reduce the HIV viral load and, consequently, the risk of virus transmission, however, HIV transmission is still high [3,4]. HIV PrEP has emerged as a strategy for the prevention of HIV infection by antiretroviral (ARV) drug use in HIV-seronegative individuals with continuous exposure to the virus. PrEP was initially approved in 2012 by Food and Drug Administration (FDA) in the United States of America (USA), by combining tenofovir disoproxil fumarate with emtricitabine (TDF 300mg/FTC 200 mg - Gilead Sciences Inc., Foster City, CA, USA). Later, it was boosted after advances in medicine with the successful use of ART as prophylaxis of congenital transmission of HIV in neonates exposed to the virus during gestation, labor and breastfeeding, and due to demonstration of protection given to the intestinal mucosa in primates against HIV [5].

PrEP is based on daily use of ARV, proposed to prevent infection in HIV-seronegative individuals at high risk of acquiring the virus, taken together with other preventive measures. In this way, PrEP is an adjunct strategy, recommended by the World Health Organization (WHO) since 2015, and is potentially effective in reducing new HIV infections in at-risk groups, because of their risky behavior or the fact that they are partners in a serodiscordant relationship [6].

At first, the WHO guidelines recommended the use of PrEP in key individuals, those being men who have sex with men (MSM), intravenous drug users, sex workers, transgender people and prisoners [6]. Nowadays, however, the WHO guidelines have expanded the population who can benefit from PrEP. Current recommendations are that therapy can be offered to all people who are at substantial risk for HIV infection, which is defined as having an incidence greater than 3 HIV-infected persons per 100 per year in the absence of pre-exposure prophylaxis. However, individual risk varies within groups at substantial risk, depending on certain factors such as behavior and characteristics of sexual partners. Locations with high overall incidence of HIV infection may have individuals at substantial risk who may benefit from PrEP. Thresholds for PrEP may vary depending on a variety of considerations, including the epidemiological context, available resources and relative costs, feasibility and demand [6]. Despite there being clinical studies that have been performed demonstrating the safety and effectiveness of PrEP, clinicians prescribe PrEP for only a minority of at-risk individuals. This review summarizes evidence regarding HIV chemoprophylaxis, focusing on PrEP efficacy and safety to provide information about who are the individuals that may safely benefit from PrEP.

2. Methods

A literature search was conducted in PubMed, Scopus and Google Scholar using the search terms: [PrEP] OR [Pre-exposure prophylaxis] AND [HIV] OR [human immunodeficiency virus] AND [Clinical Protocols] OR [Guidelines], to identify articles without language restrictions and that were published between January 2006 and March 2018 (n= 3040 studies until March 15, 2018). Randomized controlled trials (RCT), open label, observational studies and guidelines which were more updated and relevant as well as those which evaluated the efficacy and safety of drugs used in prophylaxis were selected by the authors.

3. Efficacy and Safety of HIV Pre-Exposure Prophylaxis (PrEP)

Although there has been a certain global stabilization of the number of new cases of HIV infection, in recent years there has been an increase in the incidence rate of the infection in MSM. This reflects the lack of effectiveness of the prevention campaigns targeting this group. In view of this, it is necessary to think of alternative preventive measures. In this context the PrEP has shown positive results reaching high protection rates both in trials and in real life. In addition, this strategy also proved to be adequate in terms of safety, tolerance, and cost-effectiveness [7]. Initially, the efficacy of PrEP was investigated in monkeys in a study in which low doses of TDF were given for seven days to six animals. This started one day prior to virus inoculation, and only one animal was infected by HIV [8]. Several studies (TABLE 1) are still ongoing to assess PrEP's efficacy in humans and to find which are the desirable characteristics of ARV for eligibility as safe prophylaxis. Among these characteristics, we can highlight good tolerance, resistance profile of the drug, reduced number of daily tablets and the ability to accumulate quickly in the genital and rectal tissues [9].

TABLE 1. **HIV Pre-Exposure Prophylaxis (PrEP) efficacy and safety studies.**

Author, year	Country	Design of study	PrEP regimen	Study population	Participants (n)
Baeten, 2012 (Partners prep study) [5]	Kenya/ Uganda	RCT	TDF-FTC	Men and women	4.758
Grant, 2010 (Iprex) [10]	Peru/Ecuador/ South Africa/ Brazil/ Thailand/USA	RCT	TDF-FTC	MSM and Transgender women	2.499
Heffron, 2017 [11]	East Africa	Open-label	TDF-FTC	Men and women	1.010
Thigpen, 2012 (TDF2 study) [12]	Botswana	RCT	TDF-FTC	Men and women	1.200
Grinsztjn, 2018 (prep Brazil study) [13]	Brazil	Open-label	TDF-FTC	MSM and Transgender women	450
Molina, 2015 (Ipergay study) [14]	France/Canada	RCT	TDF-FTC	MSM	400
McCormack, 2016 (PROUD) [15]	England	RCT	TDF-FTC	MSM	544
Young, 2017 (PrEP Chicago) [17]	USA	RCT	.	MSM	423
Zablotska, 2018 [18]	Australia	Open-label	TDF-FTC	GBM	3.700
gulick, 2017 [21]	Multicentric	Prospective study	MVC/ MVC-FTC/ TDF-FTC	MSM	406
Baeten, 2016 [22]	Malawi/ South Africa/ Uganda/ Zimbabwe	RCT	Dapivirine	Women	2.629
Abdool Karim, 2010 (CAPRISA 004) [24]	South Africa	RCT	TDF	Women	889

Abbreviations: RCT= Randomized controlled trials; TDF-FTC = tenofovir disoproxil fumarate with emtricitabine; TDF= tenofovir disoproxil fumarate; MVC= maraviroc; MVC-FTC = maraviroc with emtricitabine; MSM= men who have sex with men; GBM= bisexual men; USA= United States of America.

The first study of PrEP using antiretroviral drugs (TDF/FTC) as a strategy to prevent HIV infection in humans, called the Pre-exposure Prophylaxis Initiative (iPrEx) trial, which demonstrated efficacy, was conducted by Grant et al [10] between MSM or transgender HIV-seronegative individuals, and was compared with a placebo in preventing infection by the virus. After almost three years of study, a 44% reduction in the incidence of infection in treated individuals was demonstrated. The presence of the drug was detected in 51% of the individuals who remained HIV seronegative and in only 9% of those who became infected. The most commonly reported adverse event was nausea during the first four weeks of treatment, being more frequent in the TDF/FTC group. In the treated group, those with detectable serum levels of the drug had a 12.9-fold lower chance of HIV infection than those without a detectable level of the drug, corresponding to a relative reduction of risk of HIV infection of 92%. This study showed that TDF/FTC provided protection against acquisition of HIV infection and that blood levels of the drug are strongly correlated with the prophylactic effect [10].

In another study involving HIV serodiscordant heterosexual couples who received PrEP in East Africa, 97% of HIV-negative partners used TDF as PrEP. Of the total number of individuals receiving treatment, only four became infected with HIV, representing an incidence rate of 0.24 per 100 person-years, with a 95% reduction in the incidence of the HIV infection, compared to the estimated relative incidence of infection in the population in absence of the PrEP. Because of the high adherence to treatment and the small numbers of cases of HIV infection the authors of the study suggest the adoption of this strategy on a large scale, for HIV-negative African partners whose partners are known to live with HIV [11].

Studies such as the Partners PrEP [5] and TDF2 [12] were conducted and demonstrated efficacy with the use of daily doses of TDF and TDF/FTC, proving that both drugs protect against HIV-1 infection in heterosexual men and women. Furthermore, that daily TDF/FTC prophylaxis prevented HIV infection in sexually active heterosexual adults.

A recent study carried out in Brazil, evaluated the viability of daily oral TDF/FTC, provided at no cost to MSM and transgender women, both seronegative for HIV and with high risk of acquiring infection by this virus. A total of 74% had protective serum concentrations of the drugs, with at least four doses per week. It was found that two individuals seroconverted during the study follow-up; both patients who became infected had undetectable tenofovir serum concentrations. These results point to the efficacy and viability of PrEP in a real-world setting and that the supply of PrEP in a middle-income setting can retain large numbers of participants and achieve high levels of adherence to treatment, which can lead to a significant reduction in the risk of acquiring HIV infection [13].

Studies like IPERGAY were performed in France and Canada to assess the efficacy and safety of sexual activity-dependent PrEP with TDF/FTC among high-risk MSM based on the hypothesis that the rate adherence (and thus efficacy) might be higher than that with a daily regimen [14]. Between 2012 and 2014 the PROUD study evaluated MSM without the use of condoms and demonstrated the efficacy of daily TDF/FTC when compared to placebo. There were no reports of serious adverse reactions, with the most common adverse effects being nausea, headache and arthralgia [15].

In South Africa, the CAPRISA 082 observational study, which began in 2016 and is expected to be finalized in 2021; targets adolescent girls and women aged between 18 and 30 years and is evaluating demographic data, perception of HIV risk, behavior and adherence to and acceptability of therapy [16]. The PrEP Chicago is also another intervention in the USA with

423 participants aged 18-35 to increase adoption of PrEP, estimate efficacy and increase awareness, while understanding the individual target audience variables [17]. In Australia we have the EPIC-NSW study which aims for the virtual elimination of HIV transmission in Australia by 2020. Study participants receive TDF/FTC once daily and are followed up for 24 months [18].

About evaluating renal safety of daily use of TDF/FTC, the creatinine clearance (eCrCl) was dosed during the use of PrEP and after its discontinuation, showing a non-progressive decrease in renal function and a reversible recovery by treatment discontinuation [19]. Serious adverse effects were not observed, with neutropenia being more frequent in the groups using TDF/FTC compared to TDF. When compared to placebo, there were more gastrointestinal adverse effects and fatigue, but only during the first month of use, with no further worsening with continued use [5].

4. Promising Drugs for PrEP

New studies have shown that the TDF can be effective in varying degrees in multiple clinical trials of PrEP against HIV. TDF in combination with the CCR5 receptor antagonist maraviroc (MVC) significantly improves its efficacy to prevent infection by HIV. However, this efficacy is totally dependent on adherence to treatment. Incorporation of the TDF-MVC combination into intravaginal rings (IVR) may increase the adherence and efficacy of the product compared to oral and vaginal gel formulations. A new pod-IVR technology capable of delivering various drugs was evaluated in sheep using TDV-MVC, where it showed a controlled release of the drug during the study and its levels in cervicovaginal fluids was kept. No adverse events were observed, thus allowing for the advancement of clinical evaluations [20].

The safety and tolerability of MVC, a PrEP candidate against HIV, was evaluated in a phase 2 clinical study, comparing four formulations: MVC, MVC+FTC, MVC+TDF and TDF+FTC. The study group consisted of 406 individuals, including non-HIV infected men and transsexual women reporting unprotected anal sex. Of the total number of subjects who concluded treatment, 77% had detectable serum concentrations of the drugs. Five individuals acquired HIV infection during the follow-up period, four of which had been treated with MVC alone and one with MVC+TDF. The results showed that the treatments containing MVC were safe and well tolerated compared to TDF+FTC. Although efficacy was not the objective of the study, it was found that all subjects who became infected with HIV during treatment had absent, low or variable drug concentrations, indicating that further studies of pre-exposure prophylaxis with treatments containing MVC should be performed to better evaluate its efficacy [21].

The need to expand the use of ARVs has initiated several new studies on PrEP using different drugs. One of these was the phase 3 of a 2012 study of a monthly vaginal ring containing 25mg of dapivirine, an HIV-1 non-nucleoside reverse transcriptase inhibitor; involving women aged 18-45 in Africa. The monthly vaginal ring containing dapivirine reduced the risk of HIV-1 infection among African women, with greater efficacy in subgroups with evidence of increased adherence, that is, greater protection from HIV-1 [22]. The VOICE-C study interviewed 102 women who used Dapivirine vaginal gel. The participants talked about its use, the discontinuity of it and side effects. It has been observed that some women feel discouraged to use the vaginal gel because of its efficacy which is still under study, because it is double blind, because of lack of support from the partner and the connection with HIV infection, leading to fear of side effects [23]. In South Africa, the

CAPRISA 004 study was carried out which analyzed in serum negative women the daily PrEP with 1% vaginal Tenofovir gel. The authors reported a reduction in HIV infection rates of 39% [24].

In a phase II study, the Cabotegravir injectable and long-acting (CAB-LA), which prevents integration of HIV-1 viral DNA into the host chromosome, has been studied to provide insight into its potential as PrEP. In monkeys, CAB-LA 50 mg/kg applied prior to rectal exposure resulted in plasma CAB levels comparable to a 12-week dose of 800 mg in humans. Treated animals were fully protected and had a 28.2-fold fall (IC95% 5.8-136.8) in acquisition than controls (p value <0.0001). Supporting the clinical development of CAB-LA as PrEP is a viable option for treatment adhesion. However, it is important to emphasize that there is a need for an oral introduction before CAB-LA injection. There are a significant number of individuals who have detectable levels of drug circulation within one year after the injection [25].

5. Pre-Exposure Prophylaxis Protocols

In 2015, the World Health Organization (WHO) recommended that PrEP should be offered as a prevention option for people at considerable risk of HIV infection as part of combined prevention approaches [6].

5.1 North America

The Clinical Practice Guideline on Pre-Exposure Prophylaxis for the Prevention of HIV Infection in the United States of America (USA) reports that TDF/FTC has been proven to be safe and effective. The single, fixed and daily dose combinations of TDF 300 mg/FTC 200 mg are currently FDA approved for PrEP in adults at risk of contracting HIV infection. Therefore, TDF/FTC is the recommended drug that should be prescribed for PrEP for MSM, heterosexually active men and women, and people who are intravenous drug users (IDU). TDF alone has been shown to be effective in studies with IDU and heterosexually active men and women and may be considered as an alternative regimen for these specific populations. TDF alone is not recommended to PrEP for MSM, because no tests have been done. Other medications and other dosing regimens have not yet been shown to be safe or effective in preventing HIV among healthy adults and are not FDA approved for use [25].

Once PrEP is started, patients should return for follow-up at least once every 3 months. Doctors should evaluate and confirm the status of the HIV-negative test by always documenting the findings, assessing the side effects and any other difficulties with adherence to the medication, clarifying any doubts. Repeating B-HCG test for women who are at a fertile age, provide a prescription, or replenish the daily TDF/FTC authorization for no more than 90 days (until the next HIV test). At least every 6 months the eCrCl should be monitored. An increase in serum creatinine is not a reason to discontinue treatment if eCrCl remains above 60 ml/min. It is recommended to perform sexually transmitted infection (STI) tests in adolescents and sexually active adults, checking for infections such as syphilis, gonorrhea, chlamydia and B/C hepatitis [25].

5.2 Europe and Central Asia

In the European Union / European Economic Area (EU / EEA), MSM are disproportionately affected by HIV and other STIs [26]. Strengthening efforts to reduce the incidence of HIV and STI among MSM is a priority for the European Center for Disease Prevention and Control (ECDC), which in 2015 published comprehensive guidelines on HIV and STI prevention

among MSM [27]. In addition, there is the opinion that there is a need to encourage these countries to consider integrating PrEP into their existing HIV prevention plans for those most at risk of HIV infection, starting with MSM.

The European AIDS Clinical Society (EACS) published guidelines in 2015 that recommend the use of PrEP in adults at high risk of contracting HIV infection. PrEP is recommended for HIV-negative men who have sex with men and transgender individuals who are inconsistent in their use of condoms with casual partners or with HIV-positive partners who are not in treatment. A recent sexually transmitted infection or the use of post-exposure prophylaxis may be markers of increased risk of HIV acquisition. PrEP can also be considered in HIV-negative heterosexual women and men, who are inconsistent in condom use, probably have HIV-positive partners, and are not in treatment. The guidelines recommend that PrEP should be used in combination with other preventive interventions, including the use of condoms, and should be supervised by a physician with experience in sexual health and use of HIV medicines, possibly as part of a shared care arrangement [28].

Only one country offers PrEP through its public health service. In France, the National Agency for Medicinal Product Safety has authorized TDF 300 mg/FTC 200 mg (Truvada®) for PrEP as a Recommendation for Temporary Use (RTU) for three years, which can be renewed for another three years before a final decision is taken. Under the RTU, which came into force in January 2016, the use of Truvada® for PrEP is fully covered by the national health insurance system [29].

PrEP demonstration projects are completed in one country and are underway in three countries. The demonstration of a project in the United Kingdom (UK) targeting men who have sex with men at high risk of HIV has ended, but a decision has yet to be made on how the provision of PrEP through the public health system will be funded. There are ongoing demonstration projects in Belgium, Italy and the Netherlands, all of which are to be implemented in health settings. Target populations are men who have sex with men at high risk of HIV in Belgium, MSM and transgender people at high risk of contracting HIV in the Netherlands, and sero-discordant and heterosexual couples in Italy [29].

In Europe and Central Asia, PrEP demonstration projects are planned in 15 other countries. These countries are Azerbaijan, Croatia, Denmark, Georgia, Greece, Ireland, Israel, Luxembourg, Malta, Norway, Romania, Portugal, Spain, Sweden and Ukraine. Most of these planned demonstration projects will target MSM and will be implemented in health settings. Denmark is planning to implement the demonstration project in a community setting and Ireland is planning a project through a community setting partnership. Ireland, Romania and Ukraine report that national policies and PrEP clinical guidelines are in development [30].

5.3 Latin America

Brazil is currently conducting several projects. The PrEP Brazil Project (clinical trial NCT01989611), coordinated by the Oswaldo Cruz Foundation, and initially implemented in Rio de Janeiro and São Paulo in partnership with nongovernmental organizations is expanding to other sites in Porto Alegre and Manaus. The objective of this project is to evaluate the acceptance, safety and feasibility of free access to PrEP for high-risk MSM and transgender women (TGW), with the objective of generating information for the subsequent implementation of PrEP in the public sector [31]. Brazil had PrEP approval by the Brazilian Medicine Regulatory Authority in 2017 and, so far, in Latin America, only Brazil and Peru have registered TDF/FTC for preventive use.

6. Conclusion

PrEP can offer effective protection against HIV infection and represents an alternative preventative measure that can be recommended for HIV-negative people at high risk of acquiring HIV infection. Different studies show that the PrEP strategy is effective and safe for the prevention of HIV infection in people at high risk of contagion, such as MSM and TGW, as well as heterosexual adults, partners of infected individuals with HIV and IDU. The safety and efficacy of TDF / FTC for PrEP have been demonstrated since its first approval for use in 2012. Studies conducted at various locations around the world show practical examples of how PrEP can be performed with positive results. Adherence to treatment is particularly important to ensure its effectiveness. However, there are still some aspects that need to be better analyzed, such as: possibility of long-term side effects, improving safety, and proof of its efficacy and safety in TGW and adolescents.

7. Authors' contributions

Firstly, four researchers (ACM, AFC, KKA and RPA) performed the selection of the studies of interest. Subsequently, the three others (JVF, IQS and RNC) participated in the construction and review of the final manuscript.

REFERENCES

1. May M, Gompels M, Sabin C. Life expectancy of HIV-1-positive individuals approaches normal conditional on response to antiretroviral therapy: UK Collaborative HIV Cohort Study. J Int AIDS Soc. 2012;15(4):18078.
2. Riddell J IV, Amico KR, Mayer KH. HIV Preexposure Prophylaxis: A Review. JAMA. 2018;319(12):1261-8.
3. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011;365(6):493-505.
4. Cohen MS, McCauley M, Gamble TR. HIV treatment as prevention and HPTN 052. Curr Opin HIV AIDS. 2012;7(2):99-105.
5. 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.
6. World Health Organization. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: World Health Organization; 2015.
7. Sanchez CM, Vivancos Gallego MJ, Moreno GS. Pre-exposure prophylaxis (PrEP) against HIV: efficacy, safety and uncertainties. Farm Hosp. 2017;41(5):630-7.
8. Subbarao S, Otten RA, Ramos A, et al. Chemoprophylaxis with tenofovir disoproxil fumarate provided partial protection against infection with simian human immunodeficiency virus in macaques given multiple virus challenges. J Infect Dis. 2006;194(7):904-11.
9. Heneine W, Kashuba A. HIV Prevention by Oral Preexposure Prophylaxis. Cold Spring Harb Perspect Med. 2012;2(3):a007419.
10. Grant RM, Lama JR, Anderson PL, et al. Pre-exposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010;363(27):2587-99.
11. Heffron R, Ngure K, Odoyo J, et al. Pre-exposure prophylaxis for HIV-negative persons with partners living with HIV: uptake, use, and effectiveness in an open-label demonstration project in East Africa. Gates Open Res. 2017;1:3.

12. Thigpen MC, Kebaabetswe PM, Paxton LA. Antiretroviral pre-exposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med. 2012;367(5):423-34.
13. Grinsztejn B, Hoagland B, Moreira R, et al. Retention, engagement, and adherence to pre-exposure prophylaxis for men who have sex with men and transgender women in PrEP Brasil: 48 week results of a demonstration study. Lancet HIV. 2018;5(3):e136-e45.
14. Molina JM, Capitant C, Spire B, et al. On-Demand Pre-exposure Prophylaxis in Men at High Risk for HIV-1 Infection. N Engl J Med. 2015;373:2237-46.
15. 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.
16. Cowan FM, Delany-Moretlwe S, Sanders EJ, et al. PrEP implementation research in Africa: what is new? J Int AIDS Soc. 2016;19(6):21101.
17. Young LE, Schumm P, Alon L, et al. PrEP Chicago: A randomized controlled peer change agent intervention to promote the adoption of pre-exposure prophylaxis for HIV prevention among young Black men who have sex with men. Clin Trials. 2018;15(1):44-52.
18. Zablotska IB, Selvey C, Guy R, et al. Expanded HIV pre-exposure prophylaxis (PrEP) implementation in communities in New South Wales, Australia (EPIC-NSW): design of an open label, single arm implementation trial. BMC Public Health. 2018;18(1):210.
19. Solomon MM, Lama JR, Glidden DV, et al. Changes in renal function associated with oral emtricitabine/tenofovir disoproxil fumarate use for HIV pre-exposure prophylaxis. AIDS. 2014;28(6):851-9.
20. Moss JA, Butkyavichene I, Churchman SA, et al. Combination Pod-Intravaginal Ring Delivers Antiretroviral Agents for HIV Prophylaxis: Pharmacokinetic Evaluation in an Ovine Model. Antimicrob Agents Chemother. 2016;60(6):3759-66.
21. Gulick RM, Wilkin TJ, Chen YQ, et al. Phase 2 Study of the Safety and Tolerability of Maraviroc-Containing Regimens to Prevent HIV Infection in Men Who Have Sex With Men (HPTN 069/ACTG A5305). J Infect Dis. 2017;215(2):238-46.
22. 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;375:2121-32.
23. Van der Straten A, Stadler J, Luecke E, et al. Perspectives on use of oral and vaginal antiretrovirals for HIV prevention: the VOICE-C qualitative study in Johannesburg, South Africa. J Int AIDS Soc. 2014;17(2):19146.
24. Abdool Karim Q, Abdool KSS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science. 2010;329(5996):1168-74.
25. McPherson TD, Sobieszczyk ME, Markowitz M. Cabotegravir in the treatment and prevention of Human Immunodeficiency Virus-1. Expert Opin Investig Drugs. 2018;27(4):413-20.
26. CDC, U.S. Department of Health and Human Services. Pre-exposure Prophylaxis for the Prevention of HIV Infection in the United States - 2014 Clinical Practice Guideline.
27. European Centre for Disease Prevention and Control (ECDC), WHO Regional Office for Europe (WHO). HIV/AIDS Surveillance in Europe 2014. Stockholm: ECDC/WHO. 2015.

28. European Centre for Disease Prevention and Control (ECDC). HIV and STI prevention among men who have sex with men. Stockholm: ECDC. 2015.
29. European Aids Clinical Society. Guidelines version 8. October, 2015.
30. European Centre for Disease Prevention and Control. Evidence brief: Pre-exposure prophylaxis for HIV prevention in Europe. Stockholm: ECDC. 2016.
31. Veloso VG, Mesquita F, Grinsztejn B. Pre-exposure prophylaxis for men and transgender women who have sex with men in Brazil: opportunities and challenges. J Int AIDS Soc. 2015;18(3):20010.