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Education

Intravaginal ring as human immunodeficiency virus/ acquired immunodeficiency syndrome (HIV/AIDS) prevention

EDUCATION

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ABSTRACT

Summary

HIV/AIDS is one of the primary concerns of the Sustainable Development Goals. It has a high prevalence and causes significant effects for the sufferers. Several prevention methods against HIV infection have been developed, including intravaginal rings loaded with antiretroviral drugs. We aim to inform about the potential use of an intravaginal ring as pre-exposure prophylaxis.

Relevance

Recently available methods of HIV/AIDS prevention have many pitfalls, especially in compliance, resulting in inconsistent efficacy. New methods of prevention need to be addressed and intravaginal rings can be used following abundant evidence stating their efficacy, compliance, and patient preference.

Take Home Messages

Intravaginal rings have the potential to be used as a pre-exposure prophylaxis against HIV infection.

DEFINITION OF HIV/AIDS

Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) is one of the key concerns of the Sustainable Development Goals (SDGs) published by the United Nations in 2015. It is listed in the third point, "good health and well-being," which deals with various diseases that occur during pregnancy and are potentially transmitted to children. (1) There are 36.8 million people affected by HIV infection worldwide, 57% of whom are women and children. (2) There are about two million new cases worldwide each year, 47% of which come from women and children. (3) Based on these estimates, HIV incidence appears to be far from the goal of fewer than 500,000 new cases per year, emphasising the importance of preventive measures. (4)

HIV TRANSMISSION

HIV is a highly contagious virus transmitted via multiple routes. (5) HIV transmission can take the form of horizontal transmission (sexual contact with body fluids or parenteral inoculation with infected blood) and vertical routes. (6) Vertical transmission can happen through three pathways; during pregnancy (transplacental, in utero), during labour (peripartum), or during the lactation period, and is responsible for 15-45% of HIV/AIDS cases. (7) Of these, it is reported that in utero HIV transmission could occur in 11-50% of all cases without intervention. (8)

AVAILABLE METHODS OF HIV/AIDS PREVENTION AND THEIR SHORTCOMINGS

The three methods of HIV prevention are pre-exposure prophylaxis, post-exposure prophylaxis, and early intervention. (9) Pre-exposure prophylaxis involves the use of antiretroviral therapy (ART) in preparation for the acquisition of HIV infection and aims to affect the normal course of disease development, reduce morbidity, and/or minimise contagiousness. (10) Meanwhile, post-exposure prophylaxis refers to the use of short-term (28 days) ART administration to decrease the risk of HIV acquisition after the exposure (administered less than 36-72 hours post-exposure). (11) Early intervention is the prompt initiation of ART combination and is commonly used in pregnant mothers. (12) We aim to inform about the potential use of an intravaginal ring as pre-exposure prophylaxis.

Pre-exposure prophylaxis has featured in the guidelines for HIV prevention for ten years in the United States (13,14) and was introduced in the European guidelines, including in the United Kingdom, in 2021. (15) The most popular method of pre-exposure prophylaxis is the use of oral antiretroviral drugs. This method has demonstrated high efficacy in different geographical and sexual behaviour (including heterosexuals, men who have sex with men (MSM), and transgender) settings. (16,17) Nevertheless, this strategy has some drawbacks, including potential suboptimal adherence (<95% per year, as measured by the medication possession ratio (MPR), the quantity of daily antiretroviral medication doses provided by the pharmacy to every patient divided by the patient's total follow-up period in days since starting ART) (18,19), which is associated with virological failure, manifested as unfavourable amount of viral load (20,21). Inadequate drug adherence was associated with several factors, including perceived stigma, inadequate risk perception, incompatibility of dosing regimens, and adverse reactions of the drug. (22) In addition, oral drug administration contributed to more severe adverse systemic effects and inconsistent effectiveness in the range of 6%-49%. (23,24)

Another prevention method is the use of topical gels to protect against the intravaginal transmission of HIV. The use of this approach is expected to increase patient comfort for the use of preventive measures (in comparison to daily oral ART intake) in addition to reduce the risk of HIV infection by about 54%. (25) Nonetheless, in its evaluation, based on evidence from Vaginal and Oral Epidemic Control Interventions (VOICE), the use of these topical gels along with oral drugs does not provide adequate protection. (26) Vaginal gel has further been considered ineffective in preventing HIV-1 infection in the Follow on African Consortium for Tenofovir Studies (FACTS-001) trial. (27) Moreover, compliance has been shown to be even lower with this method (up to only 20% adherence). (28) Repeated use of the gel can also present a risk of dose-dependent side effects, such as epithelial toxicity.

POTENTIAL USE OF INTRAVAGINAL RINGS AS HIV/AIDS PROPHYLAXIS

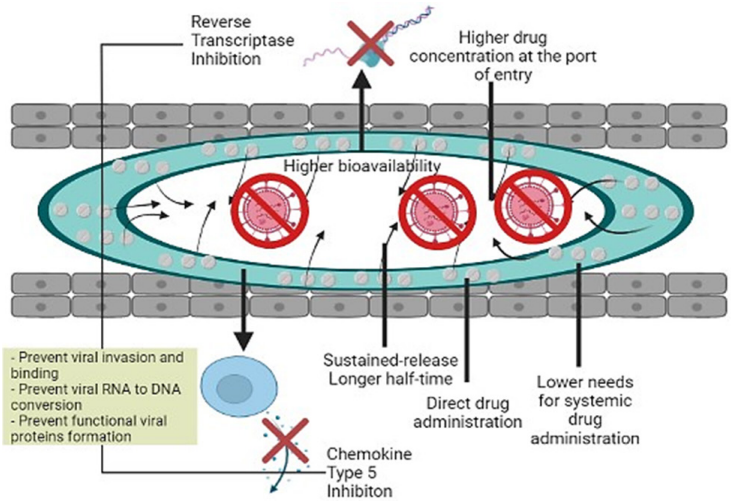

Figure 1: *Intravaginal Rings as Pre-Exposure Prophylaxis. Image created using BioRender®.*

The intravaginal ring is a female-initiated drug-delivery apparatus with polyurethane, silicone, ethylene, or vinyl acetate as the major components. (29) It is an alternative method for preventing HIV/AIDS transmission, particularly as a pre-exposure prophylaxis method from sexual intercourse, reducing the risk of vertical and horizontal transmission of HIV. (30) It can be used for storage and delivery of ART and may contain a combination of ART drugs, each with distinct mechanisms of action, reducing drug resistance risks. (31) The intravaginal ring functions by releasing continuous drug particles into the vaginal canal. The release method is regulated by a matrix or a reservoir, ensuring a steady rate of drug expenditure. The potential activity of intravaginal rings as pre-exposure prophylaxis is depicted in Figure 1.

The intravaginal ring can be modified in size (depending on the drug's capacity), material strength, material resistance, and colour. (32) The selection is geared to the affordability of treatment, access to health facilities, and other personal factors. In addition, this approach is also very suitable to be implemented in developing countries because the price is affordable (i.e., $5/month for Tenofovir Disproxil Fumarate (TDF) vaginal gel vs. less than $1/ninety days for TDF intravaginal ring). (33,34)

Drug formulations that may be inserted into intravaginal rings can include a combination of nucleoside (TDF) or non-nucleoside reverse transcriptase inhibitor (dapivirine) and complementary drugs, including a chemokine type 5 (CCR5) receptor inhibitor, maraviroc. Mechanisms of action include the provision of protein-based microbicide, the inhibition of HIV interaction with target cells, the suppression of viral genetic material transcription, inhibition of cell internalisation, restriction of viral replication, and uptake by immune cells. (30,36,37) Use of an intravaginal ring can protect the individual for an extended time (up to 90 days of use), minimise the requirement for systemic drug use, direct transport of anti-HIV drugs to the site of virus inoculation, and preserve the level of microbicide through the continuous release of drugs based on sexual activity and regular dosage. (37) The benefit of this product is that it can reduce the risk of vertical transmission to less than 10%. (38)

IMPROVED COMPLIANCE BY INTRAVAGINAL RINGS

Compliance with HIV prophylaxis by use of the intravaginal ring method is very high (94%), in addition to consumer enjoyment (100%), and comfort (93%) which led to recommendations for use by 85-90% of respondents. (29,39) This is due to ease of application, as it does not require a dose adjustment after coitus and only needs to be replaced once every 30-90 days depending on the amount of drugs given. (40)

PHARMACOLOGICAL AND CLINICAL BENEFIT

Antiretroviral administration by the intravaginal ring can prevent the occurrence of the first-pass metabolism associated with the lower dose required. (41) This method can offer greater protection as it can improve the half-time of antiretroviral drugs compared to oral or gel administration, providing a steadier state of drug concentration. (40,42) Dapivirine-containing intravaginal rings have reduced the incidence of HIV-1 infection in the mother by up to 56% to 91% as compared with placebo, thus potentially reducing the risk of HIV dissemination to the child through vertical transmission. (30,40). The variability was mainly associated with different adherence levels of the users and variable drug concentrations in the vaginal mucosa. (37,43) Efficacy could increase to 71% if the level of compliance is met (>95% MPR level). (44)

POTENTIAL DRAWBACKS OF INTRAVAGINAL RINGS HIV/AIDS PRE-EXPOSURE PROPHYLAXIS

Although the intravaginal ring shows a lot of promise for HIV prophylaxis, some drawbacks still need to be addressed before it can be extensively used. Examples of the downsides of the intravaginal ring study include differing efficacy in some clinical trials and the inability to achieve multi-compartmental protection. (45) For the first and second shortcomings, recent studies are assessing the mechanism of creating better regimens, either by combination therapy or pharmacokinetic optimization. Proposed antiretroviral drugs combinations are Vicriviroc (MK-4176)—MK-2048, (46) TDF—maraviroc, (35) and dapivirine—maraviroc. (26) It is based on the principle of HIV treatment by using a drug combination of nucleoside reverse transcriptase inhibitors (NRTIs) class in conjunction with a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), a CCR5 receptor inhibitor, or an integrase strand transfer inhibitor (INSTI) to increase drug potency and prevent resistance (table 1). (47,48) Meanwhile, awareness of the inability to provide multi-compartment protection (since HIV has some different pathways of dissemination, including the mucosa (cervicovaginal, colorectal) and blood) (49) can be resolved by using multiple prevention methods, including the proposed intravaginal ring, HIV vaccination, the use of contraceptives (new intravaginal ring research combining antiretroviral and contraceptive drugs), oral antiretroviral drugs, and government initiatives to optimise the knowledge, attitude, and practice of vulnerable populations. (50,51) Furthermore, although it is generally considered comfortable for the user, the acceptability has, in one study, been shown to be as low as 71%. (29) In addition, a study on intravaginal rings for contraceptive use has found an increase in Candida infection and vaginal inflammation due to the change of vaginal microbiota composition. (52) However, this has not been studied yet for intravaginal rings designed for the use of HIV prophylaxis.

While progress in the implementation of the intravaginal ring as pre-exposure prophylaxis against HIV infection appears to be significant, there are some potential issues restricting its worldwide use. These include no available design rules (including differing mechanical properties that are still in development), discrepancies between several clinical trials (in the presentation of efficacy and acceptability), inadequate understanding of pharmacokinetics, and risk of infection. (53)

STATUS OF INTRAVAGINAL RING IMPLEMENTATION FOR PRE-EXPOSURE PROPHYLAXIS OF HIV/AIDS

The European Medicines Agency (EMA) has approved the use of a dapivirine-releasing intravaginal ring as of July 2020 (54). This is based on several clinical trials which are showing good efficacy (although the results differ according to the adherence), acceptability, and safety. Although the standard for stating the efficacy of preventive measures in HIV transmission is still in debate, a systematic review and meta-analysis have found the long-acting intravaginal ring containing dapivirine to be the only significant measure, reducing HIV transmission by 29%, in comparison with other eight microbicides, including the vaginal gel and the second-generation microbicides containing direct-acting antiretroviral agents such as 1% tenofovir disoproxil fumarate. (49,55) In addition, the anti-HIV activity of microbicides was attributed to its potential for promoting inflammatory cytokine release and acidifying vaginal mucosa. (49,56) EMA recommends the use of a dapivirine vaginal ring to prevent HIV-1 infection through vaginal transmission, specifically for women aged 18 years or older, with negative HIV testing and unavailability or inability to use oral antiretroviral pre-exposure prophylaxis. (54) Following this approval, the World Health Organization is preparing a review of the evidence of dapivirine vaginal ring use. (57)

IMPORTANT POINTS

1. Intravaginal rings can serve as tools for pre-exposure prophylaxis against HIV infection.

2. Intravaginal ring application for pre-exposure prophylaxis can give more choice and control for women to protect themselves from HIV infection.

3, This approach is very fitting to be implemented in numerous countries due to the nature of sustained drug release by the device (intravaginal ring) compared to conventional (oral) methods.

4. More research for implementation in each country of destination is still required, depending on the demographics of the population concerned.

APPENDIX

Terminology	Explanation
Nucleoside reverse transcriptase inhibitors (NRTIs)	A drug that prevents HIV replication by inhibiting HIV reverse transcriptase (an HIV enzyme that converts RNA into DNA). The NRTI might incorporate with the DNA of the host (T-cell).
Non-nucleoside reverse transcriptase inhibitor (NNRTI)	A drug that inhibits HIV replication by impairing HIV reverse transcriptase (an HIV enzyme that converts RNA into DNA). The NNRTI did not enter the host's DNA.
Protease inhibitor (PI)	A drug that inhibits the activity of protease (an HIV enzyme responsible for the maturation of HIV)
Integrase strand transfer inhibitor (INSTI)	A drug that inhibits integrase (an HIV enzyme that inserts viral DNA into the host CD4 cell's DNA). It is useful for hindering viral replication.
Chemokine type 5 (CCR5) receptor inhibitor	A drug that restricts the CCR5 coreceptor on the surface of certain immune cells, including CD4 T lymphocytes (CD4 cells). This keeps HIV from infiltrating the cell.

Table 1: *Glossary of Antiretroviral Medication Class.*

REFERENCES

1. Chamla D, Luo C, Idele P. Children, HIV, emergencies and Sustainable Development Goals: roadblocks ahead and possible solutions. J Int AIDS Soc. 2018;21(S1):e25046. https://doi.org/10.1002/jia2.25046
PMid:29485728

2. Jahagirdar D, Walters MK, Novotney A, Brewer ED, Frank TD, Carter A, et al. Global, regional, and national sex-specific burden and control of the HIV epidemic, 1990–2019, for 204 countries and territories: the Global Burden of Diseases Study 2019. Lancet HIV. 2021;8(10):e633–51.

3. Sama CB, Feteh VF, Tindong M, Tanyi JT, Bihle NM, Angwafo FF. Prevalence of maternal HIV infection and knowledge on mother-to-child transmission of HIV and its prevention among antenatal care attendees in a rural area in northwest Cameroon. PLoS One. 2017;12(2):e0172102. https://doi.org/10.1371/journal.pone.0172102
PMid:28199373

4. Joint United Nations Programme on HIV/AIDS. UNAIDS Data 2017. 2017 [accessed 8 Nov 2020]. Available from: https://www.unaids.org/en/resources/documents/2017/2017_data_book.

5. Savaser S. Knowledge and attitudes of high school students about AIDS: A Turkish perspective. Public Health Nurs. 2003;20(1):71–9. https://doi.org/10.1046/j.1525-1446.2003.20110.x
PMid:12492828

6. Klatt EC. Pathology of HIV/AIDS. 2019 30th ed. Savannah: Mercer University School of Medicine; 2019 [accessed 7 Nov 2020]. Available from: https://webpath.med.utah.edu/AIDS2019.PDF.

7. Barral MFM, de Oliveira GR, Lobato RC, Mendoza-Sassi RA, Martínez AM, Gonçalves C V. Risk Factors of HIV-1 Vertical Transmission (VT) and the Influence of Antiretroviral Therapy (ART) in Pregnancy Outcome. Rev Inst Med Trop Sao Paulo. 2014;56(2):133–8. https://doi.org/10.1590/S0036-46652014000200008
PMid:24626415

8. Birhane T, Tessema GA, Dadi KAAAF. Knowledge of pregnant women on mother-to-child transmission of HIV in Meket District, Northeast Ethiopia. J Pregnancy. 2015;2015:960830. https://doi.org/10.1155/2015/960830
PMid:25741447

9. Grant RM, Smith DK. Integrating antiretroviral strategies for human immunodeficiency virus prevention: Post- and pre-exposure prophylaxis and early treatment. Open Forum Infect Dis. 2015;2(4):ofv126. https://doi.org/10.1093/ofid/ofv126
PMid:26512356

10. Kelesidis T, Landovitz RJ. Preexposure prophylaxis for HIV prevention. Curr HIV/AIDS Rep. 2011;8(2):94–103. https://doi.org/10.1007/s11904-011-0078-4
PMid:21465112

11. Sultan B, Benn P, Waters L. Current perspectives in HIV post-exposure prophylaxis. HIV/AIDS (Auckl.). 2014;6:147-58. https://doi.org/10.2147/HIV.S46585
PMid:25368534

12. Chi BH, Stringer JSA, Moodley D. Antiretroviral drug regimens to prevent mother-to-child transmission of HIV: a review of scientific, program, and policy advances for sub-Saharan Africa. Curr HIV/AIDS Rep. 2013;10(2):124–33.

13. Centers for Disease Control and Prevention. Interim guidance: preexposure prophylaxis for the prevention of HIV infection in men who have sex with men. MMWR Morb Mortal Wkly Rep. 2011;60(3):65–8.

14. Centers for Disease Control and Prevention. Interim guidance for clinicians considering the use of preexposure prophylaxis for the prevention of HIV infection in heterosexually active adults. MMWR Morb Mortal Wkly Rep. 2012;61(31):586–9.

15. European Centre for Disease Prevention and Control. HIV Pre-Exposure Prophylaxis in the EU/EEA and the UK: implementation, standards and monitoring. Operational guidance. 2021 [accessed 27 Jul 2021]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/HIV-Pre-Exposure-Prophylaxis-in-the-EU-EEA-UK.pdf.

16. Desai M, Field N, Grant R, McCormack S. State of the art review: Recent advances in PrEP for HIV. BMJ. 2017;359:j5011.
https://doi.org/10.1136/bmj.j5011
PMid:29229609

17. Cohen MS, McCauley M, Gamble TR. HIV treatment as prevention and HPTN 052. Curr Opin HIV AIDS. 2012;7(2):99–105.
https://doi.org/10.1097/COH.0b013e32834f5cf2
PMid:22227585

18. Kim J, Lee E, Park B-J, Bang JH, Lee JY. Adherence to antiretroviral therapy and factors affecting low medication adherence among incident HIV-infected individuals during 2009–2016: a nationwide study. Sci Rep. 2018;8(1):3133.
https://doi.org/10.1038/s41598-018-21081-x

19. Messou E, Chaix M-L, Gabillard D, Minga A, Losina E, Yapo V, et al. Association between medication possession ratio, virologic failure and drug resistance in HIV-1 infected adults on antiretroviral therapy in Côte d'Ivoire. J Acquir Immune Defic Syndr. 2011;56(4):356–64.
https://doi.org/10.1097/QAI.0b013e3182084b5a
PMid:21191309

20. Ahonkhai AA, Banigbe B, Adeola J, Bassett I V, Idigbe I, Okonkwo P, et al. High Medication Possession Ratios Associated with Greater Risk of Virologic Failure Among Youth Compared to Adults in a Nigerian Cohort. J Acquir Immune Defic Syndr. 2018;78(3):322–8.
https://doi.org/10.1097/QAI.0000000000001670
PMid:29533304

21. Cheng Y, Nickman NA, Jamjian C, Stevens V, Zhang Y, Sauer B, et al. Predicting poor adherence to antiretroviral therapy among treatment-naïve veterans infected with human immunodeficiency virus. Medicine (Baltimore). 2018;97(2):e9495.
https://doi.org/10.1097/MD.0000000000009495
PMid:29480838

22. Sidebottom D, Ekström AM, Strömdahl S. A systematic review of adherence to oral pre-exposure prophylaxis for HIV - How can we improve uptake and adherence? BMC Infect Dis. 2018;18:581.
https://doi.org/10.1186/s12879-018-3463-4
PMid:30445925

23. 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;367:423–34.
https://doi.org/10.1056/NEJMoa1110711
PMid:22784038

24. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, et al. Preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2012;367(5):411–22.
https://doi.org/10.1056/NEJMoa1202614
PMid:22784040

25. Abdool KQ, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, 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.
https://doi.org/10.1056/NEJMoa1202614
PMid:22784040

26. Fetherston SM, Boyd P, McCoy CF, McBride MC, Edwards KL, Ampofo S, et al. A silicone elastomer vaginal ring for HIV prevention containing two microbicides with different mechanisms of action. Eur J Pharm Sci. 2013;48(3):406–15.
https://doi.org/10.1016/j.ejps.2012.12.002
PMid:23266465

27. Delany-Moretlwe S, Lombard C, Baron D, Bekker LG, Nkala B, Ahmed K, et al. Tenofovir 1% vaginal gel for prevention of HIV-1 infection in women in South Africa (FACTS-001): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Infect Dis. 2018;18(11):1241–50.
https://doi.org/10.1016/S1473-3099(18)30428-6

28. Marrazzo JM, Ramjee G, Richardson BA, Gomez K, Mgodi N, Nair G, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2015;372(6):509–18.
https://doi.org/10.1056/NEJMoa1402269
PMid:25651245

29. Griffin JB, Ridgeway K, Montgomery E, Torjesen K, Clark R, Peterson J, et al. Vaginal ring acceptability and related preferences among women in low-and middle-income countries: a systematic review and narrative synthesis. PLoS One. 2019;14(11):e0224898.
https://doi.org/10.1371/journal.pone.0224898
PMid:31703094

30. Brown ER, Hendrix CW, van der Straten A, Kiweewa FM, Mgodi NM, Palanee Philips T, et al. Greater dapivirine release from the dapivirine vaginal ring is correlated with lower risk of HIV 1 acquisition: a secondary analysis from a randomized, placebo-controlled trial. J Int AIDS Soc. 2020;23(11):e25634.
https://doi.org/10.1002/jia2.25634

31. Glaubius R, Ding Y, Penrose KJ, Hood G, Engquist E, Mellors JW, et al. Dapivirine vaginal ring for HIV prevention: modelling health outcomes, drug resistance and cost effectiveness. J Int AIDS Soc. 2019;22(5):e25282.
https://doi.org/10.1002/jia2.25282
PMid:31074936

32. Guthrie KM, Vargas S, Shaw JG, Rosen RK, Van Den Berg JJ, Kiser PF, et al. The promise of intravaginal rings for prevention: User perceptions of biomechanical properties and implications for prevention product development. PLoS One. 2015;10(12):e0145642.
https://doi.org/10.1371/journal.pone.0145642
PMid:26695431

33. Williams BG, Abdool Karim SS, Karim QA, Gouws E. Epidemiological impact of tenofovir gel on the HIV epidemic in South Africa. J Acquir Immune Defic Syndr. 2011;58(2):207–10.

34. Ugaonkar SR, Wesenberg A, Wilk J, Seidor S, Mizenina O, Kizima L, et al. A novel intravaginal ring to prevent HIV-1, HSV-2, HPV, and unintended pregnancy. J Control Release. 2015;213:57–68.
https://doi.org/10.1016/j.jconrel.2015.06.018
PMid:26091920

35. Moss JA, Butkyavichene I, Churchman SA, Gunawardana M, Fanter R, Miller CS, 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.
https://doi.org/10.1128/AAC.00391-16
PMid:27067321

36. Notario-Pérez F, Ruiz-Caro R, Veiga-Ochoa M-D. Historical development of vaginal microbicides to prevent sexual transmission of HIV in women: From past failures to future hopes. Drug Des Devel Ther. 2017;11:1767.
https://doi.org/10.2147/DDDT.S133170
PMid:28670111

37. Smith JM, Moss JA, Srinivasan P, Butkyavichene I, Gunawardana M, Fanter R, et al. Novel multipurpose pod-intravaginal ring for the prevention of HIV, HSV, and unintended pregnancy: Pharmacokinetic evaluation in a macaque model. PLoS One. 2017;12(10):e0185946.
https://doi.org/10.1371/journal.pone.0185946
PMid:28982161

38. Roth C, Hrenchir PF, Pacheco CJ. HIV in Pregnancy. Nurs Womens Health. 2016;20(1):87–91.
https://doi.org/10.1016/j.nwh.2015.12.010
PMid:26902443

39. van der Straten A, Panther L, Laborde N, Hoesley CJ, Cheng H, Husnik MJ, et al. Adherence and Acceptability of a Multidrug Vaginal Ring for HIV Prevention in a Phase I Study in the United States. AIDS Behav. 2016;20(11):2644–53.
https://doi.org/10.1007/s10461-016-1299-8
PMid:26837628

40. 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.
https://doi.org/10.1056/NEJMoa1506110
PMid:26900902

41. Schurmans C, De Baetselier I, Kestelyn E, Jespers V, Delvaux T, Agaba SK, et al. The ring plus project: Safety and acceptability of vaginal rings that protect women from unintended pregnancy. BMC Public Health. 2015;15:348.
https://doi.org/10.1186/s12889-015-1680-y
PMid:25880636

42. Smith JM, Rastogi R, Teller RS, Srinivasan P, Mesquita PMM, Nagaraja U, et al. Intravaginal ring eluting tenofovir disoproxil fumarate completely protects macaques from multiple vaginal simian-HIV challenges. Proc Natl Acad Sci U S A. 2013;110(40):16145–50.
https://doi.org/10.1073/pnas.1311355110
PMid:24043812

43. Montgomery ET, Stadler J, Naidoo S, Katz AW, Laborde N, Garcia M, et al. Reasons for nonadherence to the dapivirine vaginal ring: narrative explanations of objective drug-level results. AIDS. 2018;32(11):1517-1525.
https://doi.org/10.1097/QAD.0000000000001868
PMid:29957723

44. Nel AM, Haazen W, Nuttall JP, Romano JW, Mesquita PM, Herold BC, et al. Pharmacokinetics and Safety Assessment of Anti-HIV Dapivirine Vaginal Microbicide Rings with Multiple Dosing. AIDS. 2014;5(10):1–10.
https://doi.org/10.4172/2155-6113.1000355

45. Beymer MR, Holloway IW, Pulsipher C, Landovitz RJ. Current and Future PrEP Medications and Modalities: On-demand, Injectables, and Topicals. Curr HIV/AIDS Rep. 2019;16:349–58.
https://doi.org/10.1007/s11904-019-00450-9
PMid:31222499

46. Liu AY, Zhang J, Anderson PL, Wagner T, Pan Z, Peda M, et al. Phase 1 Pharmacokinetic Trial of 2 Intravaginal Rings Containing Different Dose Strengths of Vicriviroc (MK-4176) and MK-2048. Clin Infect Dis. 2019;68(7):1129–1135.
https://doi.org/10.1093/cid/ciy652
PMid:30289444

47. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. 2019 [accessed 7 Nov 2020]. Available from: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf.

48. Clutter DS, Jordan MR, Bertagnolio S, Shafer RW. HIV-1 drug resistance and resistance testing. Infect Genet Evol. 2016;46:292–307.
https://doi.org/10.1016/j.meegid.2016.08.031
PMid:27587334

49. Baeten JM, Hendrix CW, Hillier SL. Topical Microbicides in HIV Prevention: State of the Promise. Annu Rev Med. 2020;71:361-377.
https://doi.org/10.1146/annurev-med-090518-093731
PMid:31613684

50. Brody C, Sok S, Tuot S, Pantelic M, Restoy E, Yi S. Do combination HIV prevention programmes result in increased empowerment, inclusion and agency to demand equal rights for marginalised populations in low-income and middle-income countries? A systematic review. BMJ Glob Heal. 2019;4:e001560.
https://doi.org/10.1136/bmjgh-2019-001560
PMid:31673432

51. Li J, Regev G, Patel SK, Patton D, Sweeney Y, Graebing P, et al. Rational design of a multipurpose bioadhesive vaginal film for co-delivery of dapivirine and levonorgestrel. Pharmaceutics. 2020;12(1):1.
https://doi.org/10.3390/pharmaceutics12010001
PMid:31861267

52. Balle C, Konstantinus IN, Jaumdally SZ, Havyarimana E, Lennard K, Esra R, et al. Hormonal contraception alters vaginal microbiota and cytokines in South African adolescents in a randomized trial. Nat Commun. 2020;11(1):5578.
https://doi.org/10.1038/s41467-020-19382-9
PMid:33149114

53. Kiser PF, Johnson TJ, Clark JT. State of the art in intravaginal ring technology for topical prophylaxis of HIV infection. AIDS Rev. 2012;14:62–77.

54. Committee for Medicinal Products for Human Use. Dapivirine Vaginal Ring 25 mg. 2020 [accessed 7 Nov 2020]. Available from: https://www.ema.europa.eu/en/documents/medicine-outside-eu/dapivirine-vaginal-ring-25-mg-summary-opinion_en.pdf.

55. Musekiwa A, Fernando NB, Abariga SA. Effectiveness of vaginal microbicides in preventing HIV transmission. Trop Med Int Heal. 2020;25(7):790–802.
https://doi.org/10.1111/tmi.13401
PMid:32306503

56. Ramjee G. Microbicides for HIV prevention. Indian J Med Res. 2011;134(6):930-8.
https://doi.org/10.4103/0971-5916.92638
PMid:22310825

57. World Health Organization. European Medicines Agency (EMA) approval of the dapivirine ring for HIV prevention for women in high HIV burden settings. 2020 [accessed 7 Nov 2020]. Available from: https://www.who.int/news/item/24-07-2020-european-medicines-agency-(ema)-approval-of-the-dapivirine-ring-for-hiv-prevention-for-women-in-high-hiv-burden-settings.

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