MedCrave
Step into the World of Research

Journal of Human Virology & Retrovirology

Review Article

Open Access

CrossMark

# Exploring the causes of preexposure prophylaxis of HIV failure–future developments for overcoming the same–a mini review

## Abstract

Although preexposure prophylaxis (Pr EP), which involves use of antiretroviral drugs by non infected individuals for prevention of acquisition of HIV, has been a promising prevention strategy there are still some public health questions that need an answer. Intake of oral emtricitabine (FTC)–tenofovir disoproxil fumarate (TDF) daily or oral TDF alone is highly effective in preventing HIV acquisition in HIV people at risk which might be the result of a wide range of different types of sexual exposure. Good efficacy has been seen both in women and men along with if men had sex with men (MSM) and transgender. Different studies have been conducted in various countries and epidemics. Because there is a big problem about adherence to this treatment which varies geographically questions about its public health benefit have been raised. Oral FTC/TDF has been found to be very safe, having, minimal impact on kidney, bone or pregnancy outcomes. No evidence is found that effectiveness is decreased by risk compensation outcomes and programmatic follow up. Still it is very early to assess the impact of this treatment on the incidence of sexually transmitted infections (STIs) at population level. There are many challenges on use of PrEP with limited access with disparities along with those decided by race and sex, along with different pricing and availability of the drugs in the country. Further social effects decide the use of this TDF alone or TDF/FTC. With regard to that newer drugs like cabotegavir are being explored. Aim of this mini review has been to find a way how this Pr EP can be fully utilized for HIV prevention world over.

**Keywords:** preexposure, prophylaxis, HIV

Volume 7 Issue 1 - 2019

Kulvinder Kochar Kaur,[1] Gautam Allahbadia,[1] Mandeep Singh[2]

[1]Department of Human Reproduction, India

[2]Department of Consultant Neurologist, India

**Correspondence:** Kulvinder Kochar Kaur, Department of Human Reproduction, Jalandar, Punjab, India, Email kulvinder.dr@gmail.com

**Received:** December 24, 2018 | **Published:** January 07, 2019

**Abbreviations:** HIV Prevention, Preexposure prophylaxis, tenofovir disoproxil fumarate (TDF), emtricitabine (FTC), cabotegavir, HIV heterosexual, MSM, STI's

## Introduction

Despite the introduction of preexposure prophylaxis (PrEP) and Approved by FDA, it has not been used consistently till date. The aim of this mini review has been to find out the reason for failure of use of this excellent preventive measure for the partners of at risk population of HIV positive individuals. Hence we conducted a mini review on the same.

## Methods

We did a PubMed analysis using the MeSH terms, preexposure prophylaxis,HIV high risk population ,tenofovir usage, emtricitabine, heterosexual, male having sex with male transgender, cabotegavir usage from 2007 till date .

## Results

We found a total of 3135 articles pertaining to the same, of which we selected 66 articles for this review after ruling out duplicate articles and using cross references for the advances in prevention exposure prophylaxis and how the problems with the same might be prevented. No Meta analysis was done. Use of antiretroviral medicines with regard to prevention of HIV–1 transmission remains very promising to reduce the spread of HIV.[1–4] Treating people who have been infected by HIV–1 gives a lot of benefits by decreasing the infectiousness of HIV.[5–7] For people who have not been infected with HIV, post exposure antiretroviral prophylaxis and preexposure prophylaxis(PrEP),for those who have ongoing exposures are the individuals who are potential candidates for HIV Prevention strategies.[8,9] Why PrEP needs to be used has been decided by the effectiveness of antiretroviral prophylaxis used in infants that have been exposed to HIV1 while birth and during breastfeeding,[10] along with that seen in nonhuman primate studies that demonstrated partial/full protection against mucosal simian challenge.[11] If antiretroviral medicines were given both before and following virus exposure the benefits against transmission got to the maximum both in perinatal studies as well as in animal models.[12] The antiretroviral drugs utilized for PrEP trials in humans have been tenofovir, which is used either as a gel vaginally or as oral tenofovir disoproxil fumarate(TDF) or oral TDF that is co formulated with emtricitabine(FTC/TDF).As per animal studies FTC/TDF gives greater protection against HIV–1 as compared to TDF alone.[11] Hence need for evaluating both as Prep agents is there in view of their differential efficacy, safety and cost of TDF vis a vis FTC/TDF. Thus it has been seen that HIV1 susceptible persons who are within HIV1serodiscordant partnership i.e. where one of the partners is infected with HIV–1 while the other is unaffected, remain at continuous risk of acquiring HIV.[13,14] Thus Beaten et al conducted a partnership PrEP study, which was a multisite ,phase III randomized, double blinded, three arm, placebo controlled trial of oral antiretroviral PrEP in heterosexual couples from Kenya and Uganda, where one member was HIV–1 seronegative and the other HIV1 seropositive. Seronegative Partners were assigned randomly to receive once daily tenofovir (TDF), or combination tenofovir/emtricitabine (FTC/TDF), or matching placebo and were followed monthly up to 36mths. At enrollment, HIV1 seropositive partners were not eligible for

antiretroviral therapy under national guidelines. All couples received standard HIV1 treatment and prevention services which included individuals and couples risk reduction counseling and condoms of 4578 couples that were enrolled, for62%, the HIV seronegative partner was male. For HIV1 seropositive participants, the median CD4 count was 495 cells /μL (interquartile range 375–662). Of 82 post randomization HIV 1 infections,17 were among those assignedTDF(incidence 0.65/100 person years ),13 among those assigned FTC/TDF(incidence 0.50/100 person years), and 52 among those assigned placebo(incidence 1.99/100 person years)indicating a 67% relative reduction in HIV incidence for TDF(95%CI 44–81,p<0.001) and 75% for FTC/TDF(95%CI55–87,p<0.001). HIV protective effects of FTC/TDF and TDF were not significantly different (p=0.23)and both study medications significantly decreased HIV1 incidence in both men and women. The rate of serious medical events was similar across the study arms. Thus they concluded that oral TDF and FTC/TDF give substantial protection against HIV acquisition in heterosexual men and women, with comparable efficacy of TDF and FTC/TDF.[15] Further once daily FTC/TDF got approved for HIV virus PrEP in 2012and has been found to be an effective tool for preventing HIV in high risk groups that include men who have sex with men(MSM),transgender persons, heterosexual individuals, and people who inject drugs(PWID).[15–18] In spite of these advances in prevention, nearly 40,000new diagnosis were made in 2016. HIV is a significant public health problem in the United States.[19] As per the Centers for Disease Control and prevention (CDC), an 1.1 million people had an indication for PrEP in the US in 2015, of which 44%were black and roughly a quarter of those who would benefit from PrEP were Hispanic.[20] Yet PrEP uptake in these ethnic along with racial groups was not strictly followed as per the need.[21] According to the same report, of the heterosexual active adults who required PrEP, 68%were women. Still PrEP is not fully used in this group.[22] Further risk group where need for PrEP is present is the PWID.[23] As per the US National HIV/AIDS, PWID, is a priority population needing HIV prevention, and an estimated 115000 PWID were believed to be eligible for PrEP in the US.[24] Also there has been inequality in the regional PrEP uptake based on the HIV. Like in 2017, the southern states had the lowest ratio of active PrEP prescriptions per new HIV Diagnosis as compared with other US regions.[25] Thus Garner et al decided to report the demographic, racial and regional variations along with indications for PrEP use of HIV prevention in the Vererans Health Administration (VHA). They identified people who had started FTC/TDF for the PrEPindication in the US between June 2012 and April 2016 in a VHA national database. Further they divided the PrEP use as per the provider type and VHA region. They calculated PrEP prescription for each region with the VHA population. Of the 825 individuals who started PrEP during observation period, 67%were white and 76%were MSM.PWID and transgender represented less than 1% ech of the cohort. Majority of PrEP initiation were clustered in 3states leading with California (28%) followed by Florida (9%) and Texas (8%). The Southeast had one of the lowest PrEP rates at 10 PrEP initiations per 10, 000persons in care. Infectious disease specialists issued >2/3rd of index PrEP prescriptions. Thus they concluded that uptake of PrEP in VHA is uneven along the geographic and risk categories. Understanding these gaps will be the key in expanding the use of this important prescription tool.[26] Incidence of HIV infection continues to rise in parts of the world where transmission is driven by injection drug use.[27] PWID account for 30% of new HIV infections outside the sub–Saharan Africa.[28] Russia with already one of the highest rate of HIV infection, is one of the few countries where HIV incidences increasing.[29] Of the estimated 900,000–2000,000 people living with HIV(PLWH)in Russia,[30,31] up to 80% are PWID,[32] and 47%of new HIV cases with a mode of transmission, are among PWID.[30] Thus need for slowing HIV transmission among PWID in Russia is needed. Already it has been seen that PrEP using antiretroviral like tenofovir disoproxil fumarate/emtricitabine (TDF/FTC)prevents HIV transmission within serodiscordant heterosexual couples,[16,18,33] and HIV among at risk PWID,[17,34] and MSM,[17] and thus is recommended for prevention of HIV in these populations.[35] Sexual partners of PLWH who have ever injected drugs are the prime candidates to be considered for PrEP, since research shows that both sexual and drug related risk behaviors usually occur simultaneously in these partnerships and create the potential for an injection driven epidemic to transition to the general population.[36–38] In Russia, where injection drug use is the primary driver of HIV transmission and linkage to antiretroviral therapy (ART) among PLWH who have ever injected drugs is suboptimal,[39] offering PrEP to uninfected partners who are associated with these individuals could be an important strategy for limiting the spread of HIV, as it would mitigate the transmission risks of uninfected partners who are associated with lack of viral suppression among PLWH.[40, 41] PrEP is not available right now in Russia till now although it has been seen that there is rapid rollout to MSM in New South Wales, Australia, suggests that it could help reduce the HIV incidence in other concentrated epidemic settings like Russia.[42] Female partners of male PLWH who ever injected drugs might be at particularly high risk for HIV transmission as women might experience more risk of HIV acquisition than men.[43] Moreover, women may get greater risk for HIV,from injection drug use, as has been shown in research in US, that women who inject are more likely to report a regular sex partner who also injects compared with men,[44] and having intimate injection partnerships (meaning sexual partnership with a partner who injects) which further adds to the greater chances of high risk injecting practices like receptive syringe sharing.[36] In some studies of PWID, women had greater hepatitis C virus,[44] and HIV incidence than men.[45] The frequency of partnerships, and partners HIV status, among women and men living with HIV who inject drugs has been not explored. Thus Gnatienko et al.,[46] aimed at describing the frequency of being partnered and having a HIV–negative partner, and if this differed by gender, among a cohort of persons living with HIV(PLWH), who have ever injected drugs; to describe the awareness of HIV PrEP and perceived partner interest in PrEP It was a secondary analysis of an observational cohort study of PLWH who have ever injected drugs in St Petersburg, Russia. Primary outcomes were i) being partnered and ii) being in serodiscordant partnership. The main independent variable was gender. Multivariate GEE logistic regression models were fit for binary outcomes, adjusted for age, income, education, and recent opioid use. Descriptive analyses were performed for partners HIV status, substance use, sex risk behaviors, and awareness of PrEP for a subset of participants. At baseline 50% (147/296) reported being in a partnership. After adjustment, women had significantly higher odds of being partnered compared to men (aOR=3.12; 95% CI:1.77,5.51) but there were no significant partnerships (aOR=0.58; 95% CU:0.27,1.24). Among a subsample of participants queried (n=56), 25% were aware of PrEP for prevention of injection related transmission. Thus they concluded that half of their samples were partnered and one third of these partnerships were serodiscordant, PrEP awareness was low. Substantial opportunities for HIV prevention exist along PLWH who have ever injected drugs in Russia and their HIV–negative partners. Given the high proportion of HIV–negative

partners among this ART –naïve sample, efforts address the associated inherent risks, like couple based interventions, are needed to increase condom use, PrEP awareness, or uptake of other HIV prevention modalities like ART for the HIV–positive partner.[46] Despite oral TDF based PrEP being highly effective for HIV prevention when taken as per prescription,[15–17,47–48] achieving and maintaining adherence rates sufficient for high level protection against HIV remains challenging for some individuals and populations.[49–51] Inability to adhere with daily tablets might be just forgetfulness, or involve more complicated reasons like concerns about safety, stigma related to use, and potential harms if PrEP use gets disclosed to sexual partners. From the lessons learned from contraceptive technology, it has been seen that using increased variety of product types for PrEP will increase the profitability that at least 1 product will fit a particular persons needs at a given time.[52] Because of this interest in development and evaluation of HIV prevention agents which do not need daily adherence has arisen. Cabotegavir (CAB) is an investigational strand transfer integrase inhibitor that has potent activity against HIV in vitro and in vivo.[53,54] CAB is formulated both in the form of an oral tablet given daily along with a long injectable suspension (long acting CAB[CABLA]).[55] Right now CABLA is under development for HIV therapy, with a combination of rilpivirine (NCT02951052 and NCT02938520.[56,57] In nonhuman primate (NHPmodels it has been shown that CABLA can protect against rectal, parenteral and (SHIV) challenges).[58–63] High level of protection was seen against repeated exposures, when CAB concentration in the plasma were over 4 times the protein adjusted $IC_{90}$(PA $IC_{90}$)(0.664µg/ml)and were generally maintained at drug concentrations above the (PA $IC_{90}$(0.166µg/ml). The safety and pharmacokinetics of CAB LA in humans were evaluated in a phase 2a trial ,the ÉCLAIR trial, which enrolled HIV–uninfected low risk men in the US.[64] In this trial CAB LA at a dose of 800mg every 12weeks was investigated. This study showed that although CABLA was safe, well tolerated, the pre specified pharmacokinetic targets that got established from the NHP models for preventive safety were not met consistently.[64] Both in vitro data and data from the NHP studies were used to set the pharmacokinetic targets before starting the study. The target median trough concentration was set at 1.35µg/ml, which once achieved, was predicted to attain trough concentrations of > than or equal to the 4x PA $IC_{90}$(0.664µg/ml )in 80% of participants, and > than or equal to the 4x PA $IC_{90}$(0.166µg/ml) in 95% of participants. In the NHP models, no transmissions were seen with rectal or vaginal challenge where infections occurred during the pharmacokinetic tail.[61,63] Following that, modeling based on datasets from both HIV infected and HIV uninfected individuals in ongoing studies gave a suggestion that a dose of 600mg IM every 8weeks, following an initial 4week interval between first and second injections, is more likely to meet the pharmacokinetic targets. Thus the HIV Prevention Trials Network Study 077(HPTN077), which was a double blind, placebo controlled phase 2a was undertaken by Landovitz et al.[65] Healthy individuals age 18–65 years at low HIV risk were randomized (3:1) to receive 1 CAB or placebo (PBO). In the initial oral phase, participants received 1 daily oral tablet (CAB or PBO) for 4 weeks. Those without safety concerns in the oral phase continued and received injections in the injection phase (Cohort 1:3 injections of CAB LA 800mg or 0.9%salineas PBO IM every 12weeks for 3injection cycles; Cohort 2: CAB LA 600mg or PBO IM for 5 injections cycles; the first 2 injections in Cohort2 were separated for 4weeks, the rest by 8weeks). The primary analysis included week's 5–41 of study participation encompassing the injection phase. The cohorts were enrolled sequentially. Primary outcomes were safety and tolerability. Secondary outcomes included pharmacokinetics and events occurring during the oral and injection phases. Between feb 9,2015 and may 27,2016, the study screened 443 individuals and enrolled 110 participants in Cohort 1 and 89 eligible participants in Cohort2. Participant population characteristics were as follows: 66% female at birth; median age 31years; 27% nonhispanic white, 41%nonhispanic black, 21%hispanic/Latino, 3%asian, and 6%mixed/other; and 6%trans gender men and 1 transgender woman. 22(11%) participants discontinued the oral study product; 6 of these were clinical or laboratory adverse event (AEs). Of these who received at least 1 CAB LA injection, 80% of Cohort1 and 90% of Cohort2 participants completed all injections; injection course completion rate were not different from those in the PBO arm. Injection site reactions (ISRs) were common (92% of Cohort 1 and 88% of Cohort2 participants who received CAB LA reported any ISR). ISR were mostly grade1 (mild) and grade2 (moderate), and ISR event (Cohort1) led to product discontinuation. Grade2 or higher ISRs were the only AEs reported among CAB LA recipients than PBO recipients. Two grade 3 (severe) ISRs occurred in CAB recipients. 1 in each cohort, but did not lead to discontinuation in either case, 7 incident sexually transmitted infections were diagnosed in 6particupants.One HIV infection occurred in a participant 48weeks after the last injection of CAB LA; CAB was not detectable in plasma both at the time of first reactive HIV test and at the study visit 12 weeks prior to the first reactive test. Participants in Cohort2 (Unlike Cohort 1) consistently met prespecified pharmacokinetic targets of at least 95% of participants containing CAB trough concentrations above PA $IC_{90}$ and 80% maintaining trough concentrations above 4x PA $IC_{90}$. Study limitations included a modest sample size, a short course of injections, and a low risk study population. Thus they concluded in this study CAB LA was well tolerated at the doses and dosing used. ISRs were common, but infrequently led to discontinuation.CAB LA 600mg every 8weeks met pharmacokinetic targets of both males and female study participants. The safety and pharmacokinetic results observed support the further development of CAB LA, and efficiency studies of CAB LA for HIV treatment and prevention are in progress both in the US and resource constrained countries as a requisite step in the development of CAB LA for PrEP for HIV.[65]

## Conclusion

This short review summarizes how preexposure prophylaxis (Pr EP) is as important for preventing the further spread of HIV to stop the epidemic of the same in high risk groups at risk for development of HIV like heterosexual partners of HIV positive men/women. In case of MSM, their partners who are HIV negative along with transgender and the partners of those who inject drugs TDF, FTC/TDF both have been approved since 2012 for the same, yet usage is not being done consistently in countries like US where these drugs are easily available vis a vis countries like Russia Which have limited availability of the same. Also importance of HIVPr EP for adolescents and young adults has been emphasized.[66] Further inherent problems of daily use of oral TDF has led to the development of cabotegavir, developed both in oral and injectable forms and is in phase 3 trials to overcome the problems encountered by partners of HIV positive individuals, in the form of social and other problems with the use of Oral TDF, FTC/TDF. Hopefully these problems will gradually get overcome to make prevention further efficacious with PrEP unlike the same causes which led to failure of common prevention methods like condom use etc.

## Acknowledgments

None.

## Conflicts of interest

The author declares there is no conflict of interest.

## References

1. Cohen MS, Gay C, Kashuba AD, et al. Narrative review: antiretroviral therapy to prevent sexual transmission of HIV1. *Ann of Int Med*. 2007;146(8):591–601.
2. Karim SS, Karim QA. Antiretroviral prophylaxis:a defining moment in HIV control. *Lancet*. 2011.
3. Padian NS, McKoy SI, Karim SS, et al. HIV prevention transformed: the new prevention research agenda. *Lancet*. 2011;378(9787):378:269–278.
4. Montaner JS, Lima VD, Barrios R, et al. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnosis in British Colombia, Canada:a population based study. *Lancet*. 2010;376(9740):269–278.
5. Donnel D, Baeten JM, Kiarie J, et al. Heterosexual HIV-1 transmissionadter initiation of antiretroviral therapy: a prospective cohort study. *Lancet*. 2010;375(9731):2092–2098.
6. Attia S, Egger M, Muller M, et al. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analyses. *AIDS*. 2009;23(11):1397–1404.
7. MS Cohen, Chen YQ, McCauley M, et al. Prevention of HIV1 infection with early antiretroviral therapy. *N Engl J Med*. 2011;365(6):493–505.
8. Grant RM. Antiretroviral agents used for HIV-1 in infected persons for pre and post exposure prophylaxis. *Clin Inf ect Dis*. 2010;50(Suppl 3):S96–S101.
9. Oral and topical PrEP Trials Timeline. 2011.
10. Kumwenda NI, Hoover DR, Mofensen LM, et al. Extended antiretroviral prophylaxis to reduce breast milk HIV1 transmission. *N Engl J Med*. 2008;359(2):119–129.
11. Garcia Lerma JG, Otten RA, Qari SH, et al. Prevention of rectal SHIV transmission in macaques by daily or intermittent prophylaxis with emtricitabine and tenofovir. *PLoS Med*. 2008;5(2):e28.
12. Garcia Lerma JG, Cong ME, Mitchell J, et al. Intermittent prophylaxis with oral truvada protects macaques from rectal SHIV infection. *Sci Transl Med*. 2010;2(14):14ra4.
13. Eyawo P, De Walque D, Ford N, et al. HIV status in discordant couples in Sub-Saharan Africa: systematic review and meta-analyses. *Lancet Infect Dis*. 2010;10(11):770–777.
14. Dunkie KL, Srephenson R, Karita E, et al. New heterosexually transmitted HIV infections in married or cohabitating couples in urban Zambia and Rwanda:an analysis of survey and clinical data. *Lancet*. 2008;371(9631):2183–2191.
15. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV1 Prevention among heterosexual men and women. *N Engl J Med*. 2012;367(5):399–410.
16. Thiggens MC, Kebabetswe PM, Paxton LA, et al. Antiretroviral prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med*. 2012;367(5):423–434.
17. 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.
18. Choopanya K, Martin M, Sumithatasamai P, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok. Thailand (the Bangkok Tenofovir Study): a randomized double blind placebo controlled phase 3 trial. *Lancet*. 2013;381(9883):2083–2099.
19. Centres for Disease Control and Prevention. *HIV Surveillance Report*. 2016.
20. Smith DK, Handel MV, Grey JA. By race, ethnicity, Blacks have highest number needing PrEP in the United States,2015. *Poster Presentation at:Conference on Retroviruses and Opportunities*. 2018;1(1):4–7.
21. Marcus JL, Hurley LB, Hare CB, et al. Disparities in uptake of preexposure prophylaxis in a large integrated healthcare system. *Am J Public Health*. 2016;106(10):e2–3.
22. Black stock OJ, Patel VV, Felsen I, et al. Antiretroviral prophylaxis prescribing and retention in care among women at a comprehensive sexual health clinic. *AIDS Care*. 2017;29(7):866–869.
23. Roth AM, Aumaiter PL, Felsher MA, et al. An exploration of factors impacting preexposure prophylaxis eligibility and access among syringe exchange users. *Sex Transm Dis*. 2018;45(4):217–221.
24. Smith DK, Van Handel M, Woluitski RJ, et al. Vital signs: Estimated percentages and numbers of adults with indications of preexposure prophylaxis to prevent HIV acquisition –United States 2015. 2015;64(6):1291–1295.
25. Siegler AJ, Mouhanna F, Giler RM, et al. Distribution of active PrEP prescriptions and PrEP –to need ratio.US Q2 2017. Poster presentation at : *Conference on Retroviruses and Opportunistic Infections*. 2018;1(1):4–7.
26. Garner W, Wilson BM, Bester L, et al. Gaps in preexposure prophylaxis Uptake for HIV Prevention in the Veterans Health Administration. *Am J Public Health*. 2018;108(Suppl4):S305–S310.
27. UNAIDS. Global AIDS Update 2018. 2018.
28. UN Joint Programme on HIV/AIDS (UNAIDS).The Gap Report 2014.
29. European Centre for Disease Prevention and Control/WHO Regional Office for Europe. HIV /AIDS Surveillance in Europe 2015 (2016).
30. Federal Scientific Centre for the Prevention and Combat of AIDS of the Public Office of the Central Scientific Research Institute Rospotrebnadzor. 2018.
31. Beyrer C, Wirtz AL, O'Hara G, et al. The expanding epidemic of HIV1 in the Russian Federation. *PLoS Med*. 2017;14(11):e1002462.
32. Wolfe D, Carrieri MP, Shephard D. Treatment and care for injecting drug users with HIV infection: a review of barriers and way forward. *Lancet*. 2010;376(9738):355–366.
33. Anglemeyer A, Rutherford GW, Baggaley RC, et al. Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples. *Cochrane Data base Syst Rev*. 2011;11(5):CD009153.
34. Page K, Tsui J, Maher L, et al. Biomedical HIV Prevention including Preexposure Prophylaxis and Opiate Agonist therapy for Women Who Inject Drugs:State of Research and Future Directions. *J Acquir Immune Defic Syndr*. 2015;69(Suppl2):S169–175.
35. Centers for Disease Control and Prevention (CDC). HIV Risk and Prevention: Preexposure Prophylaxis (PrEP); 2016.
36. Morris MD, Evans J, Montgomery M, et al. Intimate injection partnerships are at elevated risk of high –risk injecting: a multilevel longitudinal study of HCV-serodiscordant injection partnerships in San Francisco,CA. *PLoS One*. 2014;9(10):e109282.
37. Evans JL, Hahn JA, Page Shafer K, et al. Gender differences in sexual and injection risk behavior among active young injection drug users in San Francisco (the UFO Study). *J Urban Health*. 2003;80(1):137–146.

38. Des Jarlais DC, Feelemyer JP, Modi SN, et al. Transitors frominjection-drug –concentration to self sustaining heterosexual HIV epidemics : patterns in the international data. *PLoS One*. 2012;7(3):e31227.

39. Ministry of Health. HIV Infection in Russia in: Federal Research Centre for HIV/AIDS Prevention and Treatment; 2015.

40. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1.Rakai Project Study Group. *N Engl J Med*. 2000;342(13):921–929.

41. Mehendale SM, Ghate MV, Kishor Kumar B, et al. Low HIV 1 incidence among married serodiscordant couples in Pune, India. *J Acquir Immune Defic Syndr*. 2006;41(3):371–373.

42. Gruich A, Guy RJ, Amin J, et al. Rapid reduction in HIV 1 Diagnosis after targeted PrEP Implementation in NSW, Australia. 25th Conference on Retroviruses and Opportunistic Infections. 2018.

43. Melo MG, Santos BR, De Cassia Lira R, et al. Sexual transmission of HIV 1 among serodiscordant couples in Porto, Alegre, southern Brazil. *Sex Transm Dis*. 2008;35(11):912–915.

44. Tracy D, Hahn JA, Fuller Lewis C, et al. Higher risk of incidental hepatitis C Virus among young women who inject drugs compared with young men in association with sexual relationships: a prospective analysis from the UFO Study cohort. *BMJ Open*. 2014;4(5):e004988.

45. Des Jarlais DC, Feelmyer JP, Modi SN, et al. Are females who inject drugs at higher risk of HIV infection than males who inject drugs: an international systematic review of high seroposrevalence areas. *Drug Alcohol Depend*. 2012;124(1–2):95–107.

46. Gnatienko N, Wagman JA, Cheng DM, et al. Srodiscordant partnerships and opportunities for preexposure prophylaxis among partners of women and men living with HIV in St Petersburg, Russia. *PLoS One*. 2018;13(11):e0207402.

47. Morina JM, Capitant C, Spire B, et al. On demand preexposure prophylaxis in men at high risk for HIV infection. *N Engl J Med*. 2015;373(23):2237–2246.

48. McCormack S, Dunn DT, Desai M, et al. Preexposure prophylaxis to prevent the acquisition of HIV -1 infection(PROUD):effectiveness of results from the pilot phase pf a pragmatic open –label randomized trial. *Lancet*. 2016;387(10013):53–60.

49. Grant RM, Anderson PL, McMahan V, et al. Uptake of preexposure prophylaxis sexual practices, and HIV incidence in men and transgender women who have sex with men:a cohort study. *Lancet Infect Dis*. 2014;14(9):820–829.

50. Liu AY, Clhen SE, Vittinghoff E, et al. Preexposure prophylaxis for HIV infection integrated with municipal -and community based sexual health services. *JAMA Intern Med*. 2016;176(1):75–84.

51. Haberer JE, Bangsberg DR, Baeten JM, et al. Defining success with HIV preexposure prophylaxis: a prevention-effective adherence paradigm. *AIDS*. 2015;29(11):1277–85.

52. Schivone GB, Glish LL. Contraceptive counseling for contuinuation and satisfaction. *Curr Opin Obstet Gynaecol*. 2017;29(6):443–448.

53. Yoshinaga T, Kobyashi M, Seki T, et al. Antivural characteristics of S/GSK 1265744, an HIV integrase inhibitor dosed orally or by long-acting injection. *Antimicrobial Agents and Chemotherapy*. 2015;59(1):397–406.

54. Muller RH, Gohla S, Keck CM. State of the art of nanocrystals –special feautures,production ,nanotoxicologyaspects and intracellular delivery. *Eur J Pharm Biopharm*. 2011;78(1):1–9.

55. Spreen WR, Margolis DA, Pottage JC Jr. Long acting injectable antiretrovirals for HIV treatment and prevention. *Curr Opin HIV AIDS*. 2013;8(6):565–571.

56. Margolis DA, Brinson CC, Smith GHR, et al. Cabotegravir plus rilpivirine,once a day ,after induction with cabotegravir plus nucleoside reverse transriptase inhibitors in antiretroviral-naïve adults with HIV-1 infection(LATTE):a a randomized ,phase 2b dose ranging trial. *Lancet Infect Dis*. 2015;15(10):1145–1155.

57. Margolis DA, Gonzalez Garcia J, Stellbrink HJ, et al. Long acting intramuscular cabotegravir and rilpivirine in adults with HIV 1 infection(LATTE-2):96 week results of a randomized ,open label ,phase2b,noninferiority trial. *Lancet*. 2017;390(10101):1499–1510.

58. Andrews C, Gettie A, Russel Lodrique K, et al. Long acting parenteral formulation of GSK1265744 protects macaques against repeated intrarectal challenges with SHIV mac 251. 2013.

59. Andrews CD, Bernard LS, Poon AY, et al. Cabotegravir long acting injection prorects macaques against intravenous challenge with SHIVmac 251. *AIDS*. 2017;31(4):461–467.

60. Dobard C, Makarova N, Nishiura K, et al. Long acting Cabotegravir protects macaques against repeated penile SHIV exposures. *Retroviruses and Opportunistic Infections*. 2018;1(1):4–7.

61. Andrews CD, Spreen WR, Mohri H, et al. Long acting integrase inhibitor protects macaques from simian/human immune deficiency virus . *Science*. 2014;343(6175):1151–1154.

62. Radzio J, Spreen W, Yueh YL, et al. Long acting Integrase inhibitor GSK1265744 protects macaques from repeated intravaginal SHIV challenge .*Sci Transl Med*. 2015;7(270):270ra5.

63. Andrews CD, Yueh YL, Spreen WR, et al. A long acting intrgrase inhibitor protects female macaques from repeated high doseintravaginal SHIV challenge. *Sci Transl Med*. 2015;7(270):2704.

64. Markowitz M, Frank I, Grant RM, et al. Safety and tolerability of long acting cabotegravir injections in HIV-uninfected men(ÉCLAIR): a multcentremdouble blind, randomized, placebo controlled,phase2a trial. *Lancet HIV*. 2017;4(8):e331–e340.

65. Landovitz RL, Grinszten SLB, Dawood H, et al. Safety, tolerability and pharmacokinetics of long acting injectable cabotegravir in low risk HIV-uninfected individuals:HPTN077, a phase 2 a randomized controlled trial. *PL Os Med*. 2018;15(11):e1002690.

66. Allen E, Gordon A, Krakower D. HIV preexposure prophylaxis for adolescents and young adults. *Curr Opin Pediatr*. 2017;29(4):399–406.