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What is the Place of Pre-Exposure Prophylaxis in HIV Prevention?

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Abstract

New tools are needed to bring down ongoing high HIV incidence. This review aims to evaluate the place of one of these new tools (pre-exposure prophylaxis) in a comprehensive prevention strategy. Several trials have demonstrated the safety and the efficacy of pre-exposure prophylaxis in HIV prevention. Two large trials have, however, failed to show such efficacy. This was likely due to poor adherence in these trials. New forms of long-acting pre-exposure prophylaxis currently in trials may deal with these problems of low adherence. Pre-exposure prophylaxis has been demonstrated to be cost-effective within certain settings. The introduction of pre-exposure prophylaxis into prevention programs needs to be carefully thought through. For example, pre-exposure prophylaxis-induced risk compensation, at both an individual and population level, could undermine other aspects of a comprehensive HIV prevention program. In conclusion, pre-exposure prophylaxis could be a useful additional tool for the prevention of HIV in specific high-risk groups. It should be implemented in a way that deals with issues such as ensuring high adherence and ensuring that pre-exposure prophylaxis does not detract from, but complements, other more fundamental elements of HIV prevention programs.
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Key words

HIV prevention. Pre-exposure prophylaxis. Cost-effectiveness. Program implementation. Risk compensation.

Introduction

More than 30 years after the start of the AIDS pandemic, the incidence of HIV remains alarmingly high. Despite a decrease in incidence during the early years of the previous decade, an estimated 2.5 million people are newly infected each year[1]. In contrast, global resources available for HIV programs in low- and middle-income countries have declined since 2009[2].

One of the greatest challenges in HIV prevention is devising comprehensive prevention packages with an optimal mix of the various components tailored to specific epidemics[3]. Antiretroviral (ARV) drugs can prevent HIV acquisition in a number of ways. Besides their preventive effect when used as treatment[4,5], ARV drugs are also effective in reducing mother-to-child transmission[6], for pre-exposure prophylaxis (PrEP)[7], and in some ways for post-exposure prophylaxis (PEP)[8]. This paper aims to review the efficacy, safety, and cost-effectiveness of PrEP, as well as possible adverse outcomes such as resistance and risk compensation. It will then discuss the implementation of PrEP and its place in a comprehensive prevention approach.

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Search strategy

We searched PubMed for all PrEP-related papers. These included trials, observational studies, narrative reviews, systemic reviews, and meta-reviews published since 2004. We selected papers focusing on prevention of HIV, implementation, cost-effectiveness, or other factors relevant from a public or global health perspective. We also reviewed relevant publications

from the WHO, UNAIDS and non-governmental organizations related to PrEP together with electronic reports on recent conferences related to HIV/AIDS. Search terms included "pre-exposure prophylaxis", "HIV prevention", "cost-effectiveness", "microbicides", "behavior", "program implementation", and "risk reduction".

Pre-exposure prophylaxis explained

Pre-exposure prophylaxis involves the use of ARV drugs to prevent HIV infection. Currently, the most commonly used ARV drugs for oral PrEP are tenofovir (TDF) or a combination of tenofovir and emtricitabine (TDF/FTC). Both of these were chosen because of their potency against HIV[9], their favorable resistance profile, and limited adverse effects[10,11]. For vaginal application, a 1% TDF gel is most promising.

The Food and Drug Administration (FDA) has recently approved oral TDF/FTC with the aim to reduce HIV transmission among high-risk men who have sex with men (MSM) in the USA[12]. Important preconditions were noted before PrEP could be prescribed[13]. In particular, it should only be used in persons who are confirmed HIV negative with a normal renal function and a negative hepatitis B status (Fig. 1)[14]. Recipients need further to be tested at least three monthly during follow-up to make sure they remain HIV negative. Pre-exposure prophylaxis cannot be used in persons whose HIV status is positive or unknown.

Efficacy

Oral and vaginal PrEP have been tested in numerous animal studies and have been found effective in preventing SIV or SHIV in macaques and humanized mice[15].

Table 1 summarizes the results of recent randomized controlled trials done with PrEP in humans. Oral PrEP was shown to be effective in a population of high-risk MSM (iPrEx)[16], heterosexual HIV discordant couples (Partners in PrEP study)[17], and heterosexual men and women (TDF2)[18]. Nonetheless, two recent studies in women (VOICE[19] and FEM-PrEP[20] trials) were not able to reproduce this. While HIV incidence was very high in the recently reported VOICE results (varying from 0.8 to 9.9 per 100 person-years by site), there was no evidence of efficacy in any of the three PrEP arms (oral TDF, oral TDF/FTC, vaginal TDF daily)[19].

In each of the studies in table 1, efficacy improved with higher adherence. Likewise, the non-significant results of oral PrEP in VOICE and FEM-PrEP could be explained by low adherence rates. In FEM-PrEP, only 26% of women who acquired HIV during the trial had drug levels in the target range[20]. In VOICE, 58% of those receiving TDF had any detectable trace of TDF at any time point[19]. The better penetration of intracellular phosphorylated tenofovir (TDF-DP) in rectal compared with cervicovaginal tissue is another explanation for the differential efficacy of PrEP. A study showed the concentration of TDF-DP in rectal mucosal tissue to be 100-fold higher compared with cervicovaginal tissue[21]. This could partly explain why studies researching the effect of PrEP on a vaginal route of transmission, like FEM-PrEP and VOICE, were not able to show a protective effect. Nevertheless, the same group also showed that the concentration of emtricitabine triphosphate (FTC-TP) is 10 to 15-fold higher in cervicovaginal tissue compared with rectal tissue[21]. Further research is necessary to understand how adherence, types of sexual exposure, and/or biological cofactors are related to the failure to show efficacy in the VOICE and FEM-PrEP trials[22]. A recent meta-analysis on oral PrEP concluded that both TDF/FTC and TDF are efficacious in the prevention of HIV infection for a variety of high-risk populations coming from low-, middle-, and high-income countries[7].

As far as vaginal PrEP is concerned, the CAPRISA 004 study found a significant efficacy for the use of 1% TDF gel applied intravaginally pre and post sex[23]. In contrast, no significant effect was found in the vaginal gel arm of the VOICE study (where 1% TDF gel was applied daily)[19]. This discrepancy in outcome may again have been due to the lower adherence with the application of daily as opposed to peri-coital vaginal gel. A pivotal trial in the ongoing investigation of the efficacy of 1% TDF gel is FACTS 001[24]. CAPRISA 008 will evaluate the effectiveness of integrating TDF gel provision into existing family planning services[25].

Drug adherence

Adherence seems to be a vital condition to the efficacy of PrEP. Although self-reported adherence rates were high, drug detection in hair cells or serum shows this to be unreliable[16-18,20]. In each of the trials, participants underwent adherence counseling during their monthly visits. Participants were well-informed and actively contacted if they did not show up on study visits. Despite all this, the number of participants where any TDF or FTC was detected was low in most of the trials. An extension of the iPrEx study identified some of the barriers to adherence: incompatibility with individual lifestyle, difficulties to adopt daily medication use, being mistakenly identified as HIV positive, unintended

CDC Interim Guidance on HIV Pre-Exposure Prophylaxis

Before initiating PrEP:

Determine eligibility:

- Document negative HIV antibody test immediately before starting PrEP medication.
- Test for acute HIV infection if patient has symptoms consistent with acute HIV infection or reports unprotected sex with an HIV-positive person in the preceding month.
- Determine if women are planning to become pregnant, are currently pregnant, or are breastfeeding.
- Confirm that patient is at ongoing, very high risk for acquiring HIV infection.
- If any sexual partner is known to be HIV infected, determine whether receiving antiretroviral therapy, assist with linkage to care if not in care or not receiving antiretroviral therapy.
- Confirm that calculated creatinine clearance is ≥ 60 ml per minute (Cockcroft-Gault formula).

Other recommended actions:

- Screen for hepatitis B infection; vaccinate against hepatitis B if susceptible, or treat if active infection exists, regardless of decision regarding prescribing PrEP.
- Screen and treat as needed for STI.
- Disclose to women that safety for infants exposed during pregnancy is not fully assessed but no harm has been reported.
- Do not prescribe PrEP to women who are breastfeeding.

Beginning PrEP medication regimen:

- Prescribe 300 mg TDF plus FTC 200 mg (i.e., one Truvada [Gilead Sciences tablet] daily.
- In general, prescribe no more than a 90-day supply, renewable only after HIV testing confirms that patient remains HIV-uninfected. For women, ensure that pregnancy test is negative or, if pregnant, that the patient has been informed about use during pregnancy.
- If active hepatitis B infection is diagnosed, consider using TDF/FTC, which may serve as both treatment of active hepatitis B infection and HIV prevention.
- Provide risk-reduction and PrEP medication-adherence counseling and condoms.

Follow-up while PrEP medication is being taken:

- Every 2-3 months, perform an HIV antibody test (or fourth generation antibody/antigen test) and document negative result.
- At each follow-up visit for women, conduct a pregnancy test and document results; if pregnant, discuss continued use of PrEP with patient and prenatal-care provider.
- Evaluate and support PrEP medication adherence at each follow-up visit, more often if inconsistent adherence is identified.
- Every 2-3 months, assess risk behaviors and provide risk-reduction counseling and condoms. Assess STI symptoms and, if present, test and treat for STI as needed.
- Every six months, test for bacterial STI even if asymptomatic, and treat as needed.
- Three months after initiation, then every six months while on PrEP medication, check serum creatinine and calculate creatinine clearance.

On discontinuing PrEP (at patient request, for safety concerns, or if HIV infection is acquired):

- Perform HIV test(s) to confirm whether HIV infection has occurred.
- If HIV-positive, order and document results of resistance testing, establish linkage to HIV care.
- If HIV-negative, establish linkage to risk-reduction support services as indicated.
- If active hepatitis B is diagnosed at initiation of PrEP, consider appropriate medication for continued treatment of hepatitis B infection.
- If pregnant, inform prenatal-care provider of TDF/FTC use in early pregnancy and coordinate care to maintain HIV prevention during pregnancy and breastfeeding

Recommendations in black apply to both adult MSM and heterosexually active men and women; items in grey are specific to heterosexual women.

Figure 1. *CDC interim guidance for healthcare providers electing to provide pre-exposure prophylaxis for the prevention of HIV infection in adult men who have sex with men and who are at high risk for sexual acquisition of HIV (reproduced with permission of CDC)[14]. PrEP: Pre-exposure prophylaxis; STI: sexually transmitted infection; TDF: tenofovir disoproxil fumarate; FTC: emtricitabine; MSM: men who have sex with men.*

disclosure of homosexual identity, and partner conflicts were the most important ones[26]. This study concluded that adherence counseling should be patient-centered and take into account individual lifestyle and social barriers[26].

A study done with MSM in Thailand pointed to the advantages of intermittent dosing of PrEP[27]. Participants appeared to be only intermittently exposed to HIV and more than two-thirds reported having an opportunity to take PrEP before sexual exposure[27].

Table 1. Summary of the efficacy of and adherence to pre-exposure prophylaxis in recent trials

	Peterson, et al.[43]	IPrEx[16]	TDF2[18]	PIP[17]	Fem-PrEP[20]	VOICE (MTN-003)[19]	CAPRISA 004[23]
Number of participants	936	2,499	1,219	4,747	2,056	5,029	889
Age	18-35	18-67	18-39	18-65	18-35	18-45	18-40
Participant type	Women with high sexual risk behavior in areas with high HIV transmission	MSM with high sexual risk behavior	Women (46%) or men, unmarried (94%)	HIV-negative women (38%) or men from discordant couples	Unmarried women with high sexual risk behavior	Unmarried women with high sexual risk behavior	Sexually active women
Study location	Ghana, Cameroon, Nigeria	Peru, Ecuador, South Africa, Brazil, Thailand, USA	Botswana	Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia	Kenya, South Africa, Tanzania	Uganda, South Africa, Zimbabwe	South Africa
Efficacy[a,b] (% reduction)							
– For TDF/FTC	–	44 (p = 0.005)	62 (p = 0.03)	75 (p < 0.001)	6 (p = 0.81)	No sign. diff.	–
– For TDF	65 (p = 0.24)	–	–	67 (p < 0.001)	–	No sign. diff.	–
– For TDF 1% gel	–	–	–	–	–	No sign. diff.	39 (p = 0.017)
Self-reported adherence[c] (%)	–	> 90	94	92-97	95		–
Adherence based on pill count[d]	69	> 90	84		88		72.2
Serum/cell detected adherence[e]							
1) new HIV+ during study (%)	–	9 (3/34)	50 (2/4)	31 (9/29)	26 (7/27)	*	
2) stay HIV- during study (%)	–	51 (22/43)	80 (55/69)	82 (737/901)	35 (27/78)	*	
Efficacy adjusted for adherence[f]	–	95	78	86 (TDF) 90 (TDF/FTC)	–	–	54

MSM: men who have sex with men; TDF: tenofovir; FTC: emtricitabine.

[a]Reduction of HIV infections compared to placebo is calculated from the ratio between the incidence rate of the treated group and the incidence rate of the placebo group.

[b]For all mentioned p-values, alpha was 0.05. The p-values of the Peterson, FEM-PrEP and CAPRISA studies are two-sided.

[c]Measurement of adherence based on self-report differs among each of the trials; e.g. in the TDF2 participants were asked if they took their medication in the preceding three days and in the FEM-PrEP study participants were asked if they had usually or always taken their pills. The numbers in the table present the percentage of people that reported to have taken their pills.

[d]Adherence measured by pill count and/or the number of visits (in % of days).

[e]Serum detected adherence is expressed in the percentage of people with a detectable drug level. Definition of a detectable drug level was different for each study:

- iPrEx: Drug detection was done in plasma and hair cells. The intracellular assay is expected to detect TDF-DP at least for 14 days after the last dose was taken. Similarly, for FTC-TP at least for seven days. FTC and TDF in plasma are expected to be detectable for 2-3 days after the last dose taken. Plasma drug detection from 10 ng/ml.
- TDF2: detectable plasma level: 0.3 ng/ml
- PIP2: detectable plasma level: 0.3 ng/ml
- FEM-PrEP: Only for TDF: 10 ng/ml in plasma offered evidence that TDF had been taken within the previous 48 hours.
- VOICE: 58% of those receiving TDF had any detectable trace of TDF at any time point

[f]Different trials used different types of adherence to adjust the efficacy (risk reduction). In the iPrEx trial and in the PIP trial, serum level detected adherence was used. In CAPRISA, adjustment was based on used applicator count and in PIP on pill count.

Anticipated advantages of intermittent PrEP are: a reduction in costs, fewer side effects, and a reduced pill burden. At least one other study has, however, found it more difficult for study participants to take PrEP intermittently compared to daily[28].

Studies on the efficacy of intermittent PrEP are ongoing[29,30]. Further research should reveal the barriers to adherence in the FEM-PrEP and VOICE studies. A plausible explanation is a low risk and severity perception of HIV/AIDS among the target population[20]. If indeed these factors seem to have an important contribution to the low adherence, further social and behavioral research is urgently needed. Identification of the driving aspects behind these factors will not only be necessary in the context of PrEP, but will be of crucial importance for HIV prevention as a whole. Ongoing or planned "open-label extension" studies (where participants are informed about the proven efficacy of PrEP) of the iPrEx, Partners PrEP, and TDF2 trials will reveal barriers to adherence. The importance of adherence to the efficacy of PrEP has heightened interest in slow-release forms of PrEP[31,32]. Currently, a vaginal matrix ring with the ARV drug dapivirine is being tested in two phase III trials[33,34], research on a slow-release TDF vaginal ring is in phase I[35], and the use of long-acting injectables is currently being studied in a phase I trial[36]. Primate studies suggest that integrase inhibitors injected monthly or even quarterly could be promising options[37]. Further studies are needed to analyze what forms of PrEP will achieve the optimal balance between dosing frequency (such as peri-coital versus daily dosing), adherence levels, and efficacy. Behavioral and social research is needed to build effective adherence interventions[38]. Research should also be focused on new techniques to measure and stimulate adherence. One example is real-time adherence monitoring, whose efficacy has been established in low-resource settings[39].

Adverse effects

Serious drug-related adverse events are rare with TDF[40]. Less than 1% of HIV-infected patients in clinical trials had serious adverse events such as renal impairment or Fanconi's syndrome. Decreases in bone mineral density may be a more significant problem for long-term use[41]. Except for occasional skin hyper-pigmentation, TDF/FTC has a similar adverse effect profile to TDF[42]. None of the trials on oral PrEP reported a difference in serious adverse effects between the placebo and treatment groups[16-18,20,43]. Nevertheless, gastrointestinal symptoms like nausea and vomiting were frequent in the treatment group and occurred significantly more frequently than in the placebo group in three trials[16,18,20]. These symptoms were mainly present in the first month of treatment and completely disappeared in the majority of participants. In only one of the trials was bone density measured and a significant loss in bone density was found in the treatment group[18].

It should be emphasized that the current trials with HIV-infected patients or with PrEP are probably too short to capture the possible long-term side effects of TDF. Screening for osteoporosis is therefore probably recommended, especially in older patients or with long-term use of PrEP[44]. Kidney failure is the most frequent significant adverse effect related to TDF[45] and several trials reported a creatinine increase[16,20], which was found to be entirely reversible after stopping TDF. Renal function should be monitored in persons taking TDF[44]. Two important factors made it difficult to assess the adverse effects of oral PrEP in the currently available trials: adherence was relatively low in most of the trials and the study time was relatively short, with a maximum follow-up of three to four years and a median follow-up of one to two years.

Apart from instances of diarrhea, no important adverse effects were reported in trials with vaginal application of PrEP[23]. While TDF is absorbed systemically during topical use, serum drug levels are low, which explains the limited side effects[46].

In conclusion, serious adverse effects from PrEP occur rarely and most cases cease when the ARV drugs are withdrawn.

Drug resistance

None of the persons who acquired HIV infection whilst receiving ARV in the oral PrEP studies had any detected ARV resistance mutations. However, some participants with acute HIV infection tested HIV negative on initial testing and were started on PrEP. Among them, five persons developed resistance to TDF and/or FTC[16-18,20]. Since the study populations were tested for HIV monthly, there was less opportunity for the development of resistant strains than in a non-trial setting. For this reason, the limited occurrence of resistance in the discussed trials might be a strong underestimation of the occurrence in non-trial settings. Emergence of resistance could be a particular concern if PrEP were to lead to risk compensation[47]. These considerations provide the rationale for the FDA recommendations that PrEP must only be used by individuals proven to be HIV-negative and who remain HIV negative. HIV testing should be conducted a minimum of three monthly.

Cost-effectiveness

Three recent studies assessed PrEP for high-risk MSM from a US cost-effectiveness perspective based on mathematical modeling. Among these studies, the appreciation of PrEP varies from unattractive (US$ 298,000 per QALY gained)[48] to cost-effective (US$ 32,000-40,000 per QALY gained)[49,50]. The differences among these findings are explained by the use of a different model, a different time horizon, and different base case assumptions (e.g. the incidence of HIV infections among high-risk MSM). Studies done in other parts of the world vary a lot in assumptions, population, and study design. A modeling study in South Africa concludes that PrEP would be cost-effective if less than 65% of all HIV-positive cases were on antiretroviral treatment (ART)[51]. The time needed to scale-up ART to this level could be seen as a window of opportunity for PrEP. Another study in South Africa suggests that strategic use of PrEP in serodiscordant couples could be as cost-effective as early initiation of ART, even if PrEP had an effectiveness of only 40%[52].

The most cost-effective strategy for serodiscordant couples would be the combination of PrEP prior to ART, with ART starting at CD4 < 350 µl[52]. A more recent modeling study conducted in South Africa has shown that scaling up of ART and early ART is obviously more cost-effective than investing in PrEP for people living in a hyperendemic setting[53]. However, PrEP could still play an additional role in further reducing the incidence, even if early ART would have been adopted[53]. One study found PrEP to be cost-effective for MSM in Lima, Peru[54]. However, PrEP should only be considered in settings where well-performing ART services already have been adopted[54]. Consistent findings among these modeling studies were the substantial impact made by variations in the cost of the drugs and the assumed effectiveness of PrEP[55]. Based on sensitivity analyses, the impact of drug resistance, risk compensation, and toxicity was found to be less important[55]. The studies agree that PrEP could substantially reduce the lifetime risk of HIV infection in persons at high risk, but also that the budget needed for PrEP would be large. Since the cost of the medication has a major impact, expiration of the patent of Truvada in July 2017 may change the cost-effectiveness substantially for western countries. Start-up costs were not included in the studies, which we think could be considerable, especially in low- and middle-income countries. Two modeling studies on the topical use of PrEP in South Africa, based on the results of CAPRISA 004, estimate the intervention as highly cost-effective and able to have a substantial impact on the incidence of HIV[56,57].

Risk compensation

If a new HIV prevention technology is to result in a net reduction in new HIV infections, then its uptake needs to reach enough people at risk and its benefit should not be offset by compensatory increases in risk behavior[58]. It is particularly important that the new technology does not lead to an inflated belief in the efficacy of the intervention in those using it, and a reduction in perception of being at risk of HIV infection in the population at large. There is empirical support for a psychological theory of risk management, which posits that individuals are comfortable with a certain level of risk[59]. If a new technology is introduced that leads to a reduction in the perception of risk, then individuals may regard risk-taking behavior more favorably[60,61]. Evidence of this risk-compensation effect has been found after making the use of car seat belts compulsory and the promotion of condoms to make sex safer[61-63].

The availability of ART for the treatment of HIV has been accompanied by an increase in high-risk sex in MSM communities[64]. In the case of MSM, the increase in risky sex has been shown in a number of studies to be related to a perception of being at lower risk of HIV/AIDS in the ART era[64-68]. A meta-analysis of 25 studies conducted on this topic found that persons who believed receiving ART protects against HIV transmission were more likely to engage in unprotected sex. Persons who had less concerns about the dangers of unprotected sex, given the availability of ART, were also more likely to engage in unprotected intercourse[69].

No evidence of behavioral risk compensation was found in any of the PrEP trials, but participants received monthly counseling, free condoms, and health services[16-18,20,43]. In addition, self-reported sexual behaviors in this context may be particularly prone to a courtesy-bias, telling the researchers what they want to hear, namely that there has been no increase in risky behavior. “Open-label” studies will examine this question and will provide additional information about acceptability and adherence to PrEP[70]. A preliminary analysis of iPrEx OLE, the “open-label extension” study of the iPrEx trial, has found no evidence of behavioral risk compensation[71]. Even if no evidence of risk compensation is found in these studies, this does not mean that the introduction of PrEP could not lead to a population-level change in the fear of risky sex, as was the case with ART[61].

Implementation of pre-exposure prophylaxis

There is now good evidence that PrEP works, at least within a trial setting in certain high-risk groups. This knowledge needs to be tempered by the concerns of the programmatic consequences related to the implementation of PrEP. An inadequately conceived PrEP program might bring harm to the current health system of a country, especially if this health system is already overloaded, as is the case in several lower- and middle-income countries. Necessary services to ensure an effective PrEP program would include: infrastructure for drug distribution, adherence counseling, staff-training, risk behavior counseling, HIV-testing, and possibly viral resistance testing for people infected despite the prophylaxis. In low-resource settings, the added value of a program that may need expensive technical equipment is questionable, especially if no well-performing ART delivery program is established yet. Moreover, the allocation of staff and resources to a vertical program like PrEP may be at the expense of other vital aspects of primary healthcare. Tailored adherence counseling should deal with uptake concerns of the target population, as discussed in the section about adherence. It is also not clear who will pay for PrEP – the state, medical insurance, users of PrEP, or a mixed model.

Once established, program monitoring is crucial. The uptake among the target population, the overall effectiveness of PrEP, the costs and additional burden on the health system, and other foreseen or unforeseen effects (occurrence of resistance, risk compensation) should be carefully evaluated to decide if it is worth continuing.

Pre-exposure prophylaxis as part of a comprehensive strategy

A new tool such as PrEP should complement and not undermine other HIV prevention strategies of proven efficacy. Such a combination prevention approach must be tailored to the local epidemic and context.

In the generalized HIV epidemics of Southern and Eastern Africa, for example, HIV prevention activities need to focus on the key factors driving these epidemics. One of these factors is the high rate of sexual partner concurrency[72,73]. In a setting where high HIV transmission rates are determined to a significant extent by the practice of having main- and side-partners[74], PrEP may undermine attempts to decrease side-partnerships. This could occur if persons with concurrent relationships decided to use PrEP rather than not engage in these relationships. The complex interplay between prevention modalities is illustrated by the differences in the efficacy of different types of HIV prevention programs in sub-Saharan Africa. A key factor behind Uganda's success in bringing down HIV incidence was a collaborative campaign that led to a perception by all sexually active persons that they were at risk of HIV and that partner reduction was necessary to reduce this risk[58,75]. Rates of multi-partnering dropped dramatically and HIV incidence followed suit[76,77]. By way of contrast, in Botswana and South Africa where a much greater emphasis was placed on condom promotion and less on partner reduction, condom usage has increased substantially[63,78,79]. There has, however, been little change in the prevalence of multiple partnering[79-81], and HIV incidence, though somewhat diminished, remains high[82,83].

From the theoretical perspective of the risk-management-theory of sexual behavior, it is not difficult to see how the uncritical provision of a technological quick-fix such as condoms or PrEP could lead to individuals discounting the risk of additional partners if they use the new intervention[58]. This in turn could undermine attempts at partner-reduction strategies. This could have significant consequences in the context of epidemics driven by multiple partnering. These considerations in no way detract from the proven efficacy of both condoms[84] and PrEP in preventing HIV transmission. They are, however, a reminder that a successful comprehensive prevention strategy does not only entail the introduction of all prevention components of proven efficacy. A successful strategy depends on introducing the components in a synchronous, mutually reinforcing, and contextually appropriate fashion. Furthermore, in populations with generalized HIV epidemics, combination top-down and grassroots behavior change campaigns, such as those from Uganda, should be given due importance alongside the interventions listed in figure 2[58,75,85].

Pre-exposure prophylaxis needs to be targeted to those who would benefit from it. The following groups may be candidate targets:

High-risk men having sex with men

The CDC guidance stresses the importance of targeting PrEP to MSM at very high risk in their manual for prevention of sexually transmitted infections[86]. A similarly good case for PrEP could be made for high-risk heterosexuals who are unable or unwilling to alter their lifestyles. Unfortunately, uptake among MSM in the USA seems to be limited[87].

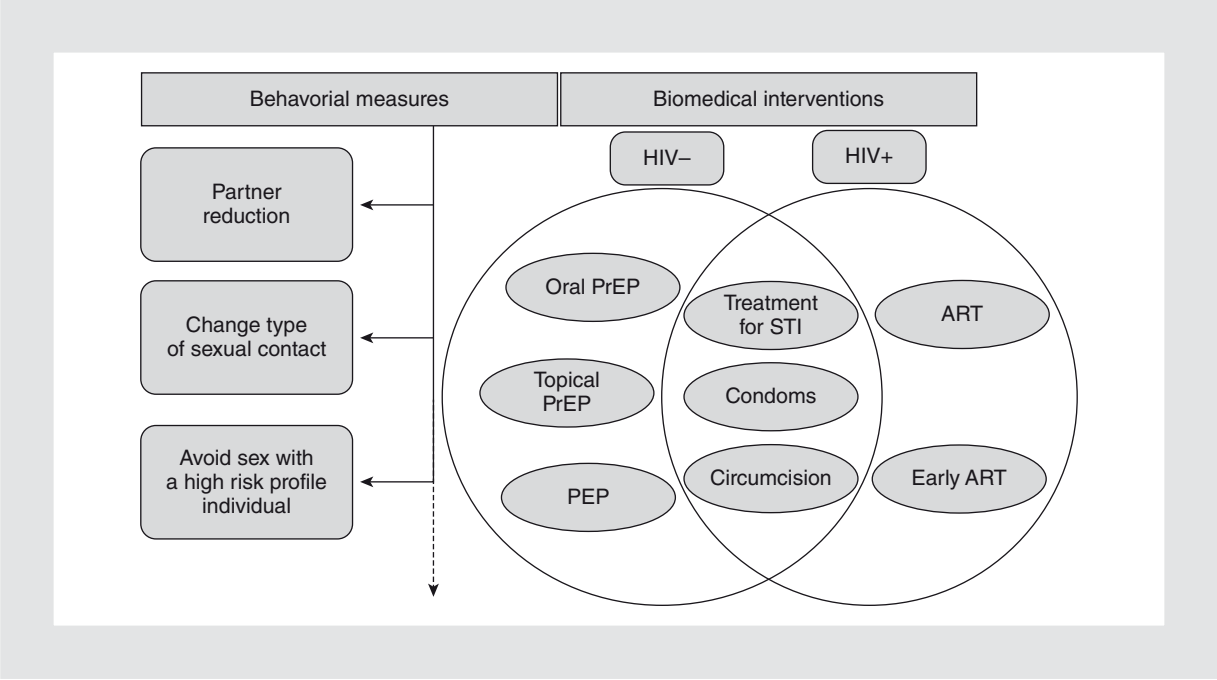

Figure 2. *Summary of options to prevent HIV transmission during sexual intercourse.*
PrEP: pre-exposure prophylaxis; STI: sexually transmitted infections; ART antiretroviral therapy; PEP: post-exposure prophylaxis.

HIV-serodiscordant couples

High adherence rates were found for PrEP in serodiscordant couples[17]. Pre-exposure prophylaxis seems to have an important complementary value to condom use[17]. Nevertheless, priority should be given to treatment of the HIV-positive partner with ART or early ART, as will be discussed later.

Sex workers

Pre-exposure prophylaxis offers a new form of self-protection to this vulnerable group. The TDF2 study showed a relatively high adherence among women who were assumed to be sex workers based on their sexual risk behavior and the place where they were working[18]. On the other hand, several factors such as alcohol and drug use, an irregular lifestyle, and frequent displacement may compromise adherence and follow-up in this group.

Sexually active young women

In some countries, PrEP might reduce HIV transmission by targeting this group. Nevertheless, in the VOICE study, adherence was low in the under-25-year-old group, and further social and behavioral research is needed to analyze barriers to adherence[22].

The following case scenarios are examples where we think that PrEP could be considered

- A 27-year-old MSM from Germany whose preferred lifestyle involves frequent anonymous sex. All oral and some anal sex is without condoms. He was completely compliant with PEP for three times in the last year.
- A 24-year-old female from Botswana has been working for several years as a prostitute. She has an average of 30 different partners per week with whom she has sexual intercourse. She insists on condom use, but some clients pay more for sex without a condom.
- A 29-year-old female, living in Kenya, has a partner who is HIV positive and is unable to access ART as he has WHO stage I disease. They do not always use a condom and have experienced condom failure on a number of occasions. She is highly motivated to use additional prevention measures.

Oral, vaginal, or injectable pre-exposure prophylaxis?

There are advantages and disadvantages for the oral, vaginal, and injectable forms of PrEP. Vaginal use

of PrEP is associated with fewer adverse effects and tends to induce less resistance compared to oral PrEP. Further trials are needed to compare both options, especially in terms of efficacy. Future trials will also evaluate novel forms of PrEP such as rectal gels. Long-acting forms of PrEP such as vaginal rings and injectable drugs may, by dealing with the serious problem of adherence, prove to be of great utility. Pivotal trials will reveal more about these options[88].

Antiretroviral therapy, early antiretroviral therapy, or pre-exposure prophylaxis?

Antiretroviral therapy used according to the current guidelines in heterosexual serodiscordant couples leads to a high reduction in transmission of HIV[89,90]. A recent study with early ART in discordant couples showed a very high protection of the HIV-negative partner, combined with clinical benefits for the HIV-positive partner[5]. The only failures of protection were found at the start of the prevention treatment. Cost-effectiveness seems to be comparable for PrEP and early ART in these couples. The additional value of PrEP in a serodiscordant couple with the HIV-positive partner on ART should still be researched. A reasonable case could be made for complementing early ART with PrEP in the initial months of ART while the partner's viral load (and associated infectivity) is declining. Among other high-risk groups, ART and early ART seem to be much more cost-effective than PrEP[53]. Nevertheless, in some cases, PrEP can offer protection where ART fails. As with all HIV prevention modalities, the place of PrEP needs to be tailored to the risks and preferences of the individuals concerned.

Conclusion

Pre-exposure prophylaxis can offer significant protection to specific high-risk populations. It appears to be safe and the development of ARV resistance is rare. Nevertheless, it remains important to monitor patients on PrEP, especially in case of long-term use. Adherence plays a vital role in the efficacy of PrEP, and lack of adherence could be the main factor why certain recent trials failed to show PrEP to be effective. Better understanding of the barriers to adherence and long-acting forms of PrEP may obviate this problem. Although PrEP has been demonstrated to be cost-effective in specific cases, the budget needed for such a program is high. Moreover, implementation of a PrEP program will face several challenges, especially in low-resource settings. If adopted, PrEP should be part of a combination prevention approach and complement other prevention strategies.

Conflict of interest

The authors declare no conflict of interest.

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