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Antiretroviral Drugs for Pre-Exposure Prophylaxis of HIV Infection

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Abstract

Though a large number of antiretrovirals have been developed for the treatment of HIV infection, new HIV infections continue to occur, especially among certain high-risk groups, such as men who have sex with men. Overall, the current estimated incidence of HIV infection is 2.5-fold higher than the number of individuals that begin antiretroviral therapy every year worldwide. Along with the personal drama caused by the diagnosis of HIV infection, other considerations in society, including economics and interpersonal relationships, make the need for HIV prevention strategies a priority. Though vaccines have shown great efficacy in the combat of other epidemics, currently there is no effective vaccine against HIV, and it is unlikely that any will become available in the near future. Thus, new approaches such as pre-exposure prophylaxis are viewed with increasing interest. The results from recent clinical trials have provided support in favor of distinct pre-exposure prophylaxis modalities. However, concerns exist about increasing risky behaviors and selection and spread of antiretroviral drug resistance with a broader use of pre-exposure prophylaxis. The aim of this review is to examine the evidence available on the effectiveness of pre-exposure prophylaxis and its potential influence on the HIV epidemics. **(AIDS Rev. 2012;14:54-61)**

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Key words

HIV transmission. PrEP. HIV prevention. Sexual transmission. Tenofovir. Microbicide.

Introduction

The implementation of highly active antiretroviral therapy (HAART) has been a milestone in the treatment of HIV-infected individuals, improving both their life expectancy and quality of life[1], transforming an otherwise lethal disease into a chronic illness. Nevertheless, HIV infection remains a major public health issue as a high number of cases are still diagnosed every year, especially in developing countries where access to HAART is still limited due to financial constraints. In developed regions, HIV incidence has rebounded, especially among certain high-risk groups such as men who have sex with men (MSM)[2]. Furthermore, according to UNAIDS, 2.7 million people became infected with HIV in 2008 worldwide[3], which roughly represents 2.5-times the number of people who begin antiretroviral therapy every year[4]. HIV infection has implications that exceed individual health issues and affect the whole society, with economic impact (i.e. monitoring and treatment-related costs, loss of job hours caused by HIV-related diseases, or early deaths in active populations) and ethics of human relationships (i.e. sexual partners, children) being amongst the most important[5].

Vaccines have proven their efficacy in the prevention of other epidemics, showing a high cost-efficacy profile, and allowing their use in large populations. Several clinical trials involving HIV vaccines have been carried out, generally with poor results. Currently, there are no ongoing phase III trials, and the development of an efficacious vaccine for HIV prevention will not be feasible in the near future[6]. For this reason, interest has shifted to new approaches for HIV prevention.

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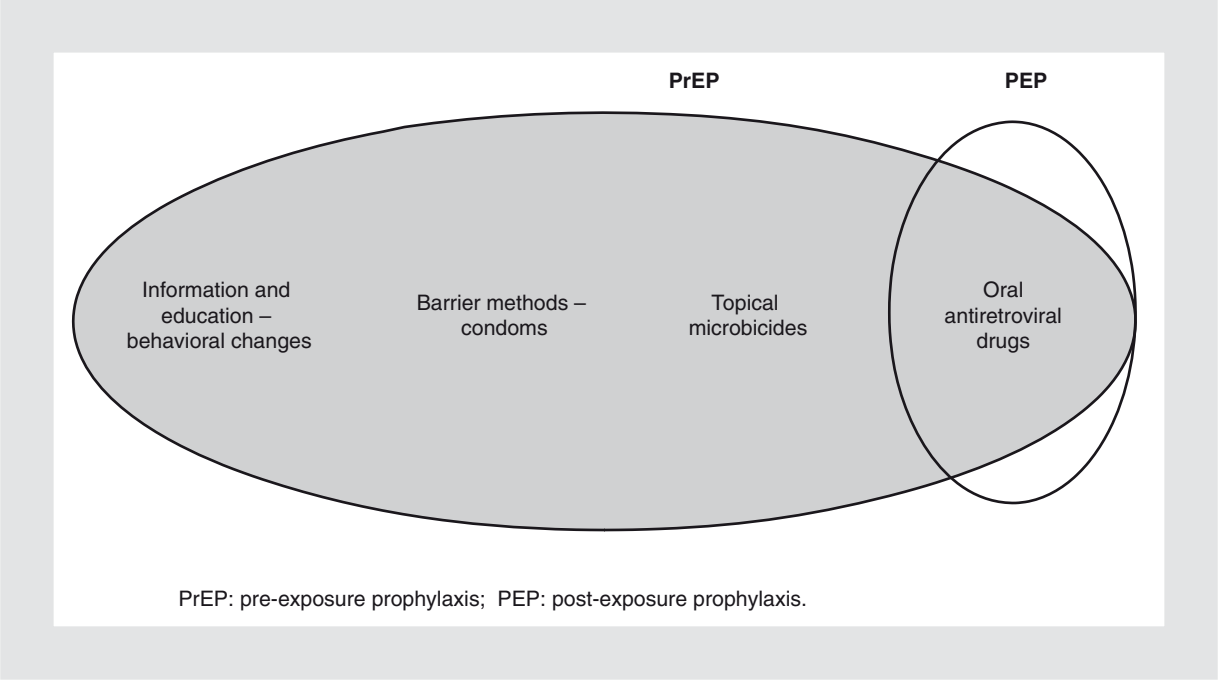

Figure 1. *Strategies to reduce sexual HIV transmission.*

Antiretroviral pre-exposure prophylaxis (PrEP), defined as the daily or intermittent administration of antiretrovirals to HIV-seronegative individuals with high risk of exposure to HIV[7], has gained the interest of the medical community within the last few years. If proven effective, antiretroviral prophylactic regimens administered to persons at risk could potentially reduce the number of new HIV infections, especially those sexually acquired. Nevertheless, when considering the implementation of PrEP at a population level, several important considerations arise, including cost, drug-related adverse events, drug interactions, selection of drug resistance, and ethics of human relationships, which often are underestimated in initial steps of enthusiasm.

When considering a drug for PrEP, several pharmacological features must be kept in mind. The ideal drug or regimen should have good tolerability and safety, a low pill burden, high potency, once-daily dosing, a long half-life, as well as a high barrier to resistance and lack of cross-resistance with other drugs[8]. For this purpose, nucleos(t)ide analogues have been assessed in several clinical trials, given that some of them display the aforementioned properties and biologically have the advantage of blocking the initial phases of viral infection, prior to integration of the viral genome into the host cell chromosomes. Other drugs, such as raltegravir and maraviroc, share this mechanism of action and have similarly been assessed in animal models[8].

Topical pre-exposure prophylaxis regimens

Women comprise almost 50% of the population living with HIV worldwide. Although less represented in Western countries, where men who have sex with men (MSM) predominate in the HIV population, heterosexually infected females are the greatest population in Sub-Saharan Africa. Topical microbicides are products that attack cellular or viral targets, intending to prevent the infection of target cells or viral replication. A reduction in virus transmission and acquisition has been shown using some microbicides, supporting their potential role as part of PrEP strategies (Fig. 1)[9].

The mechanisms by which HIV penetrates the female genital tract have been extensively characterized[10]. Both vagina and ectocervix are covered by a multilayered squamous epithelium, providing a higher protection than the single-layered epithelium of endocervix and endometrium. Nevertheless, initial HIV penetration and infection has been shown in all four sites[11]. Thus, any condition causing mucosal disruption, such as inflammation or ulcerative diseases, may facilitate HIV entry and the establishment of infection.

The acidity of the vaginal canal is protective against a number of pathogens, including a variety of viruses and bacteria. This natural defense mechanism can be overcome either by the seminal fluid alkaline pH or by

the depletion of the normal vaginal bacterial flora. The development of compounds that protect the acidic vaginal pH, either by buffering the seminal alkaline pH or by maintaining the vaginal bacterial flora, has been one of the strategies tested to prevent male-to-female HIV transmission[12,13].

There are important differences between genital and rectal mucosae, involving both histologic and immune features, which make the latter more vulnerable to HIV infection. The development of microbicides, effective and tolerable in both genital and rectal mucosae, is currently underway.

Surfactants and membrane disruptors are the first family of agents clinically assessed as topical antimicrobials. These agents cause a nonspecific membrane disruption, with activity against HIV and other pathogens causing sexually transmitted infections. Surfactant-based agents such as SAAVY (C31G) and Nonoxynol-9 (N-9) have been tested in clinical trials[14,15]. Studies that have tested C31G were halted due to lower-than-expected HIV incidence rates in the trial population, making necessary a very high sample size to find any significant difference. On the other hand, efficacy trials involving N-9 showed no benefit[16]. Furthermore, the use of N-9 was associated in this trial with a higher incidence of genital ulcers related with mucosal toxicity. Due to its lack of efficacy, further development of newer surfactants has been suspended.

Carbopol 974P (BufferGel®, ReProtect, USA) is a polyacrylic acid aimed at maintaining the vaginal acidic pH. This agent has shown its activity against HIV *in vitro*[17], as well as its safety in two phase I trials[18,19]. The HPTN-035 trial[20] was a phase II trial that tested the efficacy and safety of BufferGel® in preventing HIV infection. The product was given along with naphthalene sulfonate (PRO2000; Indevus Pharm, USA). The results of this trial showed no differences in terms of HIV seroconversion rates amongst BufferGel® and placebo groups. Moreover, BufferGel® did not decrease the prevalence of bacterial vaginosis, unlike what prior studies had shown[16].

Anionic polymers are a group of agents that bind and block the attachment of HIV-1 to target cells. They interfere with the fusion of virus and host-cell membranes, or annul the entry of HIV-1 into host cells. Anionic polymers interact with HIV envelope through their negative charge, thus interfering with the HIV attachment to target cells[13]. PRO2000 is a naphthalene sulfonate polymer that has shown its efficacy *in vitro*[21]. The efficacy of PRO2000 gel was assessed in two main trials. MDP-301[21] was a randomized phase III trial, in which the efficacy and safety of PRO2000 0.5 and 2% gels was compared with that of placebo in 9,385 Sub-Saharan African women. Though no differences in terms of adverse events were observed, there was no evidence of any advantage in terms of HIV incidence. The efficacy of PRO2000 gel was also assessed in the HPTN-035 trial[22], where a 0.5% PRO2000 gel was tested in comparison with BufferGel® and placebo. Though a slight reduction in HIV incidence was found in the PRO2000 arm, this decrease did not achieve statistical significance. Thus, the evidence so far available suggests that the use of PRO2000 gel provides little or no protection against HIV.

The use of topical antiretrovirals has been proposed as an alternative strategy for PrEP. Tenofovir disoproxil fumarate (TDF) is a nucleotide reverse transcriptase inhibitor (NRTI) with interesting features, such as a prolonged serum half-life, high barrier to resistance, and favorable safety profile, which make this drug an attractive option for topical use in PrEP[8]. It has demonstrated its activity against HIV both *in vitro*[23] and in animal models[24]. The phase I HPTN-050 trial[25] proved the safety of 0.3 and 1% TDF vaginal gel for prevention of sexual HIV transmission.

The CAPRISA-004 trial[26] was a double-blind, randomized phase II trial that assessed the efficacy and safety of a 1% vaginal gel formulation of TDF in a cohort of 889 South African women. Overall, a 39% overall HIV incidence reduction in the TDF arm was recognized ($p = 0.017$) in comparison with placebo. These figures rose up to 54% in those individuals with self-reported high drug adherence (> 80% of sexual acts covered by two gel doses), while HIV reduction in low adherent individuals was of 28%. There were no significant differences amongst groups in terms of adverse events. Two further aspects of this trial merit attention. Firstly, 40% of the women enrolled in the CAPRISA-004 trial reported low drug adherence, defined as < 50% of sexual acts covered by gel. Irregular or low adherence to antiretrovirals is associated with the development of antiretroviral resistance. Thus, if PrEP regimens are going to be used at a population level, attention must be given to a harmful impact of suboptimal drug adherence beyond poor protection. A second aspect of interest in CAPRISA-004 was a trend to have safer sex acts throughout the follow-up period by individuals enrolled in the study, including increases in condom use and reductions in the number of sex acts. Altogether, these facts might have played a role in the steady decline of HIV incidence seen in the study over time.

Table 1. Main clinical trials testing pre-exposure prophylaxis

Study name	Trial modality and aims	Sample size	Target risk group	Intervention
CDC 4323	Phase II,safety	400	MSM	Daily oral TDF
CDC 4370	Phase II-III, safety and efficacy	2,400	IDU	Daily oral TDF
TDF2 (CDC 4940)	PhaseII, safety and adherence	1,200	Heterosexual	Daily oral TDF+ FTC
Partners PrEP	Phase III, safety and efficacy	4,700 serodiscordant couples	Heterosexual	Daily oral TDF/TDF+ FTC
FEM-PrEP	Phase III, safety and efficacy	3,900	Heterosexual women	Daily oral TDF+ FTC
VOICE	Phase IIb, safety and efficacy	5,000	Heterosexual women	Daily/Intermittent TDF+ FTC

MSM: men who have sex with men; IDU: injection drug users; TDF: tenofovir; FTC: emtricitabine.

The VOICE trial is an ongoing phase IIb trial that compares the efficacy and safety of daily oral versus topical TDF PrEP regimens. The results of this trial, expected in 2013, will provide more evidence in favor or against the use of topical TDF gels as PrEP regimens. Table 1 summarizes the main characteristics of PrEP studies.

Oral pre-exposure prophylaxis regimens

Since no drugs have been specifically developed for PrEP, clinical trials have assessed the efficacy of antiretroviral agents already approved for HIV treatment as preventative agents. As previously mentioned, the ideal PrEP regimen should include drugs showing particular features, such as good tolerability and safety, low pill burden, once-daily dosing, long half-life, high potency, and a high barrier to resistance. Furthermore, from a theoretical perspective, drugs that interfere with the HIV lifecycle prior to its integration in the host cell genome might be more suitable, since HIV entry into target cells could be somehow decreased[8]. In this regard, some NRTI, and particularly TDF, are interesting drugs to be considered as part of PrEP regimens.

Tenofovir has shown its efficacy in reducing SIV transmission in animal models, both in monotherapy[24] or in association with emtricitabine (FTC)[27]. In this setting, higher doses of TDF (20 mg/kg) have been shown to provide greater protection than lower doses, and failures have been observed with 10 mg/kg oral administration[28].

In humans, the tolerance of TDF as PrEP was assessed in a phase II, randomized, double-blind, placebo-controlled trial involving 936 HIV-seronegative African women[29]. Though efficacy endpoints could not be assessed due to the low number of seroconversions, there were no significant differences in terms of adverse events or laboratory abnormalities.

The iPrEx study[30] was a multicenter, randomized, placebo-controlled trial involving 2,499 HIV-seronegative men or transgender women, in which the efficacy and safety of a daily oral co-formulation of TDF/FTC was assessed for HIV prevention. The intervention group showed a 44% decrease in HIV transmission that was statistically significant. There were no significant differences in adverse events amongst groups, though individuals on TDF/FTC experienced a higher rate of nausea and weight loss than those on placebo. Of note, protection vanished in subjects with treatment adherence below 90%, and showed no significant differences in HIV prevention in comparison with placebo. This observation is important since roughly only one-third of subjects enrolled in the study admitted suboptimal drug adherence (Fig. 2)[31].

The group on TDF/FTC in the iPrEx trial experienced a mild but significant decrease in bone mineral density at hip and femoral neck compared to placebo[32]. The loss of bone mineralization was particularly prominent within the first year of therapy. These findings were further confirmed using dual-energy X-ray absorptiometry (DEXA) in a subset of individuals[33].

Other antiretroviral agents such as raltegravir and maraviroc display features potentially attractive for their

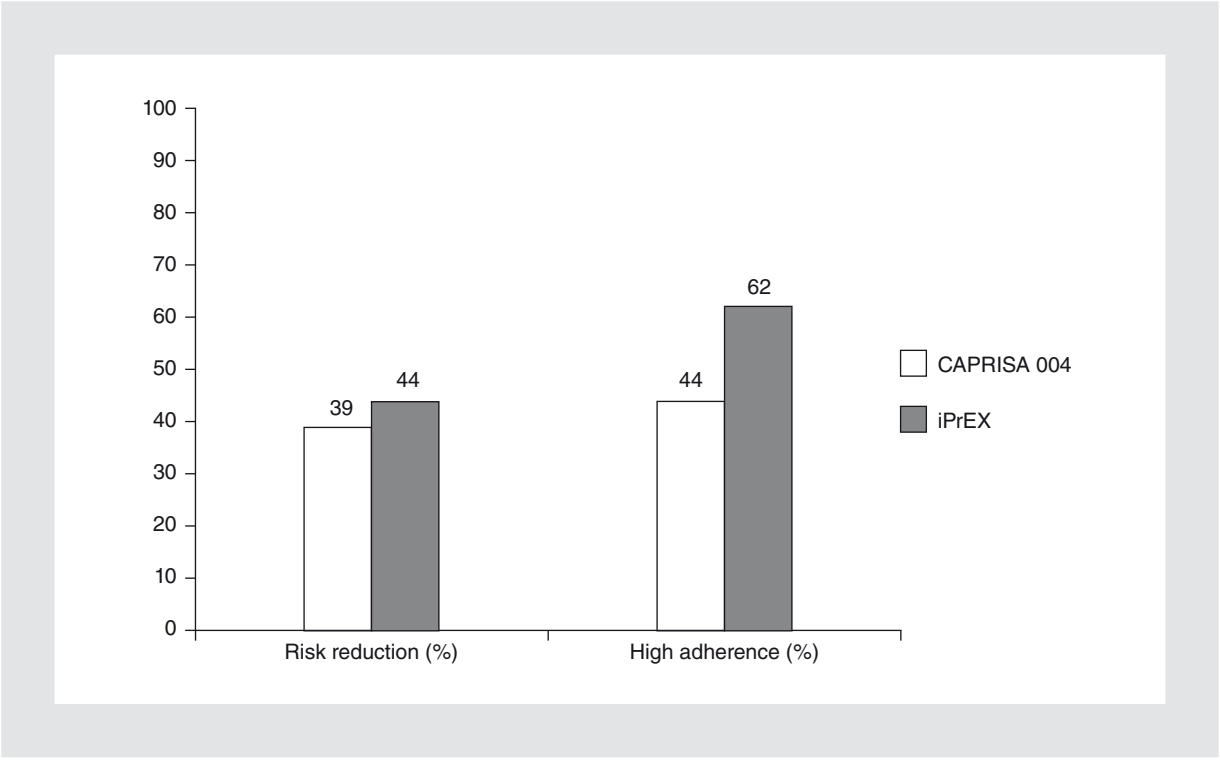

Figure 2. *Risk reduction and drug adherence reported in CAPRISA 004[26] and iPreX[30] trials.*

use as part of PrEP regimens. Both drugs act by interfering with the integration of the viral genome into the host chromosomes. A study in a humanized mice model[9] has shown the efficacy of both drugs separately in preventing HIV transmission. More evidence, though, is needed to support their use as part of PrEP regimens.

A mathematical model[34], derived from information obtained from commercial sex workers and male clients in African and Indian populations, has assessed the potential efficacy of implementing PrEP in these settings. The model suggests that PrEP could moderately reduce the incidence of HIV transmission in these populations, especially when it is provided in subjects that also use contraceptive barrier methods. Nevertheless, an increase in sexual risk practices could diminish or even reverse the efficacy of PrEP at population levels ("behavioral disinhibition")[5].

According to the available evidence, an interim guidance from the Centers for Disease Control and Prevention[35] has stated the potential benefit of PrEP usage in MSM in settings of high-risk practices and lack of use of any other prevention methods. However, the report emphasizes the critical role of adequate information, education, and promotion of safer sexual practices for the control of HIV epidemics in such risk groups.

Risk of selecting drug resistance

One of the main caveats with PrEP regimens is the risk of selection of drug resistance and further transmission. As long as TDF and FTC remain as the preferred NRTI backbone for the treatment of HIV infection[36], a clear view of the rate and potential impact of selection of drug-resistant viruses as result of widespread use of PrEP must be prioritized.

Studies in animal models have shown the emergence of drug resistance mutations in viruses that are acquired by animals that were on PrEP. Mutation M184V/I, which is selected by FTC, appeared in two out of six macaques that seroconverted while on PrEP[37]. In contrast, none of the animals selected mutation K65R, which confers resistance to TDF. It should be highlighted that both SIV and SHIV viruses have been used in macaque models. Though these viruses are classified as primate lentiviruses, they differ from HIV in genomic structure, coreceptor use, accessory genes, and target enzymes[38]. On the other hand, TDF and FTC doses used in these animals are generally higher than those given to humans, rendering the extrapolation of results questionable.

Mathematical models have assessed the risk of emergence of drug resistance if PrEP is implemented

at a population level. The most important factor to consider when designing and implementing a wide-scale usage of PrEP is "behavioral disinhibition"[5], which could be defined as the expected increase in risk practices (split into number of sexual partners, number of sex acts, and lack of consistent use of barrier methods) in risk populations once there is a decline in the perception of the likelihood of becoming infected. A mathematical model based in a MSM population[39] found that PrEP could result in an increased rate of transmission of drug-resistant viruses despite a reduction in overall HIV incidence. According to the information collected so far, the risk of emergence of drug resistance in PrEP populations is low. However, the use of combination therapy and/or drugs with high barrier to resistance is crucial to keep this risk as low as possible. Nevertheless, the emergence of drug-resistant HIV strains could dramatically increase if adherence to PrEP regimens is suboptimal or high-risk practices increase in populations at risk.

Pre-exposure prophylaxis for HIV-discordant stable couples

There is a particular situation in which PrEP may exhibit a great value. Many HIV-discordant heterosexual couples express a strong wish to conceive a child[40]. Insemination with processed semen is often offered to these couples. The low pregnancy rate of these artificial reproduction techniques, high costs of the procedures, and long waiting lists are important obstacles, which has meant that many serodiscordant couples try unprotected sexual intercourses as an alternative. While attempting natural pregnancy outside medical supervision may be risky[41], no cases of HIV infection have been documented in couples following strict protocols, ensuring fully suppressive HAART in the infected partner[42,43].

The possibility of intermittent HIV genital shedding in a residual proportion of patients on HAART with suppressed HIV replication in plasma[44] has prompted some authors to recommend PrEP and timed sexual intercourse in couples pursuing a natural pregnancy. In a recent study[45], 53 cases of natural conception were attempted using this strategy, with a successful pregnancy rate of 75% after six cycles, with no cases of HIV transmission. It should be acknowledged, however, that the possible benefit of PrEP in serodiscordant couples is difficult to prove, given the immeasurable low risk of HIV transmission in the setting of well controlled HIV replication. In some cases it may be proposed as a psychological support to ameliorate the anxiety and fear associated to an eventual HIV infection.

Economics and ethics of pre-exposure prophylaxis

Apart from efficacy and safety issues, implementing PrEP at a population level should also be considered in terms of cost. Since HIV incidence rates are significantly higher in developing countries compared to Western regions, the option of PrEP should be considered against implementation of universal test-and-treat (UTT) strategies, especially where resources for HIV treatment are scarce. A study performed in a South African HIV population assessed the cost-efficacy of implementing a TDF-based PrEP program aimed at 15-35 year-old women at high risk of being infected with HIV[46]. Assuming a PrEP cost of $150 per person per year, this trial estimated a cost of $12,500-20,000 per infection averted, depending on the level of antiretroviral coverage and baseline HIV incidence. These figures would be found in a scenario of 30-60% PrEP coverage, efficacy of at least 90%, no behavior change amongst PrEP users, and a moderate increase in antiretroviral coverage, which could be considered as a very optimistic situation. The reality may provide worse scenarios and thus reduce the cost-effectiveness of PrEP.

Another study performed in a South African HIV population assessed the efficacy and economic impact of a UTT program[47]. According to a mathematical model, implementation of UTT could potentially reduce HIV incidence to one case per 1,000 persons per year by 2016, which means a rather good cost-efficiency. Moreover, UTT could become even more promising in light of the results of the HPTN-052 trial[48], in which the early use of antiretroviral therapy in HIV-serodiscordant couples was associated with a fall in HIV transmission. Although UTT would require an extensive program of HIV testing at population levels, it would reach a higher number of people at risk of being infected[4].

The cost-effectiveness discussion runs in parallel with the ethical debate as to for whom drugs should be prioritized: those at risk of becoming infected, or already infected persons identified by massive screening campaigns. This is particularly relevant in resource-limited settings, where both HIV incidence and prevalence are high[5]. Clearly, further studies should compare the cost-effectiveness of PrEP and UTT and other behavioral interventions in order to prioritize the best prevention strategies at lower costs (Table 2).

Table 2. Advantages and disadvantages of pre-exposure prophylaxis and universal test-and-treat strategies

	Advantages	Disadvantages
PrEP	– Targeted population – Reduced populational exposure to drugs and side effects – Preliminary data on animal models available	– Requires HIV testing prior to use – Risk of drug resistance selection – Efficacy dependent on drug adherence – Requirement of medical personnel for safe administration – Unknown length of treatment – Potential increase of risk behaviors – Uncertain cost-efficacy
UTT	– Potential to decrease population HIV incidence – Enhancementof access to ART – Decrease of HIV transmission amongst serodiscordant couples – Potential decrease in incidence of opportunistic infections	– Uncertain cost-efficacy – Current limited access to ART in developing countries – Efficacy dependent on drug adherence – Need for further studies

PrEP: pre-exposure prophylaxis; UTT: universal test-and-treat; ART: antiretroviral therapy.

These studies are equally important for the developed world, which is currently facing a shortage of economic resources due to the world financial crisis.

At a population level, HIV prevention should be designed as a comprehensive strategy rather than as a sum of isolated recommendations or just moving to drugs when possible (Table 3). Clearly, the best HIV preventive strategy often depends on the target population[49] and should not be based exclusively on drug prescriptions. To illustrate this notion, the medical prevention of cardiovascular diseases is a comprehensive strategy that involves diet, exercise, and smoking cessation up front, deferring drug prescription to a second step when fist-line interventions have not been enough. Likewise, educational and behavioral interventions must be openly given to persons at HIV risk, as they have clearly demonstrated their efficacy in reducing risk practices and result in lower HIV incidence rates[50,51]. The importance of this statement is reinforced by data from studies that have reported an average of 2-3 sex partners per month within the first 12 months after HIV diagnosis in some MSM groups[52].

Conclusions

HIV is a major public health problem in most countries, and particularly serious in many developing regions where resources for prevention, diagnosis, and treatment are scarce. Implementing safe and efficacious prevention strategies, especially aimed at high-risk groups, is critical for reducing HIV incidence. Although PrEP is a novel preventative approach, which could potentially reduce HIV incidence in specific populations, its efficacy at a population level has yet to be proven. The risks of

Table 3. Comprehensive approach to sexual HIV prevention by target population

Preventive strategy	Target population		
	General	At HIV risk	HIV infected
Behavioural			
– 1st. Wise sexual debut	++ (adolescents)	NA	NA
– 2nd. Avoid promiscuity	++	++	++
– 3rd. Consistent condom use	+	++	++
HIV testing	+	++	NA
HAART	NA	NA	++
PrEP	+	++	NA

Each intervention is rated (+) by relative efficacy according to target population.
NA: not applicable; HAART: highly active antiretroviral therapy; PrEP; pre-exposure prophylaxis.

drug resistance selection, as well as economic, social, and ethical issues, must be assessed in a comprehensive evaluation of PrEP before implementation. In any circumstances, educational and behavioral interventions should be part of a comprehensive HIV prevention strategy, with or without drug-based approaches.

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