

Pre-exposure prophylaxis (PrEP) in HIV-uninfected individuals with high-risk behaviour

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ABSTRACT

The global incidence of human immunodeficiency virus (HIV) infection has decreased by 15% over the past years, but is still too high. Despite current programs to reduce the incidence of HIV infection, further approaches are needed to limit this epidemic. Oral antiretroviral pre-exposure prophylaxis (PrEP) is currently one of the most discussed possible prevention methods. This literature study demonstrates whether orally antiretroviral chemoprophylaxis in HIV-uninfected individuals with high-risk behaviour reduces the transmission of HIV.

We used the PICO method and conducted a search to identify relevant studies. Subjects of the study were HIV-uninfected individuals with high-risk behaviour. Intervention was oral PrEP with tenofovir disoproxil fumarate (TDF) alone or plus emtricitabine (FTC) versus placebo. The primary outcome was the HIV incidence among this high-risk group. Secondary outcomes were adherence to PrEP, frequency and type of adverse effects. We identified ten studies from which five randomised control trials (RCTs) were included after screening. The results from three out of five trials showed a reduction, but two trials showed no protection in acquiring HIV infection. There were no significant differences in adverse events. The adherence was different among different groups and affected the outcome of the studies.

In conclusion, this prophylaxis might offer protection when used in combination with intense monitoring and guidance in uninfected individuals with a high risk of HIV acquisition. However, there are still many unresolved questions. Drug adherence seems to be a crucial factor in the effectiveness of PrEP. Therefore, individual risk behaviour remains an important determinant for success in the prevention of HIV transmission.

KEYWORDS

Human immunodeficiency virus (HIV), HIV prevention, HIV prophylaxis, pre-exposure prophylaxis, tenofovir – emtricitabine

BACKGROUND

The global incidence of human immunodeficiency virus (HIV) infection has decreased by 15% over the past ten years. However, due to the increased number of treated patients, more people are living with HIV infection.¹ In the Netherlands, the number of newly infected HIV individuals remains stable and is approximately 1100/year. The highest incidence is found in men who have sex with men (MSM).²

Behaviour change programs have been considered the key factor to reduce the incidence of HIV in different countries. However, studies show that despite these programs, a considerable number of people are still infected.¹ Therefore, further approaches are needed to limit the expansion of HIV worldwide.³

Evidence is present that combined antiretroviral therapy (cART) has a considerable contribution to the prevention of HIV transmission in serodiscordant (one partner HIV-positive and one partner HIV-negative) couples.^{4,5} In addition, prompt treatment with antiretroviral drugs is extremely important in prevention of mother-to-child HIV transmission.^{6,7} This treatment of the pregnant mother can be considered as a form of pre-exposure prophylaxis (PrEP) of the newborn. Interestingly, introduction of PrEP also seems promising for the future in adults. It means that antiretroviral agents must be taken prior to exposure by uninfected individuals at high risk.^{1,8,9} So far,

the available agents used as PrEP are tenofovir disoproxil fumarate (TDF) and the combination tenofovir disoproxil fumarate and emtricitabine (TDF-FTC or Truvada). These drugs interrupt the reverse transcriptase enzyme from transcribing HIV genetic material (RNA) into DNA before the virus's genetic code is inserted into an infected cell's genome.^{6,10}

However, there are various concerns regarding this kind of prophylaxis. Firstly, the long-term side effects of this therapy are unknown in uninfected individuals. Secondly, when adherence to PrEP is low and the patient gets an acute HIV infection, he/she will be treated with one or two instead of three active drugs. This can result in the development of a resistant virus. Another concern is that PrEP will increase high-risk behaviour.¹¹ A fourth limitation can be the high costs of the agents.

With these points in mind, we did a literature study to answer the question whether orally antiretroviral chemoprophylaxis in HIV-uninfected individuals with high-risk behaviour reduces the transmission of HIV infection.

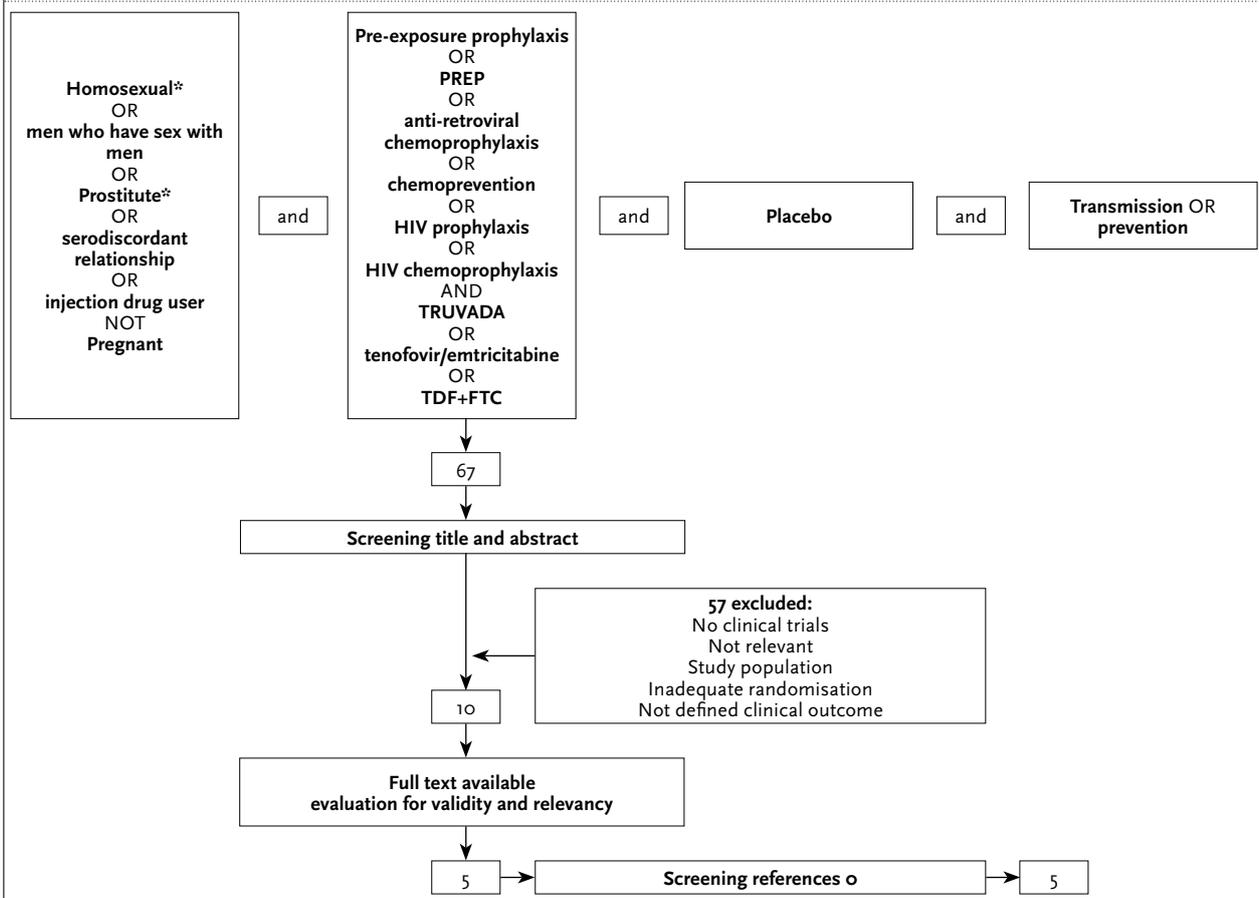
METHODS

We used the PICO (Patient/Population, Intervention, Comparison, Outcome) method, which allows you to take a more evidence-based approach when searching bibliographic databases, and conducted a comprehensive search to identify all relevant studies.

Patients (P) were HIV-uninfected individuals with high-risk behaviour, namely in serodiscordant relationships, commercial sex workers, intravenous drug users and MSM. Pregnant women were excluded. The intervention (I) was an oral PrEP regime with TDF-FTC. The studies involving topical application of antiretroviral agents such as vaginal gels were excluded. For the comparison (C) an oral PrEP regime was compared with placebo or no treatment. The primary outcome (O) was HIV incidence among this high-risk group. Secondary outcomes were adherence to PrEP, safety and frequency and type of adverse effects or complications.

The titles and abstracts of the search output from the different databases were screened to identify eligibility of

Figure 1. Flow chart with search terms and results of search strategy



the studies. Full-text articles were obtained for all citations identified as potentially eligible. Extracted information included the study design, population, intervention details, namely type of drug, comparator, dose, duration and route of administration, and primary and secondary outcomes. We searched the available and upcoming data. Inclusion was limited to randomised controlled trials (RCTs).

RESULTS

Results of the search

A total number of 67 titles and abstracts were eligible. We identified ten relevant studies, from which five RCTs were finally included after critical appraisal according to the Dutch Cochrane Appraisal Form (see figure 1. Flowchart).^{8,12,13,15-17}

Outcomes: HIV incidence and adherence

Grant *et al.* (iPrEx) studied daily TDF-FTC versus placebo in 2499 MSM aged 18 years and older, conducted in Peru, Ecuador, South Africa, Brazil, Thailand and the United States; they demonstrated in this trial that a once-daily oral tablet of a combination of TDF-FTC reduced HIV incidence among MSM by 44% after a median follow-up of 1.2 years.⁸ Adherence was evaluated in two ways. The relative reduction in the risk of HIV infection was 73% with an adherence of 90% measured by pill counts and 92% among the participants with detectable tenofovir concentrations in serum.⁸

Baeten *et al.* showed in the Partners PrEP Study that daily oral PrEP reduced the risk for HIV infection in the

HIV-uninfected partner in serodiscordant, heterosexual African couples by 67% with TDF and 75% with TDF-FTC, each compared with placebo, after a median follow-up of about two years.¹² There was no significant difference between the TDF and TDF-FTC groups.¹² Relative to placebo, the effect of TDF in women was 71% and for TDF-FTC 66%; among men, the efficacies were 63% and 84%, respectively. Among the participants in the treated group who acquired HIV, 31% had a detectable tenofovir level in plasma compared with 82% among participants who were not infected. A good blood concentration of tenofovir was associated with an estimated reduction in the relative risk of being infected of 86% with TDF and 90% with TDF-FTC, respectively.

Peterson *et al.* studied the efficacy and safety of TDF versus placebo in a phase 2, randomised, double-blind, placebo-controlled trial. The study was conducted among women between 18 and 35 years, who were at risk of HIV infection by having an average of ≥ 3 coital acts per week and ≥ 4 sexual partners per month. This study reported inconclusive data on effectiveness of the treatment, mainly because sites were closed earlier due to non-compliance.¹⁴ In the TDF2 study, daily oral TDF-FTC for at-risk heterosexual men and women decreased HIV incidence by 62% after two years.¹⁵

Two trials failed to show efficacy of PrEP in African women. FEMPrEP (Pre-exposure Prophylaxis Trial for HIV Prevention among African Women) studied women at-risk in several African countries, who took oral TDF-FTC or placebo.¹⁶ An independent Data Safety Monitoring Board (DSMB) terminated the study early because of ineffectiveness of the intervention.¹⁶

Table 1. Overview of included trials about effect of PrEP on HIV transmission

Study location [Reference]	Population and number	Design intervention	Relative reduction in HIV incidence	Agent present in blood samples
iPrEx (Peru, Ecuador, South Africa, Brazil, Thailand and the United States) Grant <i>et al.</i> ⁸	2499 MSM	RCT Oral FTC/TDF or Placebo	FTC/TDF: 44% (95% CI 15-63%, p=0.005)	92% protection with blood concentration of TDF-FTC
Partners PrEP (Uganda and Kenya) Baeten <i>et al.</i> ¹²	4747 heterosexual men and women with HIV positive partner	RCT TDF, FTC/TDF or placebo	TDF 67% 95% CI 44-81% p=0.0001 FTC/TDF 75% 95% CI 55-87%, p<0.0001	86% protection with blood concentration of TDF 90% protection with blood concentration of TDF-FTC
TDF 2 (Botswana) Thigpon <i>et al.</i> ¹⁵	1219 heterosexual men and women	RCT FTC/TDF or placebo	FTC/TDF 63% 95% CI, 22-83%, p=0.01	79%
FEM PrEP (Kenya, South Africa, Tanzania) Van Damme <i>et al.</i> ¹⁶	202 women	RCT FTC/TDF or placebo	No HIV protection	35-38% at single visit; 26% at two consecutive visits
VOICE (South Africa, Uganda, Zimbabwe) ¹³	5029 women	RCT Oral TDF, FTC/TDF or placebo Vaginal gel or placebo	No HIV protection in any arm	<30% samples had tenofovir detected >50% women in each arm had never tenofovir detect during any visit

The results of the VOICE (Vaginal and Oral Interventions to Control the Epidemic) study are particularly disappointing, because of the high rates of new HIV infection that occurred in women included in the trial. This was a double-blind, placebo-controlled, five-arm trial of daily oral TDF, oral FTC/TDF, oral placebo, vaginal tenofovir gel or vaginal placebo gel, as PrEP for the prevention of HIV acquisition by HIV-negative women. A total number of 5029 women, who had reported having vaginal sex in the three months prior to enrolment and who were willing to use contraception, were enrolled at sites in South Africa. Two years after the start of the trial the oral TDF arm was stopped by the DSMB, because it appeared to not be effective for HIV prevention.¹³ A few months later the vaginal tenofovir gel arm was stopped (and its placebo gel arm) for the same reason. VOICE continued to evaluate the effect of Truvada until the scheduled end of the study, but none proved to be effective.^{1,13}

Safety and adverse events profile

Baeten *et al.* reported no significant difference in the frequency of death, and serious adverse events as renal failure among three different groups (TDF, TDF-FTC and placebo).¹² Neutropenia was observed more in the TDF-FTC group than in the other two groups. During the first months of administration, more gastrointestinal problems were reported in the treatment compared with the placebo group.¹² Grant *et al.* presented a similar rate of serious adverse events in two groups. Nausea was reported more frequently during the first month in the treatment group than with placebo.⁸ Additionally, Peterson *et al.* documented no increase in clinical or laboratory adverse events.¹⁴

DISCUSSION

In the present review we show that randomised clinical trials with oral tenofovir-based PrEP reveal inconsistent results for effectiveness. In theory, this novel prophylaxis might offer the opportunity to combat the HIV epidemic in the distant future, but there are still many unresolved practical issues.

In the studies that failed to provide convincing evidence of HIV protection, lack of adherence to the treatment was high. Importantly, the proportion of participants with detectable levels of the study drug was far lower in the terminated studies compared with the studies in which a decreased HIV incidence was found.¹⁵ Therefore, it seems that high adherence is crucial for obtaining clinical benefit from PrEP. This issue already raises the first point of concern regarding the application of this treatment. Access, acceptability, motivating and monitoring

adherence among the populations at highest risk is of great importance. Better achievement will mainly rely on programs implemented in community settings, which show high success rates. So it is again not the agent, but the difference in human behaviour which leads to the varying degrees of success. As with behaviour prevention strategies, it underlines the complexities of achieving a new strategy with which many individuals might benefit. In addition, it is important to study how PrEP can be combined with other proven behaviours to accomplish better prevention.

Despite these summarised studies, there are many unresolved questions. In the first place, more research is needed to find the factors affecting adherence. Perhaps interviewing participants of the terminated studies can provide more information on how adherence can be improved. Moreover, a dangerous situation will occur when the adherence to PrEP is low and the patient gets an acute HIV infection. This was the case in five patients in the iPrEx trial.⁸ Most patients with an acute infection have a very high HIV load. In the above-mentioned trial,⁸ they were treated with two instead of three active drugs. This is the ideal situation for the development of a resistant virus. Because the patient thinks that he/she is not infected (or even safe), this individual has the potential to transmit a drug-resistant virus to another person which may restrict later treatment options.¹⁸

Furthermore, it would be interesting to study the best method for administration – oral, vaginal or rectal – and the optimal dose frequency: daily or intermittently before a high-risk act. Daily administration might improve protection and would offer better adherence, on the other hand not much is known about the long-term side effects in these healthy persons. Since TDF is a relatively new agent (around ten years on the market) the side effects in the long-term are still unknown, as for example progressive renal insufficiency.¹⁹ This is especially relevant because this treatment will mainly be given to relatively young and healthy persons. Another important issue that will need to be addressed is the long-term cost-effectiveness of PrEP. At this moment 30 tablets of TDF/FTC cost about 550 euros.²⁰ The members of the Dutch Association of HIV-treating Physicians (NVHB) discussed all the above-mentioned issues during a meeting in January 2012. Because of all the concerns raised, as mentioned above, they concluded that at this moment no clinical indication for PrEP is present in the Netherlands. However, clinical research about this promising form of prophylaxis is urgently warranted to answer the above-mentioned questions, but also to investigate the implementation possibilities and barriers in the Netherlands.

In conclusion, this prophylaxis might offer protection when used in combination with intense monitoring

and guidance in individuals with a high risk of HIV acquisition. However, there are still many questions which need to be answered. Since behaviour also seems to be an important determinant for success in this strategy, it is still by no means the single effective strategy in preventing HIV transmission.

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