Preventive use of HIV medication

To: the Minister of Healthcare and Sport
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Health Council of the Netherlands

contents

executive summary

Over recent decades, the HIV epidemic has been substantially reduced by the availability of effective antiretroviral drugs and prevention strategies. Even so, each year approximately 800 new HIV infections occur in the Netherlands. A relatively new way to prevent HIV is by using antiretroviral drugs: Pre-Exposure Prophylaxis (PrEP). In 2016, the European Medicines Agency (EMA) registered a combination of antiretroviral drugs for use as PrEP. In various countries, PrEP is reimbursed as a preventive drug for HIV. The price dropped from € 536 a month in 2015 to € 48 a month at the beginning of 2018. Both stakeholders and health care professionals are advocating the provision of PrEP in the Netherlands. The Minister of Health, Welfare and Sport has asked the Health Council of the Netherlands for advice on this matter. Should PrEP be regarded as essential care that should be available to the target group? What would the consequences of its introduction be on the incidence of HIV, the development of resistance and the incidence of other sexually transmitted infections (STIs)? In order to answer these questions, the Health Council set up the PrEP Committee.

Significant burden of disease

The Committee is of the opinion that the burden of disease associated with HIV is high enough to consider the procurement of PrEP. In the Netherlands, around 20,000 people are infected with HIV. It is estimated that there are another 2,600 people who are infected but unaware of it. With the correct treatment, HIV is still a severe chronic disease. Left untreated, the virus causes AIDS, which may lead to death. New cases still occur despite promotion of condom use, testing and early tracing and treatment to prevent the further spread of HIV. Two-thirds of the new infections occur in men who have sex with men (MSM). Over a quarter occur in heterosexual men and women, mainly in migrants from countries where HIV is endemic.

PrEP is effective if taken correctly

PrEP offers effective protection against HIV infection when taken correctly. It makes no difference if PrEP is taken daily, or only around high-risk sexual contact. The Committee expects that the introduction of PrEP will also have a positive effect on the HIV epidemic, but it is uncertain to what extent. It is important to reach the right target group, i.e. people who are at highest risk for hiv. Adherence among PrEP-users is also one of the essential factors. It cannot predicted what the precise effect will be on sexual risk behaviour and the transmission of other STIs.

Medical follow-up is essential

Medical follow-up is essential in order to guarantee the safe use of PrEP. The side effects of PrEP are usually mild (gastro-intestinal symptoms, headache, weight loss), but a minimal (reversible) deregulation of kidney

function may occur. In addition, users must also be tested for HIV and other STIs. Furthermore, the potential development of resistance should be monitored.

PrEP appears to be cost effective

The cost effectiveness of the introduction of PrEP depends on its price, amongst other things. Recently this has dropped considerably as generic drugs have come on to the market. Other determinant factors are which group is targeted to get PrEP, and how it will be implemented. Only when it is actually introduced will its effectiveness in practice in the Netherlands become clear. The Committee expects that at a cost of € 40 to € 50 a month, PrEP will be cost effective – or even cost saving – when used in a high-risk group who adhere to therapy.

Role of the government

The Committee sees a role for the government in offering PrEP to high-risk MSM. It is of the opinion that PrEP offers an opportunity to lower the incidence of HIV in this group, where further gain from other preventive strategies appears unlikely. In addition, MSM are a vulnerable group, as HIV and AIDS are still associated with stigma. PrEP encourages people at risk of HIV to take their own responsibility to protect themselves (agreement from a partner not being necessary). The Committee thinks it important that PrEP is available to this target group. Because people have a responsibility for their individual risk, the Committee proposes to consider a personal contribution towards the costs. As the exact effect of the introduction of PrEP on the hiv incidence is still uncertain, good monitoring is essential.

Recommendation

The Committee recommends to make PrEP available for high-risk MSM in combination with a well-organised medical follow-up system. This latter recommendation is urgent, as the recent fall in price could lead to people starting to use PrEP on their own initiative without proper guidance. In addition, the Committee recommends that the long-term effects of PrEP should be carefully monitored and that the provision of PrEP should be reviewed after a period of five years.

01 introduction

1.1 Motivation for request for advice

Due to the availability of effective antiretroviral drugs and prevention strategies, over recent decades the incidence of HIV has been substantially reduced. Even so, each year approximately 800 new infections of HIV are diagnosed in the Netherlands. HIV occurs more in specific high-risk groups, such as men who have sex with men (MSM) and migrants from countries where HIV is endemic.

A relatively new way to prevent HIV infection is the use of antiretroviral drugs by people who do not yet have HIV, but are at high risk: Pre-Exposure Prophylaxis (PrEP). In recent years, a number of scientific studies have been completed that have convincingly demonstrated the protective effect of PrEP.

The *European Medicines Agency* (EMA) registered the combination of antiviral drugs *tenofovir disoproxil fumarate* and *emtricitabine* (TDF/FTC) for use as PrEP in August 2016. In a number of European countries, PrEP has been included in the repertoire of preventive interventions for HIV that are reimbursed, and a number of other countries are considering the financing or facilitating of PrEP. The use of PrEP (formal and informal) both in the Netherlands and abroad, appears to be increasing. In the Netherlands, PrEP is rarely prescribed in routine care (general practitioner) due to its high cost (€ 536 a month in 2015) which is not reimbursed. In January 2018 a much cheaper generic drug (€ 48 a month) became available on prescription. Both stakeholders and health care professionals in the STI/HIV field are advocating the provision of PrEP to high-risk groups in the Netherlands.

1.2 Ministerial request for advice

The Minister of Health has requested the Health Council of the Netherlands for its advice on the question whether PrEP implementation is a matter of essential healthcare, collectively funded, or individual healthcare, charged directly to individuals. The assessment framework used by the Health Council for advising on vaccinations can serve as a starting point to address this question. In this framework, criteria for collective funding are evaluated to determine whether PrEP can be regarded as essential care that should be made available to the target group. The Minister has requested to assess to what extent PrEP is expected to contribute to HIV prevention, in a situation in which further prevention, testing and treatment are optimised. The Minister also asked to define a specific risk group and to describe side effects and adverse effects that are to be expected when PrEP is implemented, e.g. in relation to development of resistance and the occurrence of sexually transmitted infections (STI).

In order to answer these questions, the PrEP Committee was set up. The Chair of the Health Council of the Netherlands has presented the advisory report to the Minister. The request for advice, the members of the Committee and the letter of submission can be found on www.gezondheidsraad.nl.

1.3 PrEP in the context of HIV prevention

PrEP is a prophylactic application of HIV medication with the aim of preventing HIV infection. PrEP can be taken on a daily basis or at times when the person is at risk of exposure (intermittent PrEP). PrEP is a recent method of HIV prevention and should be seen in conjunction with other methods of prevention such as condom use, early tracing by regular testing, and treatment directly after diagnosis in order to prevent further spread (Treatment as Prevention (TasP)).

1.4 Methodology used by the Committee

The Committee bases its work primarily on scientific publications. If this is not possible, then it uses data from the so-called grey literature, i.e. reports and other data that have not been subjected to peer review. In the case of PrEP, the results of the interim analyses of two studies (carried out in Amsterdam and Antwerp) on the implementation of PrEP have also been discussed, as has one unpublished cost-effectiveness study conducted by the National Institute for Public Health and the Environment in the Netherlands (RIVM). At the request of the Minister, RIVM has delivered an overview document in preparation for the advice.[1] In addition, reports from the HIV Monitoring Foundation (SHM), RIVM and other governmental and advisory organisations from outside the Netherlands have been included, as well as conference presentations. During a meeting at the start of the advisory process, representatives from stakeholder groups were heard (SoaAids Nederland, COC Nederland, PrEPnu, Hiv Vereniging Nederland).

1.5 Reading guide

Chapter 2 describes the course of the incidence of HIV, the burden of disease of HIV in the Netherlands, and the risk groups. This is followed by Chapters 3, 4 and 5 which address the effectiveness, the safety, and the cost-effectiveness of PrEP, respectively. In Chapter 6 the Committee considers if there is a role for the government in the introduction of PrEP. In Chapter 7, the Committee sets out its advice.
In this document, the Committee summarises the current state of knowledge on effectiveness and cost-effectiveness. More detailed information on this can be found in the background document: PrEP effectiveness and cost-effectiveness – overview of the literature, which is available at www.gezondheidsraad.nl.

02 HIV in the Netherlands

HIV is a viral infection that can lead to severe illness. In the Netherlands, the burden of disease resulting from HIV is substantial. HIV infections are concentrated in high-risk groups, particularly men who have sex with men (MSM) and heterosexual men and women (and their partners) originating from countries where HIV is endemic.

2.1 Clinical presentation and transmission

The human immunodeficiency virus (HIV) was first identified in 1983.[2] Without treatment, infection with HIV almost always leads to a deterioration of the immune system, acquired immunodeficiency syndrome (AIDS) and ultimately, to death. Despite large-scale research, no curative therapy or effective vaccine has yet been developed. However, since 1996 there has been great progress with combination therapy of antiretroviral drugs (ART), which have to be taken for life. Several studies have shown that HIV has changed from being a fatal disease to being a severe chronic condition with an almost normal life expectancy.[3,4]

HIV is transmitted by sexual contact, blood contact and from mother to child at birth or through breast feeding. The incubation period is 2-6 weeks. The majority of people infected by HIV develop an acute HIV infection, which is sometimes characterised by a short period of aspecific flu-like symptoms. If no treatment is given, the acute phase will be followed by a long asymptomatic phase (average 8-10 years). Ultimately, the immune system will no longer be able to work properly and opportunistic infections, certain tumours, skin abnormalities and cerebral abnormalities will occur as a result.[5] Infectivity is particularly high during the acute phase of HIV infection and when clinical symptoms occur.

After a diagnosis of HIV has been made, the advice is to start treatment as soon as possible and to notify all partners from the suspected time of infection.[6] ART strongly inhibits the replication of the virus so that disease symptoms do not occur. If HIV medications are taken faithfully the virus is usually no longer detectable in the patient's blood and the risk of transmission is very limited. For this reason, direct treatment with ART is also important in preventing new HIV infections in sexual partners.[5,7,8]

During treatment side effects (most of them mild) may occur and it can be difficult to distinguish what is caused by the medicines and what by the infection. As well as physical effects, due to fear, stigma, discrimination or social isolation HIV can also affect psychological wellbeing.

2.2 Spread and burden of disease of HIV in the Netherlands

In the Netherlands at the end of 2016, 20,264 people had been diagnosed with HIV, 19,136 of whom were under treatment at one of the HIV treatment centres. It is estimated that there are also 2,600 people who are infected with HIV but who are unaware of it.[9] Each year around 800 new HIV infections are diagnosed, although this number has been declining for a few years.[9] It is expected that the number of newly-diagnosed cases of HIV will continue to decline if treatment is instigated more quickly and HIV-testing is made more accessible. However, it is uncertain how far the number of HIV cases will drop when continuing the current policy even when optimising the strategy.

Over recent years, the death rate among people who are HIV-positive dropped markedly from 18 out of 1,000 a year in 1996 to approximately 8 out of 1,000 a year in 2014-16. Every year around 160 HIV-positive people die, and in 12.5% of cases death is caused by AIDS. Other causes of death are sometimes indirectly related to the effects of HIV/AIDS or its

The annual number of new HIV infections is about 800; this number has decreased over the last years

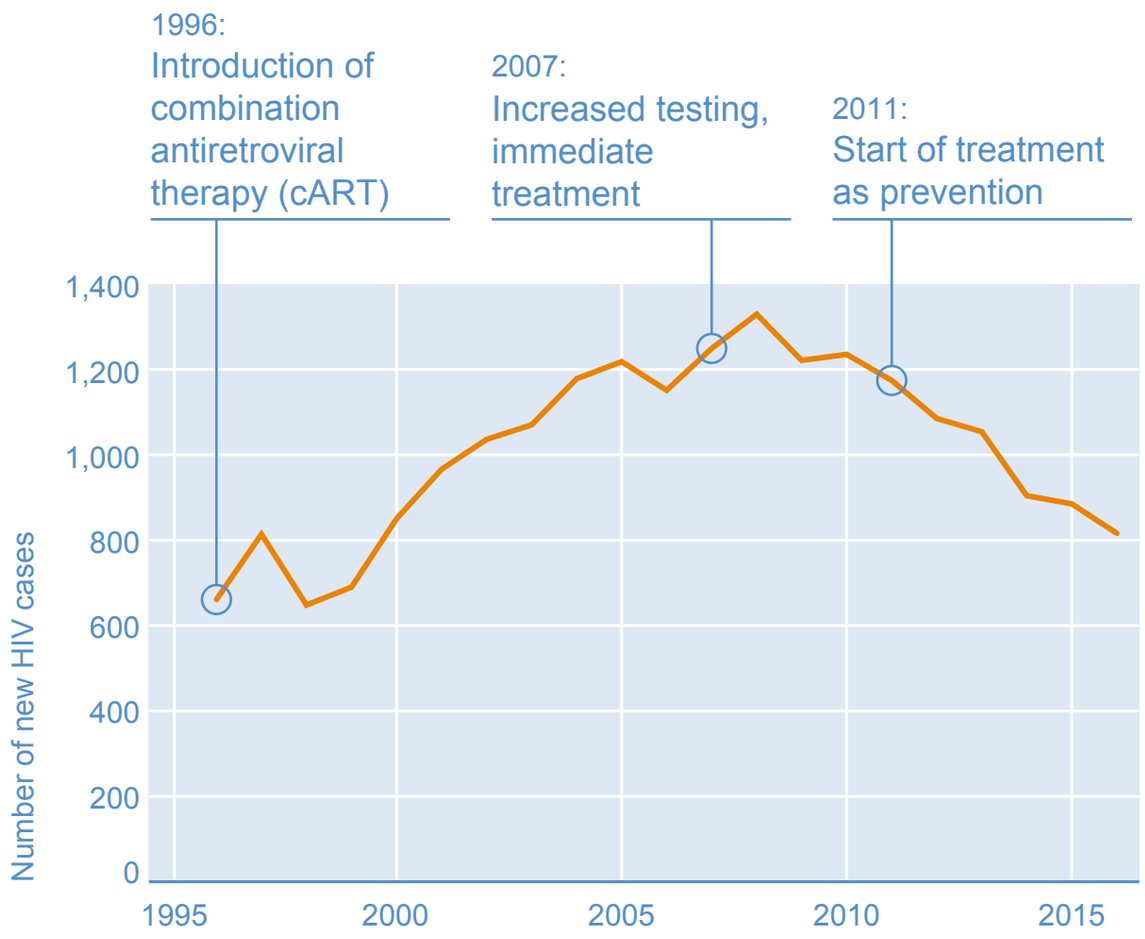

Figure 1. Annual number of new HIV diagnoses per year in the Netherlands from 1995-2016
Source: HIV Monitoring Foundation; Monitoring Report 2017

treatment. Death due to AIDS generally occurs among people who begin treatment only in the later stages. This is the case if someone has a CD4 count (a measure of the state of the immune system) far below 350/microlitre, or where symptoms of AIDS are already present. Although the percentage of patients who only begin treatment at a late stage is falling, it is still relatively high: in recent years it accounted for approximately half the new cases.[9]

The burden of disease can be calculated in loss of healthy life-years, in which both premature death and deterioration of health are included. The most recent estimate of the HIV burden of disease (2016) is a reduction of 5.6 healthy life-years per infection.[10] This is relatively high; comparable with severe infections such as invasive meningococci, or haemophilus influenza. Due to the relatively limited number of new infections each year, the total burden of disease is lower than that of most other chronic diseases. In the Dutch league table of all diseases HIV/AIDS ranks number 53,[11] comparable with the national burden of disease from whooping cough and Legionnaire's Disease and approximately twice that of measles or tuberculosis.[12]

2.3 High-risk groups

In the Netherlands, the HIV epidemic is concentrated, i.e. it is low in the general population and higher in specific risk groups. In 2012, the prevalence of existing HIV infections (both diagnosed and undiagnosed)[13] in the Dutch population was estimated to be 0.2%. Due to differences in risk behaviour and the distribution of already existing infections, the risk of becoming infected with HIV is not equally distributed throughout the population.

The majority of newly diagnosed HIV infections in the Netherlands in 2016 was among MSM

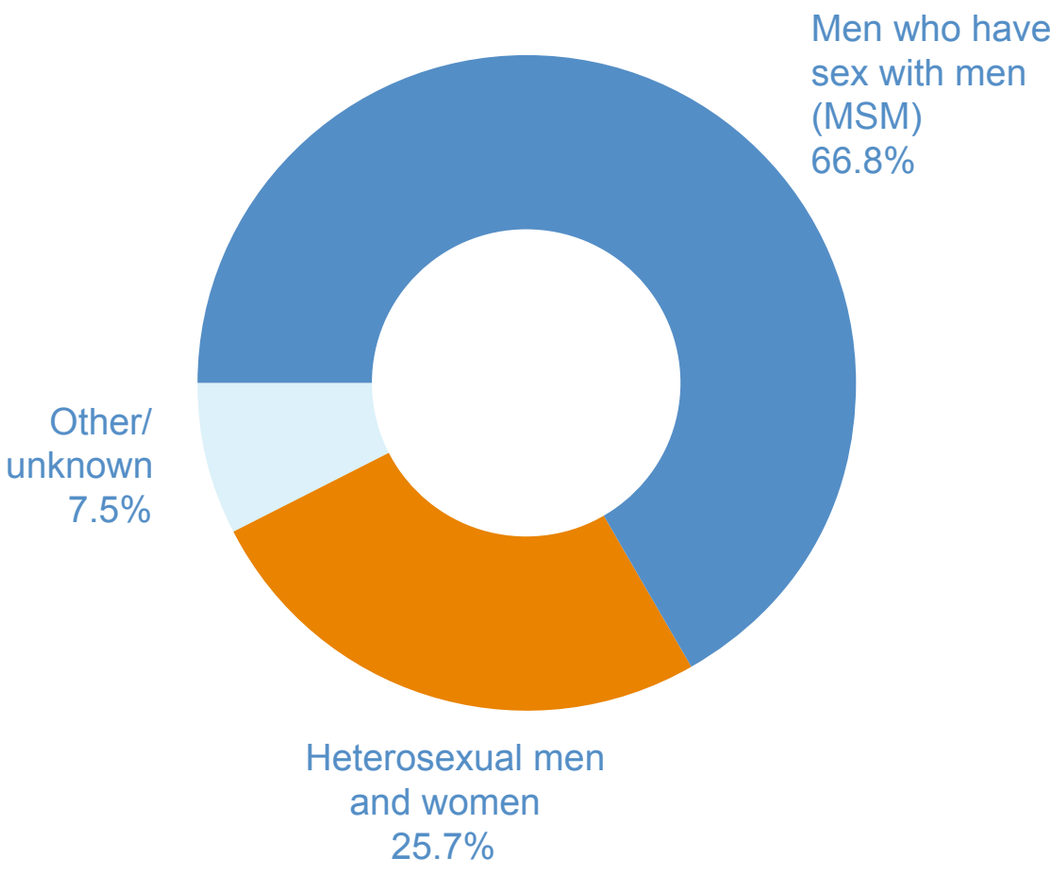

Figure 2. Proportion of new HIV diagnosis by riskgroup in 2016
Source: HIV Monitoring Foundation; Monitoring Report 2017

2.3.1 Men who have sex with other men

An important risk group is men who have sex with men (MSM). The prevalence of HIV in this group is estimated to be 8%.[13] Two-thirds of HIV patients who are under treatment were infected by homosexual contact. Due to the higher prevalence in the population in which they have sexual contacts, MSM run a higher risk of contracting HIV infection through unprotected sexual contact with someone who does not know he has HIV, or who is not on treatment or not on adequate treatment. The risk of transmitting an HIV infection on unprotected anal contact is around ten times higher than on unprotected heterosexual (coital) contact.[14,15]
In 2016, 67% of all newly-diagnosed HIV infections in Netherlands occurred in MSM. As this risk group generally gets tested for HIV more often, infections are often traced earlier. In recent years the number of new diagnoses in the MSM group has dropped.[9,16]

2.3.2 Other high-risk groups

Other high-risk groups in the Netherlands are heterosexual men and women (and their partners) originating in countries where HIV is endemic. One-third of heterosexual HIV patients who are under treatment in the Netherlands originate in sub-Saharan Africa.[9] The prevalence of HIV among migrants from this region is estimated at 2.3%. In migrants from the Caribbean this is 0.3%.[13]
Additionally, heterosexual men and women who have unprotected sex contacts with many casual partners also run the risk of HIV, but it is relatively low.16 Transgender women are also a risk group, but the extent of this group is very limited.[17] Further, 2% of HIV patients who receive treatment contracted an infection through injecting drugs. In recent years there have been no more reports of transmission through injecting drugs,

as this form of drug use occurs only very infrequently and users are provided with clean needles.[18]

Of the infections newly-diagnosed in 2016, 26% were contracted from heterosexual men and women, the majority of whom had migrated from regions where HIV is endemic (in particular sub-Saharan Africa). The high-risk group of migrants is less easy to reach for HIV testing, which means that HIV infections often remain undiagnosed and patients only receive treatment at a later stage.[19,20] Studies have shown that a considerable percentage of the HIV infections among migrants were contracted in the Netherlands and not in their country of origin.[9,21]

2.3.3 Conclusion

There are 20,000 patients in the Netherlands who have been diagnosed with HIV. It is estimated that there are 2,600 people who have HIV but who are unaware of it. Annually, approximately 800 new cases of HIV are diagnosed. With the correct treatment, HIV is a severe, chronic disease with an almost normal life expectancy. If HIV is left untreated or if treatment is implemented too late, AIDS can develop with death as a consequence. Each year, 160 HIV patients die; in 12.5% of them, AIDS is the cause of death.

Groups at risk of HIV can be clearly identified. 67% of new infections occur in men who have sex with men. In addition, 26% occur in heterosexual men and women, mainly in migrants from countries where HIV is endemic.

03 effectiveness of PrEP

PrEP is effective in the prevention of infection with HIV in individuals who adhere to therapy. This has been shown by the results of various controlled studies. The Committee expects that PrEP will also have an effect on the number of HIV infections at population level and in the long-term, but is unsure how big this effect will be.

3.1 Effectiveness of PrEP

In 2007, the first publication about the preventive effect of tenofovir disoproxil fumarate (TDF) on HIV appeared.[22] Since then, the effectiveness of TDF alone or TDF in combination with emtricitabine (FTC) as PrEP has been investigated in twenty randomised studies and follow-up studies (see background document). Five reviews have been conducted into the safety and effectiveness of PrEP.[23-27] The most recent review was compiled by the World Health Organisation (WHO) and contains data from 18 studies with over 18,000 participants.[27,28]

The effectiveness of PrEP in the prevention of HIV infection has been convincingly demonstrated. Available reviews and meta-analyses show that PrEP reduces the risk of HIV infection by half.[23-27] This is based on the collective results of studies covering various risk groups (MSM, heterosexual men and women from regions with a high prevalence, couples of whom one has HIV (serodiscordant couples), and people who inject drugs). The reported effectiveness varies greatly between these

studies which were carried out in different countries and risk groups (0 to 100%). In studies reporting good adherence to therapy, the average effectiveness was 70%.[24]

3.1.1 MSM

The reported effectiveness of PrEP is highest in the MSM group: average 66%[24] and around 90% in studies with good adherence to therapy.[29-31] Higher effectiveness was generally reported in studies conducted in high-income countries. These studies (in Europe[31,32], the United States, Canada[29,30,32,33] and Australia[34]) were primarily focused on high-risk MSM groups; participants were selected on the basis of risk behaviour such as recent unprotected (anal) sexual contact with multiple partners, sexually transmitted infections (STI) or PEP use (Post-Exposure Prophylaxis for HIV). There is less insight into the effectiveness of PrEP in other groups who could also potentially benefit from it, including young MSM, MSM with a background of migration or groups who know little or nothing about PrEP. Recent studies from the US have reported a lower level of acceptance 39 and adherence to therapy in these groups.[40]

There have been two recent trials in Europe (which appeared after publication of the WHO report[28]) concerning high-risk MSM groups (PROUD and IPERGAY).[31,32] PROUD (in the United Kingdom) investigated the effectiveness of daily PrEP use.[31] IPERGAY (in France and Canada) was the first trial to investigate the intermittent use of PrEP, in which PrEP was taken 2 to 24 hours before expected high-risk contact, and thereafter up to and including 2 days after the last high-risk contact.[32] In both trials, the effectiveness of PrEP was found to be equally high, i.e. 86%.[31,32]

In the follow-up study to IPERGAY, even higher effectiveness was reported 97%.[35]

The Committee expects that the effectiveness of PrEP in the MSM target group in the Netherlands will be in line with the results from these trials. The evidence for the effectiveness of intermittent PrEP use is weaker, due to the limited number of studies.

Only a limited amount of data from daily practice in countries where PrEP has been implemented are available. There are two PrEP demonstration projects for MSM, one in Amsterdam (AMPrEP)[36] and one in Antwerp, (Be-PrEP-ared),[37] the first results from which have been shared with the Committee. Participants can choose either a continual or an intermittent PrEP schedule. Around a quarter have chosen intermittent PrEP. In their interim results, both studies have reported very high effectiveness.[38]

Besides these two projects, demonstration projects are currently taking place in the United Kingdom (NHS, started September 2017), the United States[39,40] and Australia,[34] which will bring about more insight into the interest and willingness to use PrEP of the MSM target group and its effectiveness in the long-term.

3.1.2 Other risk groups

Data on the effectiveness of PrEP in other risk groups are only available from studies in Africa, South America and Asia on heterosexual women,

serodiscordant couples and injecting drug users.[24,41] These studies report a lower effectiveness of PrEP; this is explained by less good adherence to therapy.[25]

In women, the effectiveness of PrEP was an average of 43%, and 61% on good adherence to therapy.[24,25] There are indications that the concentration of PrEP in the vaginal tissue is lower, and a higher dosage is required to achieve the same protective effect as in rectal tissue.[42] In women, missed doses mean a potentially higher risk of HIV.[25,42,43]

The Committee expects that among other risk groups in the Netherlands, such as migrants and their partners, PrEP on an individual basis could be as effective as in the MSM group if therapy is adhered to. Transmission of HIV in this group is limited to a small group, as they usually do not show high-risk behaviour and often have a steady partner.

3.2 Adherence to therapy

Adherence to therapy is the single most important factor for its effectiveness. There is a wide variation in adherence to therapy in published studies on PrEP (30-94%).[24] Not all studies registered adherence to therapy, and also not all in the same way. Adherence to therapy can be estimated on the basis of counting the left-over pills or self-reported pill use. The most reliable method is measuring medication level in the blood.

In studies, almost all HIV infections in PrEP users are related to not taking PrEP correctly.[29-33,35,44] To date, only one seroconversion has been found in a participant who took PrEP consistently each day. This was a man (participating in the AMPrEP trial) who engaged in high-risk behaviour and had multiple STIs.[38]

In studies of MSM, adherence to therapy varied from 51% to 100%. In the iPrEX study (United States and five non-western countries), medication was present in the blood of only 51% of a random sample of participants.[23,33] During the follow-up study, adherence to therapy was 71% on the basis of medication in the blood.[45] The PROUD study[31] reported 88% adherence to therapy on the basis of dispensing prescriptions, and 100% on the basis of blood medication level in a random sample of participants. In the PrEP demonstration project in Australia, more than 90% of participants had adequate levels of medication in their blood.[34]

The effectiveness of PrEP is high in people who have demonstrable levels of medication in their blood.[24,29] Maximum adherence to therapy is not required for it to be effective, as taking 4 doses a week has proved to protect PrEP users to the same high extent as 7 tablets.[29] Where blood levels were equivalent to 4 or more tablets a week, effectiveness was optimal; on equivalence to 2-3 tablets this fell, and effectiveness was much less if fewer than 2 tablets were taken.[29]

Adherence to therapy is more difficult to measure if PrEP is taken intermittently. The IPERGAY trial showed that the number of sex contacts whereby the participant was protected by taking PrEP before and after sex was very low (43% of the number of sex contacts). However, the percentage of participants with detectable medication in their blood

(indicating they had taken TDF or FTC in the preceding 9 days) was high: 82-86%.[32] In the open-label phase of the IPERGAY trial, it was found that 71% of users had detectable levels of medication. On average, 18 pills a month were taken.[35]

In the ongoing AMPrEP and Be-PrEP-ared trials, a high level of adherence to therapy among intermittent PrEP users has also been found. Interim results from the AMPrEP and Be-PrEP-ared trials show that the majority of participants are able to take PrEP adequately around sexual contact. Insufficiently adequate adherence has not yet led to seroconversion (interim results Be-PrEP-ared). Due to the relatively short follow-up of studies, the degree of adherence to therapy in the long-term has not yet been properly investigated. A number of studies have shown that PrEP use is often interrupted or stopped and may drop off within a year.[29,33] This is sometimes related to adverse effects or illness but can also be due to changed personal circumstances that affect sexual risk behaviour.[29,46] In England, after one year only 26% of the original high-risk group of MSM who were eligible for PrEP proved to be still at the same very high risk level, and after two years this had fallen to 10%.[47]

To date few interventions to improve adherence to therapy have been developed and the effect of these interventions has not yet been studied extensively. Singly and in combination, interventions include: improved counselling, feedback of objective measurement of adherence to therapy and reminders by text message.[48] Regular check-up visits could help to improve adherence to therapy, although the optimum frequency is unclear and dependent on context: monthly check-up visits (iPrEX) do not lead to higher adherence to therapy than three-monthly check-ups (CDC and PROUD),[30,31,33] while in the group of young MSM, more frequent monthly check-ups appear to be useful.[41,42,43] Counselling could be implemented at check-up visits, not only to optimise adherence to therapy but also to provide good information on how to take PrEP (daily or intermittently), and how to switch or interrupt it in a safe way (interim results Be-PrEP-ared). Other ways of promoting adherence to therapy, such as reminders via an app (AMPrEP) can be investigated.

3.3 Effect of PrEP on incidence of HIV in the population

Adherence to PrEP therapy leads to effective protection of its users. However, it is difficult to predict what the size of this effect will be on the number of HIV infections in the population of the Netherlands. The long-term effects are unclear, as in many high-income countries the incidence of HIV in MSM is stabilising or falling. This is the result of the ready availability of effective HIV medication and rapid tracing and treatment. The effect that PrEP will have on incidence depends on various factors: reaching the high-risk group, the extent of HIV transmission within the high-risk group (between people taking or not taking PrEP), and between the high-risk group and other groups (e.g. MSM at low risk, heterosexuals).

Provision of PrEP may have an extra positive effect in that the test prior to use may reveal the presence of HIV infections. A number of HIV infections were found at the beginning of the AMPrEP trial.

3.3.1 Reaching the high-risk group

By definition, the effect of PrEP on the incidence of HIV will remain limited as long as the number of PrEP users remains limited. In most countries, the number of people receiving PrEP is still low. This is partially due to practical obstacles (limited availability, high price or unfamiliarity), or because only some of the target group are interested in using it.

In the Netherlands, the size of the group that will ultimately be using it depends on the size of the group that satisfies the criteria required for PrEP use, and on willingness to take PrEP. Two modelling studies have estimated the number of PrEP users will be 2% and 6% of the total MSM population in the Netherlands, respectively (4,500-11,000 MSM). Based on this number of PrEP users, it is estimated that in ten years' time, 1,400 to 3,500 new infections will be prevented in the MSM group, i.e. a drop of between 20% to 60% (Nichols20 and unpublished interim results from RIVM).

Modelling studies for the United Kingdom assume a lower percentage of PrEP users[47,49] (1% of the total MSM population), and predict a drop of 15-25% in the number of new HIV infections calculated over a longer period of time. One modelling study has predicted that in ten years, the HIV incidence in the US could drop by as much as one-third if 40% of the MSM population with a PrEP indication will actually use the drug.[50] This percentage has not yet been reached. PrEP has been available in the US since 2012, but its use has only grown slowly. Of a potential 1.2 million users, at the end of 2006 around 50,000 were taking PrEP.[51,52] In 2016 in San Francisco – a leader in PrEP implementation – 30% use of PrEP in MSM was reported to have been seen in STI clinics.[53]

3.3.2 Effect of PrEP together with other measures to combat HIV

The effect of PrEP cannot be seen as separate from concomitant developments. A combined strategy of PrEP and other measures will have a greater effect on the incidence of HIV among MSM than PrEP alone. Estimates based on results from the Netherlands in 2008-2010 show that approximately 20% of infections could have been prevented by direct treatment alone; 30% if PrEP was also implemented; and 66% by the combination of PrEP, direct treatment and increased annual testing.[54] The drop in the incidence of HIV in MSM which began in 2010 was promoted by more, and more frequent, testing and direct treatment causing the effect of PrEP to be potentially lower than predicted.[16,19]

Results from other countries are scant. In England, the 17% drop in HIV incidence in MSM between 2014 and 2016 was attributed to PrEP. However, this proved to have been primarily due to more frequent testing, re-testing and direct treatment.[55,56] In San Francisco, the incidence of HIV halved between 2012 and 2016, probably due to a strategy which combined PrEP with behavioural interventions and the faster and more

frequent use of antiretroviral drugs in people infected with HIV, which reduces the risk of transmitting HIV.[57] In New York a drop in HIV incidence was also seen due to a combination of diverse preventive strategies.[58]

3.3.3 Other risk groups

As well as high-risk MSM and transgender groups, the Dutch guideline names other PrEP target groups for consideration on an individual basis by a physician: heterosexual migrants in a vulnerable position, female prostitutes who have unprotected anal sex with clients, and women who wish to become pregnant by an HIV positive partner.[59] The effect of the use of PrEP in a large group with a lower HIV risk will probably be very limited, as the level of transmission is much lower and the diagnosed HIV infections were often contracted long ago. This group derives particular benefit from the strategy of implementing faster tracing and direct treatment.

3.4 Effects on risk behaviour and adherence to therapy in the long-term

PrEP can have an effect on sexual risk behaviour: if people feel they are better protected against HIV, they are likely to take more risks. This so-called risk compensation may result in an increase of the incidence of STIs (with an increased risk of HIV transmission). Conversely, there are also studies that predict a drop in STI incidence due to increased test behaviour.[60,61]

In *randomised controlled trials* (RCTs) (where participants did not know if they were getting PrEP or placebo), no difference was found in condom use, there was no increase in number of partners, and, in as far as it was measured, no difference in the incidence of STIs such as syphilis or gonorrhoea.[24,33,35] In the open label studies (all participants got PrEP), a slight drop in condom use and an increase in risk behaviour was seen. However, this has not yet been seen to be translated into more STIs.[24] In the recently published results of a demonstration project in Australia, a significant reduction in condom use and an increase in STI incidence were reported in the 12-month period following the start of PrEP.[34] In the AMPrEP trial, after 3 and 6 months of PrEP use, sexual behaviour related to number and type of sex partners had not changed, but there was an increase in the number of anal sex contacts without a condom (both in total and with casual partners). The incidence of bacterial STIs was already very high at the start of PrEP, and remained steady during the PrEP period (average of one STI a year; follow-up to 15 months).
Most studies cover a limited time only, meaning that little is known about risk compensation in practice. PrEP is used by the high-risk MSM group, both in trials and in ongoing projects. This is the group that does not consistently use condoms (and also does not take PrEP), and which has a high to very high incidence of STIs.[62] For this reason, a rise in the incidence of STIs is difficult to detect.

Further, it is unclear if, in time, PrEP will influence the sexual behaviour of a group larger than PrEP users only, e.g. by reducing the fear of HIV (as previously after the introduction of ART).

3.5 Conclusion

Adherence to PrEP therapy effectively protects the user against HIV infections, both in daily and intermittent use. In trials, the effect on the incidence of HIV is larger in groups with a high risk of HIV due to sexual risk behaviour. In the Netherlands this is the high-risk MSM group; the effect of PrEP is less strong in other risk groups. PrEP is expected to lead to a drop in the number of new HIV infections in MSM, but how strong this effect will be if PrEP is used in combatting HIV in the Netherlands cannot yet be estimated. Reaching the intended high-risk group and good adherence to therapy in PrEP users are essential in this. The effect of PrEP on risk behaviour and STIs must be monitored.

04 safety of PrEP

PrEP's side effects are limited to mild complaints and a few more serious symptoms which are subclinical and reversible. Resistance to TDF-FTC is rare, but it is important that it is detected. Further, medical counselling is indispensable to PrEP use.

4.1 Safety

In February 2016 TDF-FTC (Truvada®) was approved for use as PrEP by the *European Medicines Agency* on the basis of its reported safety and effectiveness. Virtually no serious adverse reactions to PrEP have been reported. TDF-FTC (in combination with other drugs) has been used for HIV treatment for adults and children from the age of 12 since 2004. No other side effects have been found when TDF-FTC is used as PrEP than when it is used for HIV treatment.

Mild symptoms, such as gastro-intestinal symptoms, headache and weight loss, occur in one in ten PrEP users.[24] More severe side effects may occur in a small percentage of PrEP users: a subclinical decrease in kidney function (1/200)[63], liver function[74] or a reduction in bone density (1/100).[64] It is important to detect these early (by testing for them prior to and during PrEP use), as in most cases these impairments are reversible.[65]

Depression has been previously identified as a side effect, but a follow-up study did not find a bigger risk of depressive symptoms.66 In a review based on five PrEP studies, the safety of TDF-FTC was compared with aspirin as a prophylaxis, and it was concluded that the side effects of the short/intermediate use of PrEP were less than those of aspirin.[67]

The safety of using PrEP during pregnancy and while breast-feeding has been less well studied. However, on the basis of the available data, there do not appear to be any risks to mother and child. If necessary, PrEP can be prescribed by a physician during pregnancy.[68,69]

Although transgender women are included in studies, not enough is yet known about interactions between PrEP and the hormone therapy that is used by transgender persons.[70]

There are new developments that may expand the options for PrEP in the future. In HIV treatment TDF can already be replaced by tenofovir alafenamide (TAF), which carries a lower risk of side effects.[71] New developments that may facilitate PrEP use are administration by a long-acting injection, an implant or by a vaginal ring.[72,73]

4.2 Resistance

Resistance of the HIV virus to TDF-FTC has rarely been reported, and, as yet, has not frequently occurred in PrEP users.[24,74,75] Resistant infections can be effectively treated with other antiretroviral drugs. The risk of the development of resistance is higher if an undetected acute HIV infection was present when PrEP was started. An HIV infection only becomes detectable after a few weeks or months, depending on the test used. For this reason it is important to use a sensitive HIV test which can detect early infection before PrEP is started. Furthermore, PrEP use can delay the detection of an infection because it partially suppresses the virus. This can increase the risk of resistance.[76] It is therefore important to monitor for potential resistance in any viruses that are found after seroconversion, and to detect acute HIV infections during PrEP use as quickly as possible by regularly carrying out a good, sensitive HIV test and being alert to symptoms of acute infections.

4.3 Medical counselling

Medical counselling is necessary before PrEP is started and during its use. It is essential to trace HIV infection and severe rare adverse events early. Renal function (creatinine clearance) should be monitored at the start of and during PrEP use. Additionally, testing for STIs, including hepatitis B and C, and counselling on PrEP use and risk behaviour should be included in this trajectory.[59] If HIV infection occurs, it is necessary to monitor resistance. Experiencing side effects sometimes results in PrEP use being interrupted which increases the risk of HIV infection.[9] Both before PrEP is started and during its use, tests for the presence of an HIV infection must be carried out in a certified laboratory, using a sensitive HIV test. If an HIV infection is found to be present then testing for resistance should be continued. The necessity to continue using PrEP can also be evaluated, for example when risk behaviour changes.

Whether or not PrEP users will continue to come back for medical check-up consultations is still uncertain. This has not yet been well reported in studies or implementation projects. After years of treatment, HIV positive patients have been seen to stop or interrupt attending follow-up consultations.

4.4 Conclusion

Good medical counselling is necessary to guarantee the safe use of PrEP, to prevent HIV infections going unnoticed and to monitor rare side effects and resistance to TDF-FTC.

05 cost effectiveness of PrEP

Cost effectiveness is an important component in the evaluation of new medication. To a certain extent, cost effectiveness studies are always indecisive. This is because they are based on modelling of effects and the costs and benefits associated with them and assumptions about the course in the long-term. In addition, in the case of PrEP there are scientific uncertainties about the effect on the incidence of HIV in practice. Despite these uncertainties, it is probable that if used correctly in the high-risk group, PrEP will be a cost-effective intervention in the Netherlands.

5.1 Threshold value

In cost-effectiveness studies, calculations are often made using QALYs (*quality-adjusted life year*, years of life gained in perfect health). If a preventive intervention leads to both health gains and cost-savings, then the implementation of this intervention should be recommended. However, money usually needs to be spent to bring about health gains. The question then arises: What costs are acceptable in relation to the health gain? There is no formal limit for cost-effectiveness, but the sum of € 20,000 per QALY is often taken as the threshold value for a preventive intervention.

5.2 Cost effectiveness of PrEP in MSM

The Committee has selected those existing studies on the cost effectiveness of PrEP that are most relevant to the situation in the Netherlands. These are twelve studies on the cost effectiveness of MSM in affluent countries.[47,49,77-86] The Committee has summarised the outcomes of these studies and identified those variables that play the biggest role in cost effectiveness. An overview of these studies can be found in the background document. In addition, the Committee has been informed of the interim results from an as yet unpublished RIVM study. The cost effectiveness of PrEP varies greatly between these studies: the costs per QALY differ from cost-saving (in a few of the most positive scenarios)[49,84,86,87] to extremely high (more than € 100,000 per QALY).[81,85] The differences can be partially explained by the epidemic model chosen and the time horizon used. Furthermore, there is variation in the economic parameters that are used for calculations and the estimates of costs and quality of life. In addition, the scientific uncertainties around PrEP also play a big role. The hypotheses that have the most effect on cost effectiveness are the effectiveness of PrEP, the incidence of HIV in the group that uses PrEP, and the costs of PrEP and HIV treatment (ART).

5.2.1 Hypotheses on the effectiveness of PrEP

The reported effectiveness of PrEP in MSM in large RCTs varies from 45-100%. Most cost-effectiveness analyses are founded on one of these studies, which partially explains the variation. It is unclear what the effectiveness will be in the long-term when PrEP is implemented. One of the reasons for this is that it is strongly dependent on adherence to therapy. How high adherence to therapy will be outside the study setting is

unknown. In addition, the degree of change in risk behaviour on the implementation of PrEP remains unclear. Some cost effectiveness studies hypothesise that risk behaviour will not change, others model on the basis of a 20% increase. The models hypothesise that an increase in risk behaviour will lead to a reduction in effectiveness. If this hypothesis will be verified remains to be seen. The effect of PrEP on risk behaviour is unclear in the RCTs; some studies show an increase in risk behaviour (including the interim results from AMPrEP), but this did not cause an increase in the risk of HIV. However, more risk behaviour may have an effect on the incidence of STIs resulting in additional costs of the diagnosis and treatment of the extra STIs.

The most relevant studies on MSM in Europe hypothesise that PrEP will be very effective (80-90%), and that if it is introduced correctly, adherence to therapy will remain high.[47,49,83] When the implementation projects are completed or a thorough evaluation of PrEP in practice is done, it will be clearer how effectiveness will develop under the influence of adherence to therapy and risk compensation in greater populations in the long term.

5.2.2 Hypotheses on the prevalence and incidence of HIV

The prevalence and incidence of HIV varies greatly between studies, and also between groups within a single study. If HIV occurs more frequently in a group and therefore the risk of being infected with HIV on sexual contact is greater, the number of people who need to receive preventive treatment to achieve a comparable health gain goes down. The higher the incidence of HIV in the target group of PrEP users, the lower the costs per QALY.[81,84-87] Therefore PrEP is most cost effective when it is used by MSM with the highest risk of infection. The studies also differ in their expectations concerning the spread of HIV and the duration of the high-risk behaviour of MSM. Many models expect that individual risk behaviour will remain stable for a long period, while on the basis of empirical data, other models are premised on short periods of high risk followed by phases of average or low risk behaviour.

In the Dutch situation, it is important to target the provision of PrEP at MSM with the highest incidence of HIV. The Dutch cost-effectiveness study from Nichols et al. assumed that 2-3% of MSM in the Netherlands would be reached; the as yet unpublished study from RIVM projects that this will be 6% (selected on the basis of risk behaviour or STI diagnosis).[83] It is unclear to what extent this group will be reached by the provision of PrEP, and if the provision can be limited to this group.

5.2.3 Hypotheses of costs of PrEP and HIV treatment

One last point that varied strongly in the cost-effectiveness studies was the estimated costs of PrEP and HIV treatment. This is linked to differences between countries in the price of drugs and the extent to which the costs of tests and medical counselling have been included. Also, the price of PrEP varied within a large number of individual studies. This was to ascertain the price at which it would become cost effective to offer PrEP (sensitivity analyses). As the costs of PrEP become lower, the costs per

QALY also fall; as the costs of HIV treatment become lower, the costs per QALY actually increase.

The cost of PrEP in the Netherlands has recently fallen sharply from approximately € 536 a month for daily use in 2015 to € 48 a month in January 2018.[88,89] This is because generic drugs have become available. The price of PrEP may possibly fall even further. According to Nichols et al., the reduction in the cost of PrEP in the Netherlands is so substantial, that sensitivity analysis results are indicating a move towards cost saving.[83] RIVM's recent cost-effectiveness study concludes that PrEP will be cost effective at a price of € 50 a month. This study employs wide-ranging estimates of the costs of medical counselling and diagnostic tests. The effect of the cost of necessary medical counselling is relatively higher when the price of PrEP drops sharply.

The availability of generic drugs may also have an effect on the price of ART for the treatment of HIV, as the active ingredients of PrEP also make up part of ART combination therapy. However, there is no guarantee that this will actually happen. Over the last seven years, the price of HIV treatment in the Netherlands has actually risen due to new drugs coming on to the market which are still protected by patent.[90]

5.3 Conclusion

Cost effectiveness is heavily dependent on how the price of PrEP and ART develops, and on the incidence of HIV in the PrEP target group. In addition, there are uncertainties about effectiveness on implementation. Data on this will become available from the implementation projects. On the basis of two Dutch studies, the Committee has reached the conclusion that PrEP will become cost effective (and possibly even cost-saving) for the high-risk population at a price of € 50 a month. Additionally, it is important that PrEP is provided to the target group in which both incidence and adherence to therapy are high.

06 the role of the government

Because of the contribution that PrEP is expected to make to cutting down the incidence of HIV in the Netherlands, the Committee is of the opinion that there is a role for government in facilitating PrEP use. The Committee regards PrEP as so promising that it is advising not to wait until the size of the effect on the epidemic in the Netherlands can be predicted with certainty. Its high level of effectiveness means PrEP is a promising addition to the repertoire of HIV prevention interventions, particularly in the high-risk MSM group. This approach is concordant with the national and international aims of HIV control.

The Committee has recommended that the effect of PrEP use be optimised and the associated risks for users and society be limited. For this reason it is advocating an integrated approach to the provision of PrEP to the correct target group, whereby good medical counselling and monitoring is maintained.

6.1 The facilitation of PrEP falls within the declared objectives of the Dutch government

The introduction of PrEP is compatible with international targets for combatting the spread of HIV. [91-93] Recently, stakeholders drew up a national STI/HIV action plan with the aim of reducing the incidence of HIV in the Netherlands to half of its 2017 level by 2022.[91] According to the Committee, PrEP fits within the policy on controlling infectious diseases, as prevention of HIV infection in individuals will also prevent spread to third parties, and will therefore also serve the interests of general public health. This is in line with national policy on STI control, which is based on public health law.

6.2 Medical counselling and careful monitoring are important

In order to prevent the development of resistance and a strong increase in the number of STIs, it is vital to test for HIV and STIs both prior to and during PrEP use. PrEP users must also be protected against rare, reversible side effects. It is difficult for individual users to organise the necessary medical counselling. The Committee sees a role for the government in this. The admission of PrEP to the Dutch market and the recent drop in price mean that PrEP has also become readily available for use on people's own initiative without good medical counselling. The Committee is therefore of the opinion that good medical counselling must be organised as a matter of urgency. The Committee also thinks that on national implementation, it is important to collect the necessary data on the long-term effects.

6.3 The key target group: high-risk MSM

The Committee regards the high-risk MSM group as the group who will get the most benefit from PrEP. By focusing its introduction on this group, the effect of PrEP will be maximised.

In the Netherlands, two-thirds of new HIV infections occur in MSM. Most high-risk MSM are familiar with current HIV prevention methods: consistent use of condoms, frequent testing and direct treatment (TasP). In this group condom use is high but not optimal, and it is not improving: it has remained stable (or has been falling in some groups) for years, despite campaigns and personal health education. A large proportion of this at-risk group takes advantage of the opportunity to be tested at national sexual health centres,[82,94] and the referral rate for HIV treatment is good in many cases.95,96 Early tracing, repeated testing and direct treatment have led to a drop in the incidence of HIV in this group. The acute phase of an HIV infection prior to detection continues to pose a risk. It is expected that this will play an increasingly important role in the spread of HIV in this group for as long as frequency of testing does not increase.[54,97] The Committee has established that current measures for the prevention of HIV have achieved their maximum effectiveness in high-risk MSM group. PrEP has an important role to play in further reducing the spread of HIV.

Existing prevention methods for other high-risk groups such as heterosexual people who originate from countries where HIV is endemic, have not yet been optimised. The percentage of people in this group with an HIV infection is higher than in other groups, but lower than in MSM. Typically, this group has lower risk-behaviour but enters treatment at a later stage when the infection is more advanced.[19] This has negative health effects for the patients themselves, and means that the phase during which the infection can be transmitted is longer. The stigmatisation of HIV still plays an important role in this group. This delays timely testing and consequently treatment and the prevention of further spread.[19] Optimising current prevention and testing policies could be of great benefit to this group. PrEP could be considered on an individual basis.

6.3.1 MSM as a vulnerable group

A further argument for governmental guidance is that PrEP could improve the position and the health of a vulnerable group.

The MSM group are less vulnerable in the Netherlands than internationally. The group knows how to access health care, is well organised and understands how to reach the media and the political establishment. Despite this, there are subgroups (e.g. young MSM, migrant MSM) that are more vulnerable. Although measures have been taken to reduce discrimination based on HIV status, fear and stigma are still very prevalent.[98-100] The fact that the largest risk groups for HIV infection in many affluent countries are MSM (and injecting drug users), serves to reinforce stigmatisation.[87] The high risk of HIV run by this group is determined not only by sexual behaviour, but also by the high prevalence of the infection in their sexual environment.[101,102] Therefore, MSM have a higher risk of HIV over which they do not have complete control.

The presentations given by stakeholders and as-yet unpublished data from the AMPrEP study, confirm that stigmatisation due to HIV and fear of infection continue to exist. In addition, these data show that PrEP can have a clear, positive effect on quality of life by reducing the fear of HIV. According to the Committee, this makes MSM a group that can be regarded as being vulnerable.

6.3.2 Reaching a new section of the high-risk group

There are indications from AMPrEP and other studies that some of the men who register to use PrEP comprise a group that is currently not being reached. Amongst other ways, this has been shown by the STI and HIV infections that are detected at the start of using PrEP. If this group is using PrEP they will be asked to attend for regular medical check-up consultations, HIV and STI testing and counselling. This can promote the early tracing of STI and HIV infections.

6.4 Promoting self-responsibility

PrEP encourages people at risk of HIV to be able to take responsibility for themselves. A notably important benefit for users of PrEP is that it offers

the opportunity of preventing HIV without agreement from the partner being necessary. It might be beneficial to place the responsibility on the person who wants to prevent an infection instead of sharing this between partners (by using a condom), or placing it on an infected partner (TasP).[103] Some members of the high-risk group want to take on this responsibility, and this opportunity is offered by PrEP adjunctive to condom use.

The Committee thinks it important that both PrEP drugs and medical follow-up should be available to all potential users who could benefit from them. This should specifically reach the vulnerable high-risk MSM groups (young MSM and migrant MSM). The Committee regards potential users of PrEP as being co-responsible for their individual risk of HIV, and, for this reason, recognises that a personal contribution could be asked for.

6.5 Harm reduction argument

The role of the government could go beyond creating preconditions for the safe use of PrEP and the monitoring of its effects. It could extend to the wish to prevent harm being caused by risk behaviour, even if that risk behaviour is viewed as problematic by other people. Although not every country endorses a policy of harm reduction, there has been sustained support for it in the Netherlands for a long time. The clean needle programme for drug addicts is an example of how the concept of harm reduction works in practice. Since its introduction into the Netherlands, no new HIV infections have been diagnosed in drug users, while in eastern Europe this is the main risk group. The introduction of PrEP would be in line with this if the conclusion were that an HIV infection is the consequence of behaviour to which risks are inherently attached, and all other means of damage limitation have been exhausted.

6.6 Conclusion

The Committee sees a number of arguments for the government to play a role in the provision of PrEP. It regards the possibility of reducing the incidence of HIV in a target group of high-risk MSM in which HIV prevention has reached a ceiling, as promising. It advises the government to facilitate good PrEP use so that the effect is as large as possible, the benefit-risk ratio for users is favourable, and the risks to society are as limited as possible.

07 advice

The Committee advises the Minister of Health to provide PrEP to high-risk MSM and to organise associated good medical counselling, and additionally to monitor the long-term effects so that this approach can be evaluated after five years.

7.1 Essential healthcare

When taking everything into consideration, the Committee concludes that this is a matter of essential healthcare, collectively funded. This conclusion is based on the convincingly proven high effectiveness of PrEP (both in daily and in intermittent use), and the ready expectation that provision of PrEP will have an effect on the incidence of HIV. Additionally, PrEP appears to be cost-effective and potentially even cost-saving if it reaches the correct target group at the right price. According to the Committee, the benefits for the users are greater than the disadvantages as long as careful medical counselling is coupled to the provision of PrEP.

7.2 PrEP target groups

The Committee advises that the provision of PrEP should be targeted at MSM with a high risk of an HIV infection, as the effectiveness of PrEP has been shown to be the most convincing in this group in affluent countries. People from other risk groups (in particular heterosexual men and women originating from countries where HIV is endemic) would be eligible to be provided with PrEP on an individual basis and in consultation with a physician.

The Committee advises that access to PrEP should be guaranteed for potential users who run a high risk of HIV, and in particular for those who are extra vulnerable, such as young MSM and migrant MSM. The Committee considers potential users of PrEP to be partially responsible for their individual risk of HIV. For this reason, it recommends that a personal contribution be considered.

7.3 Medical counselling is essential

The Committee recommends that PrEP should be introduced in the form of a programme that links counselling to the provision of PrEP. This is necessary to guarantee that the benefit for the participants weighs against the risk. Counselling should include initial testing for HIV and the provision of good information at the start of PrEP use, and tracing of rare side effects and regular testing for STI and HIV during PrEP use. The Committee emphasises that good medical counselling should be organised as a matter of urgency, as it expects that the recent drop in price could lead to a rapid increase in individual use.

7.4 Monitoring the effect of PrEP on HIV incidence in the Netherlands

The extent to which PrEP will contribute to HIV prevention in the Netherlands cannot currently be established scientifically. On the basis of data on effectiveness from studies on an individual level, the Committee expects that PrEP will contribute to the further reduction of the incidence of HIV.

The Committee recommends that the long-term effects of PrEP be carefully monitored. On the implementation of PrEP, its effect on HIV

incidence in the Netherlands can be monitored by careful registration of data on the numbers and profiles of users and new HIV infections. There is relatively good access to data concerning the specific high-risk group MSM via the national centres for sexual health, and numbers of new HIV diagnoses in the HIV treatment centres in the Netherlands. There are other important sources of data for monitoring PrEP and HIV outside the high-risk group, these include data from general practice registries. The Committee regards the following key points as being important to the monitoring process:

- availability of PrEP and reaching the high-risk group on a national level
- the effect on the incidence of HIV in the Netherlands (trends in the number of new HIV infections per risk group)
- the demand for PrEP from the high-risk and other groups
- the developments in adherence to therapy and the effectiveness associated with them
- changes in risk behaviour and STI incidence
- the development of resistance.

7.5 Evaluation is essential

The Committee advises that the effect of PrEP use should be evaluated after five years. This should be based on the data collected during the monitoring process and on changes in cost effectiveness. In this, the most important point is a drop in the number of new HIV infections. In the light of the results, the provision of PrEP for a further period may be considered. If the provision of PrEP is continued, the Committee recommends that HIV incidence and effectiveness continue to be evaluated periodically.

In conclusion, the Committee emphasises that PrEP is a new drug in the control of HIV, but that the implementation of PrEP should not displace any of the other preventive strategies such as condom use, frequent testing and direct treatment. The Committee regards PrEP as a useful addition to the existing preventive arsenal.

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