Pre-exposure prophylaxis - PrEP - opportunities for successful implementation in Norway

Summary

This memorandum will summarize international knowledge and experiences with pre-exposure prophylaxis against HIV infection (PrEP) and is intended as a decision basis for the Ministry of Health and Care Services as to whether PrEP should be implemented as a supplement to the Norwegian prevention efforts against HIV.

In Prop. 1 S. 2014-2015, Chapter 6 Public health policy, 6.7 Environment and health care - infection control, the Ministry of Health and Care Services wrote:

The World Health Organization has changed the guidelines for HIV prevention work in 2014 and recommends more use of treatment to prevent infection. The recommendations mean that more people will have access to HIV medicines to prevent infection. This also applies to medicines that can be taken before infection is detected, so-called pre-exposure prophylaxis (PrEP). National health authorities will, in collaboration with relevant professional communities and voluntary organizations, study the consequences of the changes in the Norwegian context.

The Norwegian Directorate of Health, in collaboration with the National Institute of Public Health, other professional communities and civil society, has studied the issue. The Norwegian Directorate of Health recommends that arrangements be made for PrEP to be used as a supplementary tool in Norwegian HIV prevention among the population groups that currently have the highest risk of becoming infected with HIV. The Norwegian Institute of Public Health has endorsed this recommendation. This mainly applies to certain subgroups among men who have sex with men (MSM) who have a particularly high risk of becoming infected with HIV. An important prerequisite for a successful and prevention-effective implementation is that there are clear inclusion criteria, routines for screening potential users and frequent checks which, among other things, must ensure guidance and testing of HIV and other sexually transmitted infections.

The memorandum provides a review of studies of the PrEP method's preventive effect against HIV, as well as a review of research and experiences related to possible changes in condom use and / or an increase in the incidence of sexually transmitted infections other than HIV among users of PrEP, which is a known concern. which is often raised in connection with PrEP. It will also provide an overview of available cost / benefit assessments made in other countries.

What is PrEP and does it have an effect?

Pre-exposure prophylaxis (PrEP) means that people who are not infected with HIV use antiretroviral drugs to prevent HIV infection.[1]PrEP as a method is most relevant for people who have a particularly high risk of becoming infected. The person in question is given an extra opportunity to protect themselves by either taking a pill daily or by using PrEP before and after sexual situations where the risk of infection is high.

PrEP is being recommended by an increasing number of professional communities, interest groups, as well as international organizations such as the World Health Organization (WHO), as an important supplement to, and in combination with, traditional HIV prevention. The recommendations are mainly that PrEP should be available to HIV-negative people with a significantly increased risk of HIV and that the use should be initiated by competent personnel who provide the necessary examinations before PrEP is used, as well as regular and frequent testing for HIV and other sexually transmitted diseases. infections (soi).

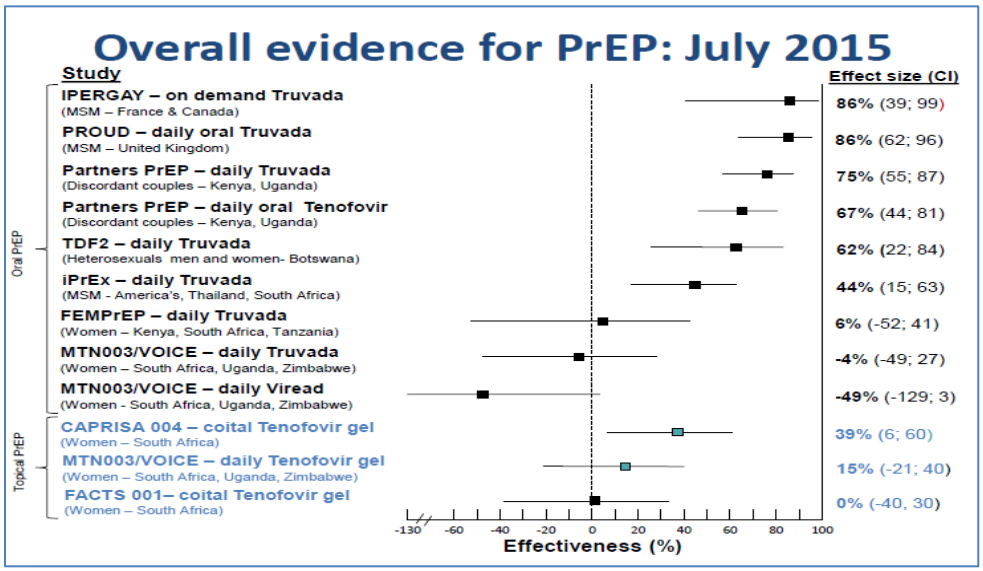
The effect of PrEP has been shown in four randomized controlled trials (iPREX, Partners PrEP, PROUD and IPERGAY).[i] [ii] [iii] [iv]. The international iPREX study (2010) showed that a daily pill reduced the risk of HIV infection by 92% among participating men who have sex with men (MSM) with blood values that indicated daily use. Later, both the UK-based PROUD and the French Ipergay study showed that daily PrEP in PROUD and "on demand" before and after sex in Ipergay significantly reduced the risk of HIV infection for MSM (see also Figure 1 for an overview of completed studies). A Cochrane review from 2012 also confirmed that prophylaxis against HIV reduces the risk of infection in high-risk populations[v].

In July 2016, the European Medicines Agency (EMA) recommended that the EU Commission grant marketing authorization for Truvada® as PrEP, in combination with safer sex practices to reduce the risk of sexually transmitted HIV viruses. The Committee for Medicinal Products for Human Use (CHMP), which is responsible for reviewing the knowledge base of applications prior to the EMA's recommendations, based its decision on studies showing a significant reduction in the risk of HIV infection when Truvada® was used as a PrEP.[vi]. The EU Commission decided to grant such a marketing authorization on 22 August 2016 and the EU / EEA states will thereafter be able to decide on a price and any reimbursement scheme based on national circumstances.

In the United States, HIV prophylactic use of Truvada® was approved in 2012.

[1] Currently, the current drug regimens are either a combination of tenofivir (TDF) / emtricitabine (FTC) (Truvada®) or tenofivir alone.

Figure 1



Overview of effect results in PrEP studies. WHO, 2016

Key recommendations and guidelines

In existing guidelines in Europe and the USA, there is a consensus that PrEP should be made available to the groups in the population that have the highest risk of HIV. This applies in particular to MSM and trans women, based on the HIV incidence in the group, individual sexual risk behavior and external factors that make safer sexual behavior difficult. Introduction of PrEP to groups at high risk of becoming infected with HIV is also strongly emphasized in WHO's new global strategy for the health sector's efforts to prevent HIV, which was launched in June 2016[vii].

In the WHO's guide (guidelines) for PrEP from the autumn of 2015, the target groups are roughly identified as belonging to population groups with an HIV incidence of 3 per 100 people / year[viii]. This is an incidence level that can be recognized in some subpopulations of gay / bisexual men, trans women and heterosexual women and men with HIV-positive partners who do not go on treatment. The risk will of course vary and must be assessed on an individual level.

The European Center for Infection Control (ECDC) published a statement in 2015 where EU and EEA Member States were encouraged to consider the integration of PrEPs into their existing HIV prevention programs for groups at particular risk, especially MSM, in the context of each state's health system.

The clinical guidelines from the European AIDS Clinical Society recommend that PrEP be evaluated for HIV-negative MSM and transgender people who are inconsistent in condom use with random partners or have HIV-positive partners who are not on treatment. [ix]. The Center for Disease Control and Prevention (CDC) in the USA, like the WHO, recommends PrEP for high-risk HIV for MSM, based on individual risk[x]. Like a number of other countries, such as the United Kingdom, the Netherlands and France, the Norwegian Association for Infectious Diseases also has in itsprofessional guidelines for 2016 based on similar definitions of risk and recommends PrEP to the same target groups [xi].

WHO has prepared an implementation guide for PrEP which is currently being consulted. It has been announced that this guide will be published in the autumn of 2016.

The HIV situation among men who have sex with men

The Norwegian HIV figures show that men who have sex with men (MSM) as a group make up a disproportionately high proportion of people who are diagnosed with and who live with HIV (Figure 2). The infection situation among MSM is still characterized by the fact that many are infected through casual or anonymous sex in Norway or abroad. In 2015, 74% of the reported HIV cases among MSM (n = 70) stated that they were infected by a random partner, 7 people by a permanent partner and for 11 people the relationship to the infection contact was unknown.

PreP is most relevant for the group msm in Norway. MSM is by far the largest single group infected with HIV in Norway. In the period 1986-2015, MSM accounted for 32.6% of all cases of HIV infection reported to the Norwegian Institute of Public Health. Of all those who became infected in Norway or abroad and lived in Norway (ie susceptible to preventive measures) in the ten-year period 2006-2015, 59% were MSM.

Measures to limit the spread of HIV among MSM have been a priority area in all strategic HIV plans that have been prepared over the years, most recently the plan Acceptance and Coping - National HIV Strategy (2009 - 2014) which was extended for 2015. Despite the significant preventive efforts made in recent years, an increase in HIV among MSM has been seen in the last 10 years. In 2015, a decline in the number of newly diagnosed was seen for the first time. This may be due to the fact that over 90% of diagnosed MSM are now on treatment and thus have a minimal risk of infecting others. Another obvious reason is increased test activity among MSM as a result of easily accessible test opportunities in several arenas and a generally high focus on the importance of regular testing.

There are no reliable figures for how many sexually active gays, bisexuals or other men have sex with men in Norway. Based on previous population studies nationally and internationally, there is reason to assume that the proportion of MSM in the male population is between 3-7 per cent. Despite the fact that MSM relatively makes up a small part of the male population, the group has in all years accounted for well over half of new annual HIV cases, which gives a clear indication that the infection pressure is very high among some groups of MSM.

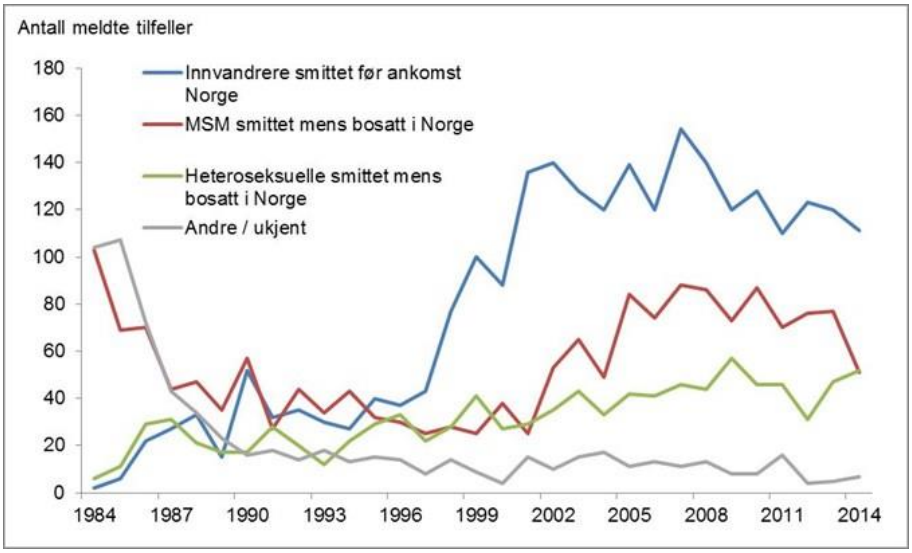
The UN's new political declaration on HIV and AIDS, which was adopted by the member states in June 2016, assumes that MSM globally has a 24 times greater risk of contracting HIV than other adults in the general population. Similarly, trans people are 49 times more likely to live with HIV than

others. PrEP is also mentioned in the declaration as one of several biomedical interventions that should be considered to achieve the goal of eliminating HIV and AIDS by 2030[xii].

Overall, in the EU and EEA countries, there has been a general increase in new HIV cases among MSM. 53% of all new cases of HIV are found among MSM and this group is the only population group that has an increase in new cases of HIV (Figure 3).

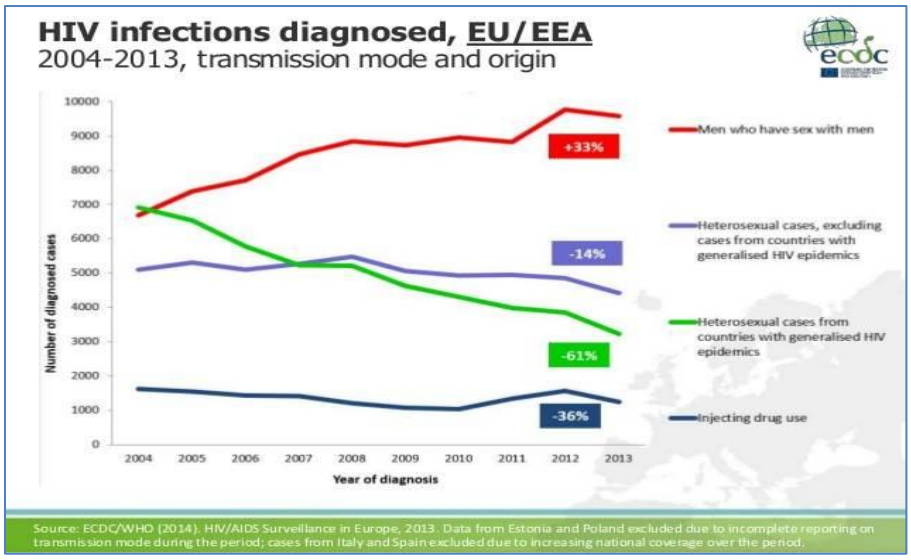
In 2010, a European Internet survey was conducted in 38 countries among men who have sex with men. In the Norwegian part there were 2096 participants. The Norwegian results showed that 30% of the participants did not use a condom during the last intercourse with a random partner. This proportion was higher among HIV-positive participants. The study also showed that knowledge about HIV and how to avoid infection was very high. In addition to behavior change and increased condom use, early diagnosis and rapid treatment will continue to be central to the preventive work. Nevertheless, it seems that this is not sufficient for a group of MSM. The use of PreP will therefore be an important supplement for part of the MSM group, which must be regarded as a main target group for HIV prevention in general and for PrEP as a supplementary tool.

Figure 2:



HIV infection in Norway reported MSIS 1984-2015 by year of diagnosis and groups at risk. National Institute of Public Health 2016.

Figure 3:



HIV infection diagnosed in the EU / EEA, 2004-2013. ECDC 2015.

Status of international implementation of PrEP

The two European studies PROUD and Ipergay have greatly accelerated the implementation of PrEP in several parts of the world.

As of May 2016, PrEP is approved, recommended and incorporated into public and private health programs in the United States, South Africa, France, Kenya, Canada and Israel. Furthermore, Peru and Switzerland have also recommended the use of PrEP, but it is not part of the public offer. A survey conducted by ECDC in the European countries in May 2016 shows that there are ongoing pilot / pilot projects in Belgium, the Netherlands, Italy and England.

Furthermore, Denmark, Greece, Ireland, Luxembourg, Portugal, Spain and Sweden have plans for various pilot projects during 2016/17.

USA

The US Food and Drug Administration (FDA) approved Truvada® for the indication pre-exposure prophylaxis to HIV-negatives in 2012. Demand for PrEP among MSMs has increased sharply since 2014 (Figure 4), partly because PrEP has been increasingly promoted as an opportunity to have good sex life and relationships without fear, rather than just focusing on virus prevention and disease. The use of "innovators" who publicly appear as users of PrEP and tell about their experiences are believed to have contributed to the increase[xiii].

In the USA, PrEP is covered by both private and public health insurance and for those without insurance coverage, the medicine is currently covered by the pharmaceutical company Gilead, as well as public funds.

There are a number of players offering PrEP in the United States. This applies to specialist clinics for sexual health, student health services, GPs and voluntary organizations. There are also several

websites, as well as services that deliver PrEP at the door, provided that you can document from elsewhere that you satisfy the criteria / indications for PrEP.

The experience from the USA points to two key factors that must be carefully considered when implementing PrEP. It is about estimating the size of populations that can benefit most from PrEP and tailoring messages to reach those who meet the criteria / indications for PrEP. The Center for Disease Control (CDC) has estimated that approximately 1.2 million people in the United States may benefit from PrEP based on estimates of the size of the individual groups at risk for HIV infection and the proportion of the population that meets the indications for PrEP. For example, it is estimated that 24.7% of MSM (18-59 years) will be able to meet the criteria, while among heterosexually active adults only 0.4% will meet the criteria for «significant risk»[xiv].

Experience from the USA has shown that the prevalence of PrEP, or breakthrough among the target groups, coincides and reflects well with classical innovation theory. Individuals in each step of the spread of PrEP have specific information needs and reasons for assessing or applying PrEP. As shown in Figure 5, therefore, the messages in connection with a possible offer of PrEP in Norway should be tailored in line with this.

Figure 4:

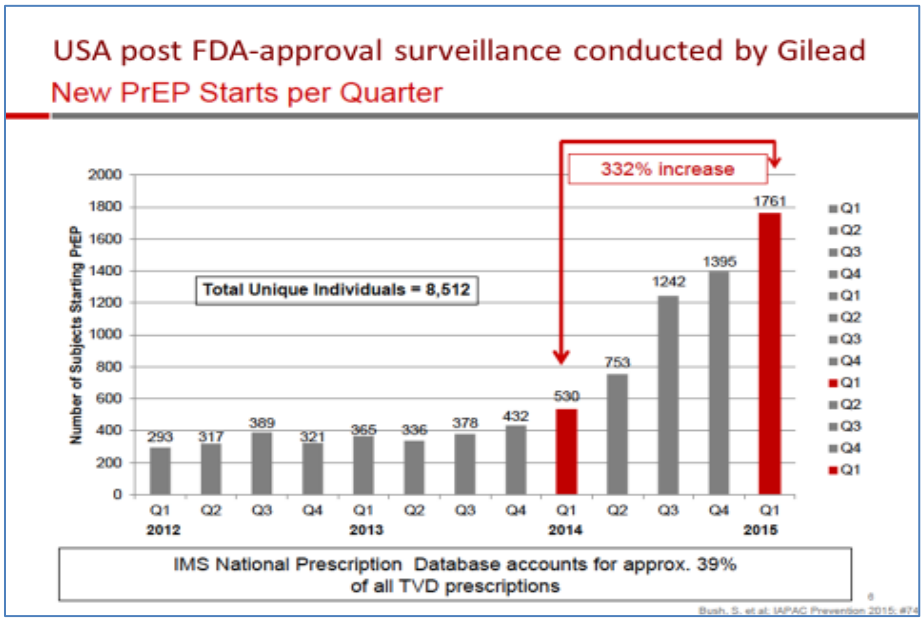
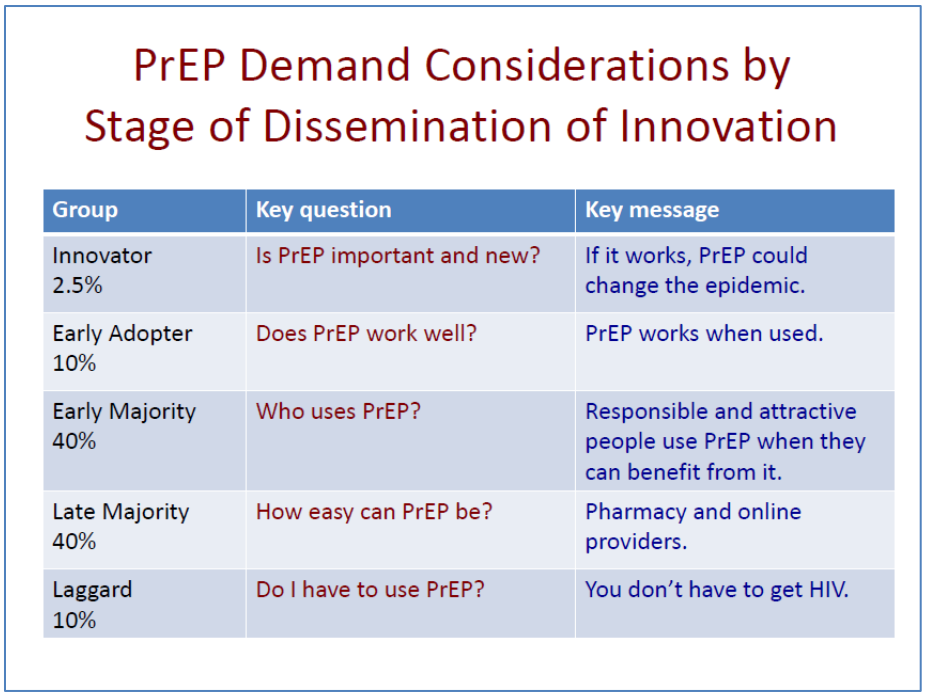


Figure 5



PrEP Demand Considerations by Stage of Dissemination of Innovation

Group	Key question	Key message
Innovator 2.5%	Is PrEP important and new?	If it works, PrEP could change the epidemic.
Early Adopter 10%	Does PrEP work well?	PrEP works when used.
Early Majority 40%	Who uses PrEP?	Responsible and attractive people use PrEP when they can benefit from it.
Late Majority 40%	How easy can PrEP be?	Pharmacy and online providers.
Laggard 10%	Do I have to use PrEP?	You don't have to get HIV.

Robert Grant, University of California, San Francisco. Presentations ECDC 2016.

France

As the only country in Europe so far, France introduced PrEP from 6 January 2016 as a fully funded public offer. The lack of pan-European approval of Truvada® as a preventive medicine has been solved in France by the National Medicines Agency (ANSM) having temporarily approved the medicine used as PrEP for a three-year period.

The criteria for PrEP in France are that you are over 18 years old, have a high risk of sexually transmitted HIV infection, test negative for HIV, have no signs of acute HIV infection or have not been exposed to HIV until very recently. Those who are considered to have a high risk of HIV infection include:

- MSM and transgender peoplewho have either had unprotected anal sex with two or more partners in the last six months. Or had another sexually transmitted infection in the last twelve months. Or used PEP[2]the last twelve months. Or used drugs through sexual contact.
- Others are assessed on an individual basis. This applies, for example, to sex workers who are exposed to sexual intercourse without a condom, persons who are exposed to sexual intercourse without a condom with a person who belongs to a group with a high HIV

[2] Post-exposure prophylaxis (PEP) after exposure to HIV is a medical treatment with antiviral drugs that normally lasts for four weeks.

prevalence (for example from a high-prevalence country, a person with many sexual partners, injecting drug users).
- Others who are considered to be exposed to high risk and who have limited ability or opportunity to protect themselves in other ways, may also be offered PrEP.

The standard recommended dose is one tablet a day as long as you are at risk of HIV. Msm can also choose intermittent use, ie 2 tablets 2-24 hours before sex, 1 tablet 24 hours after sex and 1 tablet 48 hours after first intake.

Full reimbursement is given for all necessary health care and medicines in connection with PrEP, as well as follow-up interviews, counseling and testing of all sexually transmitted infections every three months. As of July 2016, there are about 90 clinics offering PrEP. As in the USA, preliminary data indicate that MSMs who apply for PrEP are those who are most at risk of HIV and who will have the greatest benefit and effect of PrEP.

From 6 January to July 2016, a total of 1,077 people started on PrEP, but the French authorities have estimated that between 10,000 and 20,000 can meet the criteria. In 2014, a total of 6,600 new HIV cases were diagnosed in France, of which 42% were MSM.

Inclusion criteria

From both a public health and an individual perspective, it is essential that it is the groups that will benefit most from PrEP that have access to it. On a largermeeting under the auspices of ECDC in Stockholm in AprilIn 2016, a review of inclusion and exclusion criteria for PrEP was conducted. The review of PrEP studies, demonstration / testing projects in Europe and the USA and existing guidelines show that the suitability criteria are very similarly designed.

The criteria generally focus on population groups with the highest risk of HIV, ie MSM and trans women, based on HIV incidence, sexual risk behavior and external factors that affect risky sex. Unprotected anal intercourse, proven sexually transmitted infections in the last six months, previous use of PEP are factors that support the use of PrEP. This is in line with recommendations and guidelines from WHO, CDC and EACS and others.

There is less agreement on the benefits of PrEP for sex workers and for heterosexuals, as well as the effect PrEP can have in addition to harm-reduction measures such as clean syringes and drug-assisted treatment for people who inject drugs. There are also insufficient data on HIV incidence among first-generation migrants from countries with high HIV prevalence, which makes it difficult to determine whether these population groups will be able to gain general health benefits through the use of PrEP.

Follow-up and monitoring of PrEP users

The main topics related to clinical follow-up and monitoring of people who use PrEP are adherence in use, control for the development of resistance and frequent screening for soi.The positive results regarding protection against HIV when using PrEP presuppose that the medicine is used properly

during the periods when one is exposed to a high risk of HIV infection. If, despite this, HIV is nevertheless detected, the use of PrEP must be stopped immediately to, among other things, prevent the development of resistance. Frequent testing for other soi, such as gonorrhea and syphilis, is recommended as an important offer to PrEP users.

Compliance

The large studies referred to in the introduction have shown that PrEP is effective if the treatment is taken as intended. Ensuring compliance with the dosing regimen is therefore crucial regardless of whether PrEP is used daily or takenintermittent. An important question is whether compliance is better with a daily dosing regimen than with intermittent use. Although there is some evidence to suggest that compliance is better with a daily regimen, there is no evidence that compliance is not good enough with intermittent use. Both the larger studies and ongoing pilot projects in several countries have shown that compliance is good with both forms of use. Known barriers to compliance include stigma, lack of acceptance from the environment and society, the need to hide the use of PrEP, involvement in chemsex, problems with intoxication and mental health, social factors and mobility.

Resistance

Questions have been raised as to whether a generalized or uncontrolled use of PrEP may result in the development and transmission of HIV-resistant viruses. On the other hand, it is argued that PrEP is expected to reduce the incidence of HIV infection, including primary and secondary drug resistance, thus reducing the overall development of resistance.

Drug resistance associated with the use of PrEP, for example in the United States and in PrEP studies, has been low. A systematic review of knowledge about drug resistance in PrEP studies showed that five cases of resistance events were found among 9,222 people who received PrEP, ie the risk of drug resistance was 0.5%. It is also conceivable that compliance with the treatment will be worse when used outside of clinical studies. The risk is highest in people who have an acute HIV infection when they start on PrEP, ie in the "window period" between infection transmission and detectable virus during testing. The risk is low among those who seroconvert while taking PrEP. Worldwide, there is so far one[known case of seroconversion with HIV despite good adherence to the PrEP regimen](#).

In the PrEP context, risk reduction for the development of resistance is thus linked to ensuring that the person in question has not recently been infected with HIV when starting PrEP and frequent testing (every 3 months) while using PrEP. One way to reduce this risk may be to use more sensitive assays to detect acute HIV infection during the window period. This can be done by making PrEP available to the relevant target groups in the health service, who can ensure that relevant anamnesis, testing and follow-up both before and after the start of PrEP. The drugs that can be used as PrEP are increasingly available on the internet and in some other countries. This applies to both original products and considerably cheaper generic variants. With extensive self-medication due to low availability in the public health service, there is reason to believe that the risk of developing

resistance will be higher than it could and should have been. Both due to lack of testing and due to the risk of importing counterfeit drugs.

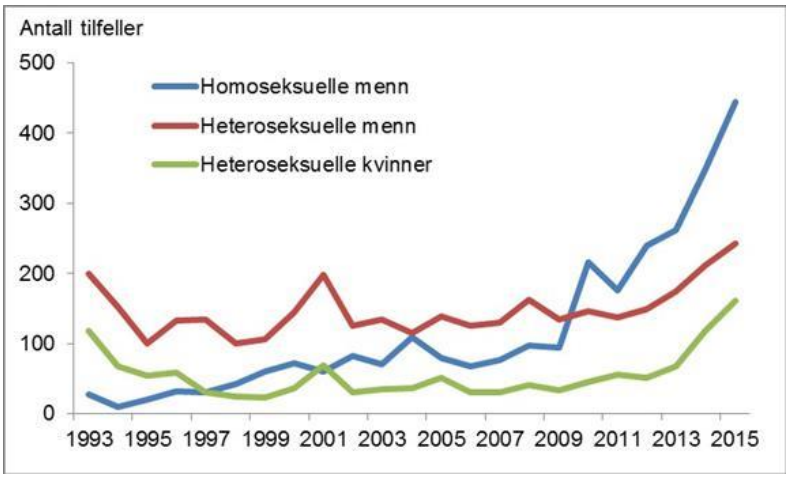
Screening for sexually transmitted infections

The risk that the incidence of other sexually transmitted infections (soi) will increase with the introduction of PrEP is often raised as a main objection to PrEP as a method.

Men who have sex with other men (MSM) have a significantly higher risk of being infected with soy, in addition to HIV. Overall, it was found at European level in 2014 that 47% of gonorrhea cases, 72% of syphilis cases and 100% of cases of lymphogranuloma venerum (LGV) were detected among MSMs.[xv]. Also in Norway, there has been a worrying increase in gonorrhea and syphilis among MSM in the last decade (see Figure 6 and Figure 7). Internationally, there is particular concern associated withoccurrence of multiresistant gonorrhea.

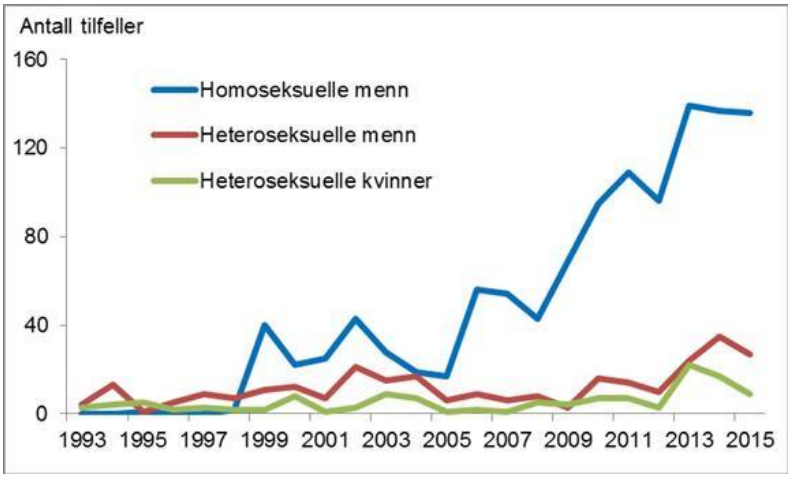
The increase in soi among MSM started before PrEP became relevant and the increase is greatest among groups of MSM with a high degree of risk behavior. Among other things, British data show that MSMs that are already HIV-positive make up a significant proportion of MSMs that test positive for gonorrhea and syphilis[xvi]. Norwegian monitoring data and previous studies have confirmed the same trend[xvii].

Figure 6:



Number of gonorrhea cases in Norway, by sexually transmitted infection. FHI, 2016.

Figure 7:



Number of syphilis cases in Norway, by sexually transmitted infection. FHI, 2016.

Data from the PROUD study, which was conducted among HIV-negative MSMs who had a high number of self-reported previous soi, showed that there was no difference in the distribution of soi after 12 months between the group that received PrEP and those who did not go on PrEP. Both groups had routine follow-up with testing for HIV and soi every 3 months during the trial period.

Follow-up for soi among those who receive PrEP

The incidence of soi among MSMs in Europe is increasing and is likely to remain at a high level with or without PrEP. On the other hand, enrollment in a PrEP program can play a strong positive role in the control and control of soi in that a prerequisite for PrEP will be a high frequency of asymptomatic screening for all soi, rapid treatment and infection detection. At the same time, frequent contact

with the health service gives the most vulnerable MSM more opportunities to receive guidance, for example by wanting to reduce sexual risk behavior.

In summary, it can be said that the incidence of soi is already high among the MSMs that best meet the criteria for using PrEP and by starting with PrEP, one achieves both staying HIV-negative and the opportunity for close follow-up of other soi, as well as traditional prevention measures such as motivational interviews. , easy access to condoms and slides etc.

Results from clinical practice

One of the first and largest published studies of PrEP users in a major clinical practice showed that despite high rates of sexually transmitted infections and a decline in condom use, there were no new cases of HIV in this population. During a 32-month observation period, the Kaiser Permanente San Francisco Medical Center had a total of 1,045 referrals for the assessment of PrEP and 657 individuals (MSM with particularly high vulnerability to HIV) started with PrEP. The average useful life of PrEP was 7.2 months, resulting in a total of 388 person observations of PrEP.

Among 143 patients who were asked about any changes in sexual behavior after six months of using PrEP, 74% answered that the number of sexual partners was unchanged, 15% stated that the number of partners had decreased and 3% that the number had increased.

Six months after starting PrEP, 30% of users had been diagnosed with at least one sexually transmitted infection (soi). After twelve months, 50% had been diagnosed with one or more soi; 33% rectal soi, 33% chlamydia; 28% had gonorrhea and 5.5% had had syphilis[xviii].

The researchers behind this study could not conclude whether the real findings of soi among the participants are higher or lower than they would among people with a similar risk profile who do not use PrEP. However, other studies have shown that men seeking PrEP services tend to report more sexual partners and less condom use than average, so a relatively high prevalence of soi among those starting PrEP is common.[xix].

Costs and cost-effectiveness for PrEP

The current price for 30 Truvada® tablets in Norway is NOK 6,164. The price varies greatly from country to country, also within Europe. Truvada® will be patented in 2017, but it is currently uncertain what this may mean for access to cheaper generics in countries such as Norway.

It is difficult to predict how many within the target groups will want to use PrEP if this becomes available with a refund. Likewise, over how long a period or how many times the individual will use PrEP. Experience from the USA and France indicates that at the beginning of the implementation there were relatively few among the target groups who used the offer and that the majority of those (MSM) who use the offer use PrEP intermittently.

Depending on the method of use for PrEP (daily use or intermittent / on demand), the following cost images can be outlined for one year:

Continuous daily use 1 year **(205, 40 per issue x 365 days):**

Per person: 74,971 kroner

50 people: NOK 3,748,550

150 people: 11,245,650 kroner

200 people: 14,994,200 kroner

Intermittent / on demand **(ex. 4 tbl x every 14 days (26 weeks / times per year) = 104 tbl per year:**

Per person: 21,361 kroner

50 people: 1,068,080 kroner

150 people: 3,204,150 kroner

200 people: 4,272,200 kroner

In addition to the medication costs, there are start-up consultation costs and checks every three months as long as the patient uses PrEP. If you think that start-up and check-ups are performed outpatiently in the specialist health service, you can use DRG code 918O as a basis, which as of today is NOK 1262 per consultation. If PrEP for people at high risk for HIV is considered as infection control assistance, cf. the Infection Control Act, the patient shall normally not pay a deductible of NOK 345. In that case, the outpatient clinic will receive a refund from HELFO corresponding to the deductible amount. In total, the amount will then be NOK 1,607.

4 inspections per year x 1607 kroner:

Per person 6428 kroner

50 people: 321,400 kroner

150 people: 964,200 kroner

200 people: NOK 1,285,600

Expenses for necessary tests and analyzes of, among other things, kidney function are in addition to this. The same applies to expenses for HIV tests and tests for other sexually transmitted infections. As for the latter tests, these are tests the target groups for PrEP are anyway recommended to take frequently.

In comparison, drug costs alone for the treatment of HIV infection are approximately NOK 100,000 per patient / year. According to figures from the Prescription Register, in 2015 just under NOK 350 million was spent on combinations of antiviral drugs for the treatment of HIV infection, distributed among approximately 3,600 patients. In addition, there are costs associated with regular inspections.

Drug treatment of HIV has a lifelong perspective. Beyond the financial situation, it is well documented that many HIV-positive people still experience a significant degree of psychosocial strain when living with a potentially infectious disease.

Some foreign cost-effectiveness analyzes have shown that a significant reduction in the price of Truvada® is necessary for PrEP to be considered cost-effective in a short-term perspective. However, every new HIV infection that can be avoided now will prevent the cost of health care and medication for many decades to come. It is therefore most relevant to assess cost-effectiveness in a long-term perspective.

A modeling carried out by British researchers indicates that Truvada® as PrEP can be cost-effective if it is prescribed to MSM who have had unprotected anal sex with five or more partners in the last three months or if the price of Truvada® is significantly reduced. [xx]. Another analysis has been performed by Public Health England. It concludes that even with current drug prices, PrEP will be cost-saving if given to individuals in groups with an HIV incidence of over 5.2% per year. This incidence corresponds to HIV prevalence among MSMs in the UK who have been diagnosed with at least one rectal soi per year.[xxi]. The same analysis concludes that cost-effectiveness is very sensitive to the cost of drugs, to one-year HIV incidence and patient compliance with treatment. Both of the two English studies find that PreP can be cost-effective for small (and not larger) high-risk groups of patients.

Truvada® is relatively highly priced in Norway compared to several other European countries.

It will be important in the future to follow the results from the implementation of PrEP in the USA and in France and from the many demo projects in Europe. Positive results showing a decrease in new infections will be relevant with regard to decisions on financing PrEP for people with a particularly high risk of HIV infection.

Model for possible Norwegian implementation

PrEP is used in Norway today, but the scope is uncertain and there is no clear public communication about availability or messages about who should consider PrEP. PrEP is prescribed by some infectious disease physicians in line withthe medical association's professional guidelines for HIV treatment, but there is no overall overview of the number of discharges and to which target groups. There are also a number of anecdotal reports from both professional and interest groups that more, mainly MSM, obtain PrEP on their own via the internet, from friends or by requesting a PEP cure (four-week cure with the same medication) which is then used as PrEP .

The Norwegian Directorate of Health invited relevant user and interest organizations in the field of HIV to a joint meeting on 3 May 2016 to discuss perspectives on PrEP and a possible Norwegian

implementation. [3]There was a broad consensus among the participants from the organizations that PrEP should quickly become an easily accessible offer for those with a significant risk of HIV, that there must be full reimbursement for treatment and follow-up and that a rollout should be anchored in a project that ensures good monitoring and documentation. Common position and messages among civil society actors in other countries have proved to be crucial with regard to a successful implementation of PrEP in the right groups of the population.

Olafiaklinikken is the country's largest low-threshold service and clinic for sexual health and HIV and they have for years had a special focus on MSM. Olafia is also the National Competence Service for Sexually Transmitted Infections and part of OUS, which has the country's largest environment of infection medics working with HIV patients. When rolling out a public PrEP offer, the Norwegian Directorate of Health believes that it would be natural to anchor this at the Olafi Clinic. The clinic is well placed to reach the main target groups, which are MSM, mainly in Oslo. Olafia is also well placed to ensure quality and document an implementation of PrEP. Furthermore, the clinic can ensure that PrEP is also available to the target groups outside Oslo by providing guidance, skills development and guidelines to selected service providers, for example in the largest cities.

As previously mentioned, there is a large degree of international consensus on inclusion criteria and indications for PrEP. The National Institute of Public Health, in collaboration with the Norwegian Directorate of Health and relevant professional communities, has prepared proposals for inclusion criteria, contraindications and follow-up of patients who use PrEP. These are in line with, for example, WHO's and UNAIDS 'recommendations, as well as guidelines used in several other countries.

Financing

There is a long tradition in Norway that all infection control assistance to people who are infected with generally dangerous infectious diseases or are at particular risk of becoming infected receive free guidance, testing and treatment. This principle is based on both an individual and a public health perspective, where consideration is given to the individual's health and society's need to prevent the spread of a generally contagious infectious disease.

The Norwegian Directorate of Health recommends that this principle should be followed when implementing PrEP for groups that are at particular risk of HIV infection.

According to its wording, section 4 of the Blue Prescription Regulations seems to open up for reimbursement of PrEP "Benefits are provided for anti-infectious drugs for the prevention of generally dangerous infectious diseases in persons who, according to a professional assessment, are considered to be at particular risk of infection in Norway". How this provision is to be interpreted in more detail, not least in light of the basic conditions according to the National Insurance Act, Chapter 5, it will be up to the Ministry to decide.

[3]Participants in the meeting were the Health Committee for Better Gay Health, HivNorge, Nye Pluss, Foreningen Fri (formerly LLH), Aksept. The National Institute of Public Health, the Olafia Clinic and the Ministry of Health and Care Services also attended the meeting.

If a possible implementation of PrEP to special groups can be anchored at the Olafia Clinic, it should be considered to allocate grant funds from chapter 762 item 73 to support a follow-up project that ensures documentation and knowledge of effect from 2017 after further dialogue with the competence service.

Conclusion and recommendation

The Norwegian Directorate of Health believes that traditional HIV prevention, which is based on consistent condom use, easy access to condoms, knowledge and information, frequent testing for HIV and soy, early treatment of HIV and universal access to treatment, will continue to be the mainstay of prevention efforts against HIV and other sexual transmissible infections.

At the same time, there is a clear need to improve the effectiveness of HIV prevention for men who have sex with men (MSM). This is especially important for subgroups of MSM who are at particularly high risk of becoming HIV-positive, but who are not reached by or respond adequately to the prevention measures that exist today. By offering PrEP to MSM who are at particular risk for HIV, we will have an opportunity to reduce the transmission of the virus and thus reverse the increase in new HIV cases that have been seen in this population over several years.

PrEP can be a necessary and effective supplement in combination with other prevention efforts, given that the method is offered to the groups and individuals who have the greatest risk of becoming infected with HIV. Based on the current knowledge base about PrEP, this primarily applies to MSM and trans women who may be exposed to a particularly high risk of infection. Serodiscortant couples of all genders should be able to be assessed individually, especially until the HIV-positive partner is well treated.

Achieving the desired effect of access to PrEP for these target groups depends on several factors; clear messages about PrEP and who can benefit most from it, gradual acceptance of PrEP in the relevant target groups and low-threshold enrollment in PrEP treatment. A robust system for monitoring at individual and national level must be in place to document the effect of this measure. To ensure a good implementation where the need is epidemiologically greatest, namely Oslo, it is recommended that the offer of PrEP be anchored at the Olafi Clinic, OUS. The clinic is also the National Competence Service for HIV and sexually transmitted infections and will thus be able to play a key role in the preparation of professional frameworks and inclusion criteria for PrEP so that an equal offer can quickly be provided in large parts of the country.

To ensure access to PrEP for the relevant target groups, as well as to avoid social inequality, treatment and follow-up should be free of charge for those who meet the inclusion criteria. This will mean that the medicines for PrEP and necessary health care in connection with the use of PrEP are covered in accordance with ordinary regulations for benefits and reimbursement.

[i]Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010; 363 (27): 2587-99.

[ii]Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012; 367 (5): 399-410.

[iii]McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomized trial. Lancet. 2016; 387 (10013): 53-60.

[iv]Molina JM, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. N Engl J Med. 2015; 373 (23): 2237-46.

[v]Okwundu CI, Uthman OA, Okoromah CA. Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals. Cochrane Database Syst Rev 2012; 7: CD007189.

[vi]European Medicines Agency (EMA). First medicine for HIV pre-exposure prophylaxis recommended for approval in the EU. 2016.http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/07/news_detail_002578.jsp&mid=WC0b01ac058004d5c1

[vii]World Health Organization. Global health sector strategy on HIV, 2016-2021. World Health Organization, 2016.

[viii]World Health Organization. Guideline on When to Start Antiretroviral Therapy and on Pre-Exposure Prophylaxis for HIV. Geneva: World Health Organization, 2015.

[ix]European AIDS Clinical Society. EACS guidelines version 8.0, 2015.www.easociety.org

xUnited States Centers for Disease Control and Prevention. Pre-exposure prophylaxis for the prevention of HIV infection in the United States, 2014. Atlanta: CDC, 2014.

xiNorwegian Association for Infectious Disease Medicine. The Norwegian Medical Association. Professional guidelines for follow-up and treatment of HIV, 2016.www.hivfag.no

xii United Nation. Political Declaration on HIV and AIDS: On the Fast-Track to Accelerate the Fight against HIV and to End the AIDS Epidemic by 2030. New York, 2016

xiiiNoori T, Pharris A. Meeting report: Pre-exposure Human Immunodeficiency Virus Prophylaxis in the EU / EEA: Challenges and Opportunities, Stockholm April 2016. Euro Surveill. 2016; 21 (25): pii = 30263.

xivSmith DK, et al. MMWR. 2015; 64 (Early release): 1-6)

[xv]European Center for Disease Prevention and Control. Annual epidemiological report 2014 - sexually transmitted infections, including HIV and blood-borne viruses. Stockholm: ECDC; 2015.

xviMalek, Mitchell et al. Euro Surveill. 2015; 20 (15): http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=21093

xviiJakopanec I, Grjibovsk AM, Nilsen Ø, Aavitsland P. Syphilis epidemiology in Norway, 1992-2008: resurgence among men who have sex with men. BMC Infectious Diseases. 2010; 10: 105. DOI: 10.1186 / 1471-2334-10-105

[xviii]Volk JE, Marcus JL, Phengrasamy T, et al. No new HIV infections with increasing use of HIV preexposure prophylaxis in a clinical practice setting. Clin Infect Dis 2015; 61: 1601–3.

[xix]Grant RM, Anderson PL, McMahan V, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. Lancet Infect Dis 2014; 14: 820–9.

[xx] McCormackk S, Gill ON, Nardone A, et al. Is pre-exposure prophylaxis for HIV prevention cost-effective in men who have sex with men who engage in condomless sex in the UK? Sex Transm Infect 2015; 91: O1.

xxiOng KJ DS, Desai M, Nardone A, van Hoek AJ, Gill ON. Will HIV PrEP given to high-risk MSM in England be cost-effective? Preliminary results of a static decision analytical model. Public Health England Conference; Coventry.2015.