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The provision of Pre-exposure prophylaxis in a Norwegian setting

A cost-utility analysis of PrEP-provision to MSM with different incidence rates.

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The provision of PrEP in a Norwegian setting

-A cost efficiency analysis of PrEP to MSM that are at a high risk of acquiring HIV

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Abstract

Background: There is a need for evidence concerning the cost-efficiency of PrEP in a Norwegian setting, as it became available to MSM at risk of acquiring HIV in 2017 and no CUA has been performed on the subject for a Norwegian setting.

Objective: The main objective of this thesis is to inform relevant decision-makers of the relationship between yearly HIV incidence rates, and the potential cost-efficiency of PrEP for MSM that are at high risk of acquiring HIV.

Methods: The cost-effectiveness of providing daily PrEP to 35 year old MSM for three different incidence rates of HIV were analyzed using three state-transition Markov models. The model used a 45 year time horizon, emulating a life time perspective. Three different incidence rates were used, 1.8 %, 3.0 % and 5.2 %. A WTP-threshold was used utilizing the absolute shortfall approach where the WTP is contingent on the calculated severity of HIV as a condition. The analysis was performed from a health care perspective.

Results: For the estimated WTP-threshold of 275 000 NOK PrEP would be cost-saving compared to the option of not providing PrEP for an incidence rate of 5.2%. The provision could be cost-effective for an incidence rate of 3%, but is not found cost-effective for MSM with a yearly incidence rate of 1.8% or lower. The sensitivity analysis showed that the analysis is robust for small changes in parameters. The value of information-estimates indicated that there is large potential savings to be made from more research for incidence rates of 3% and lower.

Conclusion: Based on the results of this analysis PrEP is found to be cost-effective for MSM with a yearly incidence rate higher than 5.2 %. There is considerable uncertainty concerning the provision of PrEP for incidence rates of 3% and lower, and further research is therefore recommended.

List of abbreviations:

AIDS:	Acquired immune deficiency syndrome
ART:	Anti-retroviral therapy
CEA:	Cost-efficiency analysis
CEAC:	Cost-efficiency analysis curve
CEAF:	Cost-efficiency analysis frontier
CUA:	Cost-utility analysis
DRG:	Diagnosis related group
EU:	European Union
EVPI:	Expected value of perfect information
FTC:	Emtricitabine
GBD:	Global burden of disease
HIV:	Human immunodeficiency virus
HPV:	Human papillomavirus
HRQoL:	Health related quality of life
ICER:	Incremental cost-efficiency ratio
INSTI:	Integrase strand transfer inhibitor
MSM:	Men who have sex with men
NDH:	Norwegian directorate of health
NNRTI:	Non-nucleoside reverse transcriptase inhibitor
NMB:	Net monetary benefit
NoDA:	Norwegian doctors association
NRTI:	Nucleoside reverse transcriptase inhibitor
PeP:	Post-exposure prophylaxis
pEVPI:	Expected value of perfect information for the population
PrEP:	Pre-exposure prophylaxis
PI:	Protease inhibitor
PY:	Person year
STI:	Sexually transmitted infection
TASP:	Treatment as prevention
TDF:	Tenofovir disoproxil fumarate
WHO:	World health organization
WTP:	Willingness to pay
QALY:	Quality adjusted life year
QoL:	Quality of life
RAVN:	Report on anti-viral therapy in Norway

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1 Introduction

The objective of this paper is to perform a cost-utility analysis (CUA) of the provision of pre-exposure prophylaxis (PrEP) to a cohort of 35-year-old men who have sex with men (MSM) that are in high risk of acquiring the human immunodeficiency virus (HIV). HIV is a complex virus that affects the immune system and has since the start of the epidemic in the early 80s infected over 6000 individuals in Norway. HIV was prior to the introduction of anti-retroviral therapy (ART) in the late 90's expected to lead to immune system-breakdown and would in most cases lead to death within 10 years. ART suppresses the virus and stops the progression towards immunodeficiency, and HIV is today largely considered a chronic condition given that the infected follows the prescribed treatment regimen. MSM is a group that is disproportionally overrepresented in Norway in terms of who gets infected with HIV. MSM is believed to consist of 2-7 % of the population and has accounted for 33% of all HIV-infections in Norway [1, 2]. The Norwegian directorate of health (NDH) evaluated in 2016 the possibility of introducing PrEP as an additional prevention tool offered to MSM at a high risk of acquiring HIV, and concluded that PrEP ought to be implemented with a basis in the communicable disease regulations (blåreseptforskriften) which states that people at high risk ought to get preventive treatment. The final recommendation was that PrEP ought to be offered to individuals at a high risk of acquiring HIV. Additionally the treatment was recommended to be fully reimbursed with no co-payments for those who receive PrEP in order to ensure equity. Norway, as the second country in Europe, started to provide PrEP to MSM in January 2017. However, as the NDH-recommendation put less weight on the cost-effectiveness the provision of PrEP became the subject of debate with regards to the expected costs and benefits from the provision of this drug [3]. Others argued that the alternative costs from providing PrEP was to large, and that the money could be better spent elsewhere [4]. This thesis will examine these claims, and provide evidence on the cost-efficiency of PrEP-provision in a Norwegian context.

1.1 The chapters

The second chapter contains background information concerning risk factors, etiology and the epidemiology of HIV. The chapter looks at how HIV is prevented today, and take a closer look at PrEP with regards to the current evidence, risk compensation and the different

regimens that are available. Finally the chapter gives an introduction to how the Norwegian health system prioritizes between different conditions, what criterion that are considered when evaluating different treatments, and the willingness to pay for that treatment.

The thesis third chapter outlines the methodological framework used in order to perform this analysis. It explains the patient population that is being examined, the choice of model and also outlines how the model is structured. The chapter then takes a further look at what the health outcomes are and the choice of time horizon and cycle length. After that the chapter outlines the central elements of the analysis itself with regards to the willingness to pay, uncertainty and the sensitivity analysis.

Chapter four is concerned with the inputs and materials used in order to construct the model and explains how the different parameters within the model have been chosen. The chapter then goes through how the transition probabilities for the different states have been chosen, in addition to how the different mortality rates have been created. Further the chapter looks at the different health states that are likely to occur in this pathway and the utilities gained from those. Lastly the chapter outlines the relative risk reduction that occurs from PrEP and the costs used in the model.

Chapter five concerns itself with the results of the analysis and looks at the costs and effects of the treatment at different points in time in addition to look at the deterministic cost effectiveness. A large part of this chapter is dedicated to the deterministic and probabilistic sensitivity analysis performed in order to account for the uncertainty within the model.

Chapter six is the discussion part of the thesis where the main findings are summarized, and put in context to previous research. There is additionally provided an interpretation of the results, as well as the limitations of the model is explained.

In chapter seven the conclusion of this thesis is presented.

2 Background

This chapter aims to provide the necessary background information in order to better understand HIV as a condition, the patient population group, their condition and its treatment. Furthermore this chapter examines how HIV is prevented, and managed. There is extra weight put on PrEP and factors that are important to take into account when evaluating the provision of PrEP. Lastly this chapter looks at how the Norwegian health system prioritizes between different interventions and a framework is introduced in order to quantify the severity of being HIV positive and how this could affect the willingness to pay (WTP) for PrEP.

2.1 HIV

The human immunodeficiency virus (HIV) is believed to have spread to humans from non-human primates. The disease came into the public eye in the 1980s as homosexual men in urban centers across the world, but especially in the US, started to experience an immunodeficiency stemming from a virus never seen before. This condition became known as acquired immune deficiency syndrome (AIDS) which was later found to be an advanced stage of HIV, and is transmitted through contact of infected body fluids with mucosal tissue, blood or broken skin. HIV is a retrovirus meaning that the virus integrates its own RNA using existing cells in the host body through a mechanism called reverse transcription. The virus primarily targets $CD4^{+}$T cells and causes a loss of these cell over time that if left untreated will typically lead to progressive immune system failure, AIDS and most common death within ten years. Although, some progress faster, and some slower [5].

2.1.1 Risk factors, etiology and epidemiology

HIV has infected over 75 million people since the 1980s, and today around 36.7 million people live with the virus. There are over 450 000 reported cases of HIV since the start of reporting within the EU, 101 000 cases in the UK, and 6277 cases in Norway. The highest risk of transmission is receptive anal sexual intercourse, followed by insertive anal sexual intercourse and sharing of injecting drug paraphernalia [5, 6]. In most regions of the world, certain groups are more likely to attract HIV. The key populations are MSM, intravenous drug

users, people in prisons and other closed settings, sex workers and transgender people. This is reflected when looking at the HIV surveillance data for Europe from 2016 where the highest proportion of HIV diagnoses was reported to be in MSM (40%), with heterosexual contact the second most common transmission mode (32%), and transmission due to injecting drug use accounted for 4% of HIV diagnoses. However, for 23% of new HIV diagnoses the transmission mode was not reported or was reported to be unknown indicating that the MSM-proportion of HIV diagnoses could be higher than reported. 40 % percent of those diagnosed in the EU/EEA in 2016 were migrants, defined as originating from outside of the country in which they were diagnosed. However, this varied widely from 80% of cases in Sweden to less than 5% of cases in Bulgaria, Latvia, Lithuania, Poland, and Romania [7]. A high proportion of HIV infections originating from migrants is also the case in Norway, where 51% all new cases originated from individuals born outside of Norway in 2017. When it comes to transmission of HIV within the EU, men who have sex with men (MSM) has been the most vulnerable population. In the UK 47 000, (46.5%) [8], and in Norway 2077 (33%) of all HIV infected has been MSM [2]. The increased risk of acquiring HIV for MSM compared to the general population is ascribed to a relatively higher probability of transmission during receptive anal sexual intercourse, a higher number of exposures, and smaller sexual networks [5].

2.2 Disease prevention

The Norwegian guidelines for follow-up and treatment of HIV recommends condom use, post-exposure prophylaxis (PeP), pre-exposure prophylaxis (PrEP), and treatment as prevention (TASP) in combination with frequent screening of people at high risk of attracting HIV as preventive measures against HIV. Condom use by men has been a cornerstone of HIV prevention, as perfect use should completely prevent HIV transmission, as well as transmission of many other sexually transmitted diseases. However, condoms have been estimated to be approximately 80% effective against heterosexual transmission of HIV and 70% effective for male-to-male sexual transmission. This less than perfect protection is generally believed to be a consequence of over-reporting and incorrect use [5]. However, condoms aren’t used too often and was found to be insufficient as a preventive measure against HIV alone during the 80´s and 90´s [9].In addition to condoms, PeP is provided after the fact when the risk of attracting HIV is high. PeP is an antiviral therapy consisting of

Isentress and Truvada that is provided as fast as possible after a significant risk of HIV infection has occurred. The treatment will be administered for 4 weeks after the incident [6]. TASP is another preventive measure that has become more favorable in the later years. The goal is to initiate ART as early as possible, as initiation with a $CD4^+$T count above 500 cells/mm^3 compared to initiation below 500 cells/mm^3 has been shown to reduce the risk of progression to AIDS and subsequently death. It further has been shown to reduce the risk of developing non-AIDS-defining illnesses, while at the same time increasing the likelihood of immune system recovery. In addition, high-quality evidence from one randomized controlled trial indicated that earlier ART can markedly reduce the risk of sexual transmission to HIV-negative sexual partners. In Norway ART is recommended as soon as possible, for all CD4-counts[6, 10].

2.3 PrEP

PrEP is usually administered to MSM at a high risk of attracting HIV. Indicators for being at high risk is defined by the Norwegian Doctors Association (NoDA) as unprotected anal sexual intercourse with several partners, with a self-reported high chance of repetition, in addition to a confirmed STD or need for PEP within the last 12 months and sexual intercourse under the influence of a substance[6]. In January 2017 PrEP became available to MSM in Norway that are at high risk of acquiring HIV. Norway was the second country in Europe that provided this drug fully reimbursed after France. PrEP is specifically provided to MSM as MSM is at a higher risk of acquiring HIV compared to the general population [1, 2, 11-14]. Furthermore, the efficacy of PrEP is believed to be higher for MSM as the concentration of the active substance in Truvada, TDF/FTC, has a concentration that is between 10 and 100 times higher in the anal tissue compared to vaginal tissue, which is believed to increase the protective capabilities of the substance [5].

2.3.1 The current evidence

Several studies have been performed on the efficacy of Truvada as a pre-exposure prophylaxis for MSM with an estimated efficacy ranging from below 30% up to 97%. The largest and most cited studies relevant for a European setting are the iPrEx, IPERGAY and PROUD-studies. The iPrEx-study from 2010 was a randomized controlled trial with 2499 MSM and

transgender male-to-female adults in Peru, Ecuador, Brazil, South Africa and the US. The participants were either administered Truvada or a Placebo, and there was a follow up every four months including an interview, HIV testing, risk reduction counseling, adherence, pill count and dispensing of pills. The risk reduction was estimated to be around 44%. However, the efficacy increased to 73% for those with a reported adherence larger than 90%, and to 92% for those participants who had detectable drug levels.[15]. Two studies were performed in Europe in 2016. The PROUD-study took place in England and enlisted 544 HIV negative MSM. The participants were randomly assigned to daily Truvada or deferred to a waitlist. There was a three month follow up with HIV testing and screening for other sexually transmitted infections (STIs). The study was halted after six months, and everybody participating in the study was provided PrEP as the differences in HIV incidences between the groups was so large that it was not considered ethical to continue the study. The efficacy of PrEP was in this study estimated to be 86%. The HIV incidence of the "no PrEP"-group was markedly higher than the average MSM and was estimated to 9 per 100 person years (PY) [16]. A third much cited study was the IPERGAY-study from France. This study enlisted 400 participants to an on demand regimen of Truvada or a placebo. This study also showed a relative risk reduction of Truvada for MSM to be 86%. The difference in efficacy between studies seems largely to be connected to differences in adherence between patient groups. The World health organization (WHO) argues in their guidelines from 2015 that PrEP should be provided to populations with a HIV-prevalence of 3 per 100 PY [17]. In the recommendation from the NDH the incidence rate suggested for when PrEP could be cost effective was 5.2 per 100 PY [1].

2.3.2 Daily or event-driven

PrEP can be taken daily with one pill of Truvada a day or event-driven where two pills are taken 2-24 hours before sexual contact, and then one pill a day until the high risk exposure has ended. Then the person takes one pill 24 and 48 hours after last exposure. NoDA recommends both daily and event driven PrEP in order to be flexible with regards to each individuals' sexual activity [6]. This need for flexibility is highlighted by the fact that the proportion of individuals that gets infected within Norway is quite low. In 2017, only 37 of 88 (42%) of all MSM-related infections happened within the Norwegian borders. This could indicate that the provision of event-driven PrEP might be the most appropriate mode of

provision for a large proportion of Norwegian MSM where the risk of HIV-acquisition is very high for short periods of time, but maybe moderate to low while in Norway.

2.3.3 Risk compensation

A much expressed concern in the literature on PrEP is a potential increase in risk behavior owing to an overestimated feeling of safety from PrEP. This could be a critical problem for implementing PrEP in current HIV prevention strategies as it could lead to higher rates of other sexually transmitted infections (STIs). This would in turn increase the risk of acquiring HIV, as an existing infection increases the likelihood of acquiring HIV [18]. However, there is no current evidence to support the claim that PrEP systematically leads to risk compensation [19]. Additionally, there has been shown reductions in STIs such as gonorrhea in the UK among MSM, which is believed to a result of more tests for HIV and STIs being performed as consequence of both TASP and increased PrEP use [20]. It is worthwhile to mention that there has been observed an increase in gonorrhea and syphilis incidences in 2017 for MSM in Norway compared to previous years, at the same time been a reduction in MSM HIV-incidences. This developing trend makes it hard to rule out that there could be some increase in risk behavior associated with the provision of PrEP for the Norwegian MSM-population [2].

2.4 Disease management

Since the mid-90s HIV has been treated with ART. Although not a cure, it creates a viral suppression of the virus to the point where the loss of CD4-cells is stopped, and the immune system recovers much of its lost function. If full viral suppression is met, and the infected reaches CD4 counts larger than $500mm^3$ the mortality rate is expected to be similar to that of the general population within five years [21]. However, a successful HIV-treatment with viral suppression requires patients to take their medicines every day throughout their lives to avoid treatment failure. Antiretroviral therapy spans five different classes which all target different stages of the life cycle of the virus. These are nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs) and protease inhibitors (PIs) NRTIs act by blocking an enzyme called

reverse transcriptase which tries to copy the HIV-virus, effectively negating the virus ability to replicate. NoDA recommends tenofovir alafenamide/emtricitabin (TAF/FTC) or abacavir/lamivudine [5, 6]. NNRTIs inhibit reverse transcriptase in a manner that is very different from the NRTIs. These drugs bind to a pocket near the active site, which causes a change in the reverse transcriptase enzyme which effectively stops the replication of the virus. As a class, the NNRTIs are potent, safe and easy to produce (making them affordable). When used by adherent patients as a part of three-drug regimens, these drugs have proven to be very effective [5, 6]. INSTIs prevent the HIV genome from being integrated into the host genome. As a class, these drugs are potent, well tolerated and safe [5, 6]. PIs block the later steps in the virus life cycle. These drugs are rapidly metabolized by the liver and are often co-administered with drugs that are called boosters [5, 6]. NoDA recommends several combinations of these drugs to be administered to people infected with HIV. These combinations are typically a combination of 2 NRTIs with a supplementary pharmaceutical such as an INSTI, NNRTI or PI with a booster. [6]. A person that has been diagnosed with HIV will, in addition to be offered ART, be offered psychosocial counseling, given information about rights and challenges linked to the condition, in addition to vaccines, and asked to come in for controls at least once every 12 months [6]. The report on usage of antivirals and the occurrence of antiviral resistance in Norway (RAVN-report) from 2017 show that just over 4100 individuals received ART in 2016, and the most common combination therapy used in the treatment of HIV is a fixed NRTI-combination of tenofovir disoproxil and emtricitabine (TDF/FTC). This is the same combination that is used as PrEP. This combination has seen a decline in recent years in favor for a combination of a new prodrug of tenofovir called tenofovir alafenamide (TAF) that has been introduced in three different combinations. It is one 2 component NRTI-combination consisting of FTC and TAF, one 3 component combination of FTC, TAF and rilpivirine, and a 4-substance combination of FTC, TAF, elvitegravir and cobistat. The argument for these new combinations is that they use lower doses and have higher bioavailability in the relevant body tissues compared to TDF. The second most used combination in 2016 was a NRTI-combination of lamivudine and abacavir with an additional INSTI, dolutegravir [22].

2.5 The MSM population and HIV incidence rates

MSM as a group includes homosexuals, bisexuals and people that define themselves as heterosexual or other and sometimes has sex with men. MSM is therefore a complex, non-homogenous group and it includes a large range of different people with different lifestyles. A central challenge when evaluating the cost-effectiveness for a drug that is mainly administered to a cohort of MSM is to define a base case as the size of the population is largely unknown. The existing evidence on HIV prevalence in the MSM population is a consequence sparse. However, there was performed one net-survey in 2007 with 2430 respondents, and the European MSM internet survey (EMIS) from 2009 had 2096 respondents from Norway. The results in these two net surveys differed vastly with the one from 2007 reporting the equivalent of a yearly incidence rate of HIV of 1.72% (42 out of 2430) and the one from 2009 reported a yearly incidence rate of 0.19% (4 out of 2096) [23, 24]. Another article from 2013 used the numbers from EMIS in order to calculate the most likely size of the MSM population in 38 different countries, and among them Norway. The writers of this article estimated that the total Norwegian MSM population would be just over 47 500 individuals, or 3.6% of the total population giving a HIV prevalence of 0.185% for the MSM population as a whole. The writers of the article do however argue that a MSM population above 3% of the total population is larger than expected and that there might be uncertainty in the estimates due to a small sample sizes [25].

2.6 Priority setting

As the Norwegian health sector has become characterized by increasingly constrained budgets the need to prioritize activity after clear and well thought out principles has become evident. The consequence of constrained budgets is that a decision to provide a treatment to one group very likely entails an implicit choice of not providing treatment to another group. In the context of this thesis, the resources spent in order to ensure the provision of PrEP as a prevention measure against HIV most likely has an alternative use, such as the provision of HPV-vaccines for young men [4]. In order to ensure that the provision of PrEP is resources is well spent, it has to be evaluated on equal terms as other alternative treatments after a certain set of standardized criteria. The existing criteria on prioritization has been developed over three prioritization-groups since the 90's, popularly referred to as the Lønning I-, Lønning II- and the Norheim-group. The latest report on prioritization was delivered by the Norheim-

group in 2014, and stated that the goal of the Norwegian health system is to achieve "as many good life years as possible for all, distributed fairly". This statement was an amendment from a previous priority-setting report, Lønning I from 1991 which stated that the goal of the health sector should be to provide "more good life years for all". This amendment highlighted the increased necessity of ensuring equity within the provision of health services in Norway. The Norheim-group recommended three overarching criteria to be used for priority setting in order to ensure the desired balance between equity and efficiency. These were the health benefit-, resource- and health loss-criteria. The health benefit criteria states that the priority of an intervention will increase with higher expected health gains. The consequences of health gains are often increased time of survival, and increased health related quality of life (HRQoL). Survivability and HRQoL are often combined to one measurement of life quality, namely quality adjusted life years (QALY), which will be looked closer at in chapter 3. The resource criterion is concentrated around the expected amount of resources that is required for implementing an intervention. A health intervention is expected to have higher priority the less resources it is believed to require, as the alternative cost often will be lower. The combination of the health benefit and resource criteria could result in a cost-utility criterion. However, while the Norheim-report acknowledges the utility of cost-effectiveness-analysis (CEA), it does not recommend it as a strict priority criterion on its own. The reasoning behind this is that some factors that are potentially difficulty to quantify, such as benefits related to information, dignity, relief of burden on next of kin, future productivity and resource use ought to be taken into consideration as well, not just the cost-efficiency of the intervention. The last criterion, the health loss-criteria, emphasizes the severity of health loss of the individual patient as central for priority setting. The health loss-criteria is argued with a basis in the principle of equity where it is acknowledged that health benefits becomes more important the worse off the beneficiary is when receiving treatment. The Norheim-report argued that one ought to use a lifetime perspective when evaluating the expected health-loss. It was furthermore recommended that the trade-off between health gains and resource use ought to be evaluated with a basis in the fraction between the two criteria where the priority of an intervention decreases with a higher fraction. The health loss is suggested to be evaluated in relation to the health gain and resource use, where the size of the expected health loss would place the condition in one of three health loss-classes which each has its own weighted willingness to pay (WTP). The provision of PrEP to MSM that are in high risk of acquiring HIV is a preventive measure where the benefits are expected to be a reduction in the

number of HIV infections in Norway, which is believed to increase both the HRQoL of the individuals at risk of HIV and over time reduce costs related to HIV [1]. When evaluating the prioritization of preventive measures the Norheim-report recommended to utilize the framework proposed above, where the expected benefit is looked at in relation to the expected cost subject to a constraint provided by the severity of expected health loss [26].

2.7 Quantification of severity

The Norheim report did give a framework as it could be possible to look at the severity of health loss and its place in priority setting, but it was never operationalized. As a consequence a workgroup, commonly referred to as the Magnusson-group, was established in 2015 by the Norwegian Department of Health. The group was asked to evaluate and operationalize severity as a factor in priority setting. The final recommendation was presented later in 2015 and recommended that the severity of a condition ought to be evaluated with basis in:

- The risk for death or loss of function
- The degree of physical or psychological loss of function
- The level of pain, physical or psychological discomfort

The workgroup considered four different approaches to the operationalizing of severity, and recommended in the end the absolute shortfall approach. This approach measures the amount of QALYs lost as a consequence of a potential early death and reduced HRQoL in the period of illness, and quantifies the severity of the disease based on the calculation [27].

2.7.1 Absolute shortfall as a quantification of severity

Absolute shortfall describes how many future years of living one could expect as a consequence of a disease or condition. Absolute shortfall is calculated from the amount of QALYs that are expected to remain from the condition. An example of how the absolute shortfall is calculated:

*A group of 35 year old men is suffering from a chronic condition where the HRQoL is reduced from 1 to 0.8. The absolute shortfall will be the remaining years of survival multiplied with the loss of HRQoL per year (1-0.8 = 0.2). In our example the absolute shortfall is 9 (0.08 * 45).*

The workgroup recommended in line with the Norheim-reports recommendation that there ought to be a weighted relationship between the severity of health loss, calculated from the absolute shortfall approach, and a WTP-threshold. See table 1 for an overview of the absolute shortfall

Table 1: Relationship between absolute shortfall and WTP per QALY

Group	1	2	3	4	5	6
Absolute shortfall	0 - 3.9	4 - 7.9	8 - 11.9	12 - 15.9	16 - 19.9	20+
Weight	1	1.4	1.8	2.2	2.6	3
Upper limit (1000 NOK) WTP per QALY	275	385	495	605	715	825

**Source: På ramme alvor, alvorlighet og prioritering (2015)*

It is worth to mention that the whitepaper from 2015 emphasized that the severity criteria as presented here should be taken into account together with other criteria such as the costs, benefits and the relationship between the two.

3 Methods

3.1 Patient population

The model is calibrated for a cohort of MSM at age 35 that are at high risk of acquiring HIV for the next five years as a baseline. This is because the median age for acquiring HIV for MSM in Norway the last ten years has been 35 years [2]. Two scenarios is observed, one where PrEP is not provided, and one where PrEP is provided for three different HIV incidence rates.

3.2 The choice of model

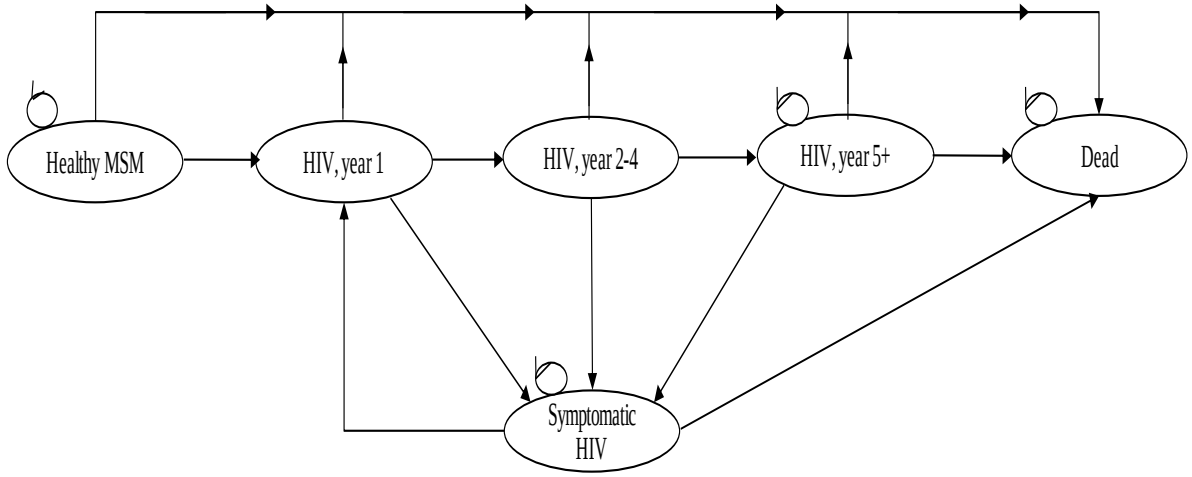
A Markov model has been constructed in order to compare the long-term consequences, in terms of costs and QALYs, of implementing PrEP as a preventive measure for HIV in a Norwegian setting. A Markov model is structured around mutually exclusive health states, which each represents a possible outcome at a given point in time. It is because of these features such a model is well suited to capture the central characteristics related to a HIV-pathway, which includes a transition from healthy to HIV positive, the lifelong treatment of ART, the probability of worsening life states, and increased mortality rates associated with acquisition of HIV and increasing age [28]. One characteristic of the HIV-diagnosis is the increased but decreasing mortality rates that arise the first years after acquisition of HIV [21, 29]. One of the disadvantages of a state-transition model such as a Markov model is that the current state is not dependent of time spent in a previous state. Consequently, changes in mortality rates will not be captured in a traditional Markov model. This problem was addressed by constructing several tunneling states where the individual progressed, with no retention in current state, to the next state with changes in the mortality rates in the years after HIV acquisition [29].

3.2.1 Overview of model

At the initial time period a cohort of 35-year-old MSM at a high risk of acquiring HIV is observed while being assigned to one out of two treatment scenarios, one being offered PrEP, the other not being offered PrEP. Each individual starts out healthy in health state “Healthy”. For a given probability, based on the HIV-incidence rate, the individual either stays in the

initial health state or transitions to health state "HIV_1" or "Death". "HIV_1" signifies the first year of being HIV positive. The individual received ART early after transmission and has a CD4 count larger or equal to 500 cells/mm^3. If found HIV positive the person will move through a tunneling state over the next four years to state "HIV_{5+}", which is signifies being HIV positive with CD4 count larger or equal to 500 cells/mm^3 for a time period over five years. The mortality rates are higher in the first years compared than in the general population in the tunneling state but falling. The mortality rate for state H_{5+} is equal to that of the general population. For each HIV positive state there is a probability of transferring to state "Symptomatic HIV", or "Death". State "Symptomatic HIV" signifies a CD4 count less than 500 cells/mm^3 and represents all treatment failures that faces HIV positive individuals, in this state the individual either returns to state HIV_1 or progresses to "Death". "Death" is a cumulative state and is the end point of the model. A graphic presentation of the model is presented in figure 1.

Figure 1: Overview of the transition states in the model



3.3 Health outcomes

This analysis' primary health outcome is quality-adjusted life years (QALY) as recommended by NoDA [30]. QALY is a health metric that combines two components of health: survival and a weight reflecting the HRQoL and is calculated through multiplying the weighted life quality from being in one or several state(s) with the time spent in that state. HRQoL typically range from 0 (death) and 1 (perfect health). A QALY of 0.72 indicate that a year in that state is worth 0.72 of a year with perfect health. A state with less than 0 would signify a year in a

state worse than death [31, 32]. HRQoL is mostly scored using two approaches. The first is using pre-scored health state classification instruments, and the second is through estimating preference scores directly from the participants' preferences for their own health [31]. The model utilizes QALYs as a health effect measurement. The values for each health state has been estimated from the Global Burden of Disease study (GBD). In this study the HRQoL has been calculated from pre-scored health state classification instruments from 195 different countries resulting in a aggregated estimate of the burden of disease [33].

3.4 Perspective

The model assumes a healthcare sector perspective where the incremental cost-effectiveness ratio (ICER) is reported for the deterministic results, and the net monetary benefit (NMB) framework for a given threshold, is utilized for the reporting of the probabilistic results from the model. The model aims to include all current and future formal healthcare sector costs borne by the health care sector related to PrEP and HIV in the Norwegian health system. In Norway the provision of PrEP is covered under the public health insurance (folkehelsetrygden), ensuring no co-payment for the patients receiving both PrEP and ART. The health care costs associated with HIV and the provision of PrEP is the cost of pharmaceutical drugs, testing, outpatient visits, and HIV-related hospital admissions. The cost for Truvada has been gathered from the pharmaceutical pricing list. The cost for ART varies greatly between different regimes. The costs for ART in the model has therefore been calculated as the mean cost of the most used antiviral therapies used by HIV positive men in Norway. The data has gathered from the Norwegian pharmaceutical registry. In addition to pharmaceutical costs, there are costs associated with outpatient visits and hospital admissions from HIV related diseases. Outpatient visits are associated with tests for HIV and other STDs for those receiving PrEP, and tests on HIV-rna levels and CD4-counts in addition to testing of STDs for HIV positive. The costs for outpatient visits and HIV-related hospital admissions has been calculated from the diagnosis related groups (DRGs) presented in the activity-based regulations for 2018 by the NHD. The DRGs is weighted as a proportion to 1 DRG and is calculated from the mean cost associated with specific diagnosis groups. 1 DRG is in 2018 calculated to be 43 428 NOK [34]. The DRGs used in this thesis from main diagnosis group 18: Infectious- and parasitical-diseases. The costs associated with outpatient visits have been calculated from DRG-code 9180: "Outpatient consultation concerning infectious- and

parasite-diseases without significant procedures", which is given a DRG-weight of 0.032. For HIV-related hospital admissions the costs was calculated from the mean DRG-groups 489 and 490 for 2017 from Oslo university hospital (OUS). DRG 489 is "HIV with considerable HIV-related illness", and DRG 490 is "HIV with or without bi-diagnosis". DRG 489 is weighted at 2.77 DRG and 490 is weighted at 1.39 DRG [35].

3.5 Half cycle correction

In a Markov model transitions between states either happens at the start or the end of a cycle. This is not a very realistic assumption to make. Individuals can get HIV throughout the year, and will on average, as a function of the central limit theorem, transition between states closer to the middle of the cycle rather than at the end of it. Another consequence of assuming that transition between states happen at the start or end of the cycle is that costs or health outcomes becomes overestimated. As a means to counteract this, half-cycle correction is used in order to avoid over or under-estimating the model outcomes. The half-cycle correction is performed by calculating the mean of the second and first output value of the mean, and setting that as the first value. This is repeated for all successive outputs.

Eq.1. $$Value_{t+1} = \frac{Value_t + Value_{t+1}}{2}$$

3.6 Time Horizon

When modeling it is important that the appropriate time horizon is chosen in order to capture all important differences in consequences from the different interventions [32]. The Norwegian guidelines for economic evaluation recommend using the mean age of death when assuming a lifetime perspective. As HIV-treatment is life-long, the model assumes a time horizon of 45 years, ending when the cohort reaches an age of 80 years. Both the deterministic short-run and medium-run perspective will be reported in addition to the long-run perspective.

3.7 Discount rate

The future is uncertain, and in order to address this uncertainty the Norwegian guidelines for economic evaluation recommends to recalculate future costs and benefits to present value

through discounting at a rate of 4% for both future health benefits and costs [30]. This is performed through creating a "discrete-time" model where the present value of future outcome can be calculated as given by equation 2.

Eq. 2. $$\Delta O = \sum_1^T \left[O_j(t) - O_b(t)\right]/(1+i)^{t-1}$$

In equation 2 $O_j(t)$ is an outcome (cost or effect) in time period t for individuals that receive intervention j, in our case PrEP. $O_b(t)$ is the outcome for the group that receives the comparator, in our case that is no provision of PrEP. Here i is observed as the discount rate selected to convert future consequences to their present value [32].

3.8 Cycle Length

As HIV is a lifelong condition where progression between different states happens relatively slow a cycle length of 1 year has been chosen, as this keeps the number of cycles at a manageable level, as well as it still captures all clinically relevant effects over time.

3.9 Cost-utility analysis

Both the Norwegian guidelines on economic evaluation and the Norheim-group recommends to perform analysis which considers the relationship between costs and benefits from a treatment. One way of doing this is through a cost-utility analysis (CUA). CUA is essentially a sub-group of cost-effectiveness analysis (CEA) and is often referred to as such. The difference being that the outcome in a CUA is measured as the relative difference of costs and a utility measurement such as QALYs, a CEA can measure the difference in cost and any natural unit as long as it is equal for all interventions that looked at. The results of a cost-utility analysis are often reported through the ICER which is the relative size of differences in cost and effect between the interventions, given by equation 3.

Eq. 3. $$\text{ICER} = \frac{Cost\ A - Cost\ B}{QALY\ A - QALY\ B} = \frac{\Delta\ Costs}{\Delta\ QALY}$$

The ICER signifies here the relationship between the resource and the benefit criteria that was suggested in the Norheim-report.

3.10 Absolute shortfall

Absolute shortfall is the expected future loss of health years from a given health state. In this analysis the loss of health years is presented through QALYs, where the severity of the health state is corresponding to the amount of QALYs lost.

The severity of acquiring HIV for the observed cohort is therefore calculated from the expected disutility from acquiring HIV multiplied with the expected remaining life years, as given by equation 4:

Eq. 4. $$Absolute\ shortfall_{HIV} = expected\ remaining\ life\ years * Disutility_{HIV}$$

Equation 4 gives the absolute shortfall for MSM with HIV. The absolute shortfall will in this thesis be used as reference-point for discussion, and is not suggested as an absolute WTP-threshold with respect to the decision question at hand.

3.11 Scenarios

The goal of this thesis is to inform relevant parties about the potential cost-effectiveness of providing PrEP to the part of the Norwegian MSM population that are at high risk of acquiring HIV. However, the consequences in terms of cost and effect from providing PrEP to MSM with different incidence rates of HIV is largely unexplored in a Norwegian setting, and what constitutes being at high risk is not very clearly defined in the literature. This thesis will therefore investigate the potential costs and effects from providing PrEP for three different scenarios. Each scenario simulates a cohort of MSM aged 35 with a given incidence rate, which has been selected from suggestions by WHO, and NDH in addition to a lower bound, which is an 1.2% lower than the median of 3% an incidentally almost equal to the highest

incidence rate found in a national net-survey. The incidence rates used for the different scenarios are 1.8%, 3% and 5.2%.

3.12 Uncertainty analysis

The model applied in this analysis is based on a certain set of assumptions and parameters. These parameters has been chosen through best judgement based on the available literature, public documents and personal communication with people that work with PrEP and HIV daily. Some of the assumptions that have been made in in order to perform this analysis might not reflect the real world perfectly. The analysis will therefore have some level of uncertainty associated with it, and sensitivity analyses have been utilized in order to measure, illustrate and evaluate the effects of the uncertainty within the model. The end goal of this thesis is to facilitate better decision making for those who work with the provision of PrEP at a daily basis. When doing modeling it is common to encounter four different types of uncertainty. There is variability, also referred to as stochastic uncertainty, which relates to the variance that exists between different individuals. Two different individuals might have the same probability of attracting HIV for a given point in time, but for some reason one, both, or none might attract HIV. This variance in outcome is referred to as the variability of outcome. Where unexplained differences in outcome for equal probabilities is referred to as variability, heterogeneity refers to the second type of variability in outcome which can be explained by some characteristic of the patient group, such as age, gender or preferences. As an example one could look at age and observe how different age groups might respond differently to different treatments. Another example of heterogeneity is how older individuals can have a higher probability of dying compared to younger individuals when facing the same diagnosis. These differences between age and effect or outcome are known as heterogeneity. The final form of uncertainty is concerned with methodological uncertainty, and refers to the uncertainty within our parameters and model as a whole. The parameter uncertainty refers to the chosen estimates for the parameters of interest and is analogue to the standard error of an estimate in regression analysis. If the number of observations used in order to calculate the parameter value is small, one could expect a larger parameter uncertainty. The parameter uncertainty goes down for a larger number of observations. The final form of uncertainty is model uncertainty, or structural uncertainty as it also called, which refers to the underlying assumptions in the decision model, and the degree the model reflects the real world [28, 32].

3.12.1 Deterministic sensitivity analysis

Deterministic sensitivity analyses are done in order to in order to explore the effect the individual parameter has on the output of the model. Several one-way sensitivity analyses were performed in order to check the effect of changes in one parameter, all other inputs constant, on the output of the model for four different prevalence of HIV. There was performed one-way sensitivity analysis on changes in prevalence of HIV in the MSM population, changes in costs for PrEP, ART, cost of outpatient visits and cost of hospital stays, in addition to changes in efficacy of Truvada as PrEP. It should be noted that a one-way sensitivity analysis only gives an indication of the potential importance of a parameter to the results of analysis and does not provide sufficient information to the decision-making question. This is largely because a one-way sensitivity analysis does not take into account the parameter uncertainty within the model, as such the changes in output does not say anything about the precision as to which the parameter was chosen [32].

3.12.2 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) has become a staple in economic evaluation, largely because of the limited value of deterministic sensitivity analysis. Where the deterministic sensitivity analysis changes the input value on one or two variables, for all other variables equal, the PSA characterize uncertainty in all parameters simultaneously. The PSA explicitly reflects the likelihood that the parameters take on a particular set of values and does through this quantify the decision uncertainty within the model. The PSA is performed through ascribing each parameter a probability distribution. The distribution represents the range of all possible values of that can occur, and the probability of that value occurring for each parameter. The model will then selects a value for each individual parameter based on the distributions and provide an output for a given combination of all parameter values. This process is performed a large number of times, in our case 10 000 times, providing a distribution of outputs that is dependent on the variability of the parameters within the model.

3.12.3 CEAC

The cost-effectiveness acceptability curve (CEAC) represents the probability of one of the treatments being cost-effective for a given cost-effectiveness threshold. The CEAC is based

on the net-monetary benefit (NMB) framework where the total effect and the total cost is used together with a given threshold in order to estimate the NMB, as presented in equation 4.

Eq.4 $$NMB = \lambda * E - C$$

The λ represents the willingness to pay (WTP) threshold, the E the total effect, and C the total cost. For all iterations the option with the highest net benefit is identified, and the probability of being cost-effective is equal to the proportion of iteration that had the highest benefit. The CEAC is constructed through plotting this proportion for given thresholds. The cost-effectiveness acceptability frontier (CEAF) is constructed through taking the mean NMB and plotting it the option that has the highest probability of being cost-effective for a given threshold, λ [36].

3.12.4 EVPI

In order to evaluate the expected cost of uncertainty, the expected value of perfect information (EVPI) has been calculated for different threshold values through calculating the difference between the expected net-benefit with current and perfect information. This is done through calculating the maximum net-benefit for each simulation from the PSA for a given set of values for the parameters. The mean is then taken over the maximum net-benefits for the given parameter value. The EVPI is the difference between the expected value of the decision made with perfect information about the parameters and the decision based on existing evidence. This is presented analytically through equation 5-7.

Eq. 5 $$max_j\, NB(j, \theta)$$

Eq. 6 $$E_\theta max_j NB(j, \theta)$$

Eq. 7 $$\text{EVPI} = E_\theta max_j NB(j, \theta) - Max_j\, NB(j, \theta)$$

Where j is the alternative interventions, θ represents the unknown parameter values, E the expected or the average value, max indicates that the value is maximized, an NB is the net-benefit. Equation 5 represents the max net-benefit for the current information, and equation 6 represents the max net-benefit from averaging the joint distribution of parameters [28].

3.12.5 pEVPI

The EVPI gives a value for the decision each time it is made at an individual level. However, the decision will be made several times for several individuals both now and in the future. It is therefore important that the EVPI is expressed for the total, discounted, population of patients that could benefit from additional information over the lifetime of the technology. The population EVPI (pEVPI) is given by equation 8:

Eq. 8 $$pEVPI = EVPI \sum_{t=1,2,\dots,T} I_t \,/(1+r)^t$$

Here T is given as the effective life time of technology which is the time over which information about the decision will be useful, r is given as the discount rate, and I_t is the expected number of incidences. The pEVPI is expressed for a range of WTP thresholds, where a low WTP will give a lower probability that additional information is likely to change the decision making outcome. This in turn results in a low pEVPI. The uncertainty surrounding a decision is highest at the point where the WTP and the ICER is the most equal. This will increase the pEVPI as the probability of error is higher around this point which in turn increases the probability of making a decision error. The pEVPI will as a consequence peak where the WTP is equal to the ICER, and decline again for all points where the WTP is higher than the ICER. This is because the intervention is expected to be cost-effective and the decision is not as likely to change from increasing the evidence.

3.13 Key assumptions

There has been made a number of assumptions in order to construct a model to evaluate the effect of providing PrEP to MSM at a high risk of acquiring HIV. The assumptions are the following:

Target population: The state transition model is looking at a cohort of 35 year old MSM that are at a high risk of acquiring HIV. The comparison is made between those who do not receive PrEP and those who receive PrEP.

Health outcomes: This state transition model is utilizing QALYs as the health outcome in order to capture the benefits from treatment and harms from living with HIV.

Perspective: A health care perspective was chosen in order to estimate the different costs borne by the health care sector from either not providing or providing PrEP to MSM that are at a high risk of acquiring HIV.

Treatment strategy: A cohort of 35 year olds will at the initial time period either not be provided or be provided with PrEP (no PrEP/ PrEP) for five years. The result of the model reports the health and cost outcomes associated with either no PrEP or PrEP.

Time horizon/Cycle length: A lifetime horizon of 45 years with a cycle length of a year was chosen for this model.

Quantification of severity: The absolute shortfall-approach was used as a reference point for a discussion concerning a potential WTP-threshold for the provision of HIV.

3.14 Software

All modeling and subsequent analysis was performed in Excel 2016. Macros were written in visual basic (VBA).

4 Input and material

4.1 Literature

The model inputs were gathered from literary sources such as articles, systematic reviews, and official national and regional guidelines. A literature search was performed using the search words “HIV”, “pre-exposure prophylaxis”, “PrEP”, “cost-utility”, “cost-effectiveness”, “Europe” and “Norway”. This resulted in 5121 hits. 254 articles were included after non-relevant articles were filtered out based on title. 124 articles remained after duplicates and non-relevant articles based on abstract were removed. Articles was deemed not relevant if they were looking at a dramatically different area in terms of socioeconomic standards, if they cohort was different than MSM, if they were looking into different subjects, if the questions asked already has been answered in other literature, and if they was looking at other treatments than PrEP. Other literature have been added to the literature list based on references from other articles, recommendations from professionals within the field. The recent literature regarding HIV in a Norwegian setting is very limited, and several parameters have been made relying on research from abroad. Several guidelines from Europe, the UK and Norway has additionally been added to the literature list, as well as national data mortality rates and costs. In total about 45 articles, books, and reports has been used on the subject of HIV, PrEP, cost-effectiveness and economic evaluation in order to write this thesis. The final material was largely selected based on the relevance of the article, the degree they had been previously cited, and the availability of sources concerning one or several questions that was relevant in order to write this thesis.

4.2 Distributions

A distribution was assigned to each of the inputs in order to facilitate a probabilistic approach where the uncertainty was represented. The transition probabilities were assigned Dirichlet-distributions, as these are well suited to capture the variation between dependent probabilities. Utilities and relative risk is given a Beta-distribution. Costs are assumed to increase exponentially with a long tail, indicating that a very large proportion of the costs will be concentrated around a small amount of services, operations, actions, which is well represented through Gamma-distributions. As the HIV-population is somewhat unknown, and the model

is based on extrapolation from results published in existing studies, the utility and costs are given a confidence interval equal to 80 %, in order to capture the potential variation in the parameters.

4.3 Transition probabilities

4.3.1 Probability of acquiring HIV

The transition probabilities used in order to estimate the HIV-prevalence in this model was based on estimates from WHO and the recommendation document regarding PrEP that was written in 2016 by the NDH. The estimate from WHO states that PrEP is expected to be cost-efficient for yearly HIV incidence rates larger than 3% and in the recommendation from NDH it was referenced a study from the UK where PrEP was expected to be cost-efficient for yearly incidence rate of 5.2% and used this when exemplifying who could be considered at high risk of getting HIV. There have been run three different models with different probabilities of acquiring HIV, in order to evaluate the effect of PrEP for different risk-groups. The incidence rates are 1.8%, 3.0% and 5.2%. There has been done additional analysis for the estimated MSM population as a whole, where an incidence rate of 0.19% has been used as well, and the result of that analysis is found in the appendix.

4.3.2 Probability of treatment failure

The model includes a treatment failure state that represents a drop in CD4-count and/or an increase in HIV-RNA, which leads to a lower probability of good health. In 2016 there was 52 HIV-related admissions at Oslo university hospital (OUS). There was just over 1700 persons that received ART at OUS in 2016. The transition probability for experiencing treatment failure was estimated from the number of admissions, referencing the number of individuals on ART in Oslo as the cohort. This leads to a yearly probability of experiencing treatment failure to be 3% for the HIV positive cohort. Some individuals does not receive ART. These individuals often have serious health issues. According to NORHIV 80 (5%) out of 1707 did not receive ART in 2016. This has been assumed to be the probability of remaining in the treatment failure state [37].

Table 2: Transition probabilities, first five years of model

Parameter	Probability	Distribution	Source
Remaining healthy	0.9811	Dirichlet	
Becoming HIV positive	0.018/0.03/ 0.052	Dirichlet	[1, 10]
Death	0.0009	Dirichlet	[38]
HIV, year 1	0.96715	Dirichlet	
Treatment failure leading to hospitalization	0.0306	Dirichlet	[35]
Death	0.00225	Dirichlet	[21, 38]
HIV, year 2-3	0.9676	Dirichlet	
Treatment failure, leading to hospitalization	0.0306	Dirichlet	[35, 37]
Death	0.0018	Dirichlet	[21, 38]
HIV year 4	0.9676	Dirichlet	
Treatment failure leading to hospitalization	0.0306	Dirichlet	[35, 37]
Death	0.0018	Dirichlet	[21, 38]
HIV year 5+	0.9685	Dirichlet	
Treatment failure leading to hospitalization	0.0306	Dirichlet	[35, 37]
Death	0.0009	Dirichlet	[38]
Back on treatment regime	0.92496	Dirichlet	
Remaining in treatment failure leading to hospitalization	0.07	Dirichlet	[37]
Death	0.00504	Dirichlet	[21, 38]

4.3.3 Mortality rates

The mortality rates have been assumed to be equal for healthy MSMs and the population in general. The data has been gathered from the national bureau of statistics, where the mortality rate for the population is presented in five year intervals. There is also evidence suggesting that the mortality rates are equal to the general population for individuals that are HIV positive, receive ART and have a CD4-count higher than 500 cells/mm^3 if they've been on the regimen for more than five years. The mortality rates has been assumed to be 2.5 times higher than the standard mortality rate (SMR) for the first year being HIV positive but on ART, 2 times higher between the second and fourth year on ART, and equal to the SMR for that age-

group from five years and on. The mortality rate is assumed to be 5.6 times higher than the SMR for those that experience treatment failure reflecting the increase from SMR from symptomatic HIV. However, there is generally believed to be an increased probability of developing comorbidities which might affect HRQoL and mortality as a consequence of long time usage of ART. As ART is relatively new, there is not available data that captures these effects, and they are therefore not included in the model [5].

Table 3: Mortality rates for Norwegian men

Age	Number of deaths
35-39	90
40-44	110
45-49	178
50-54	295
55-59	469
60-64	792
65-69	1330
70-74	2098
75-79	3564
80-84	6804

**Numbers are given per 100 000, and are from 2016*
Source: National bureau for statistics, Norway [38]

Table 4: Increases in mortality rates from HIV

Years after ART initiation	Increase from SMR
1	2.5
2-4	2
5+	1
Symptomatic HIV	5.6

4.4 Health states

The model uses QALYs from the Global Burden of Disease Study 2015 (GBD 2015) Disability Weights, where being HIV positive but asymptomatic is estimated to a QALY of

0.92, and symptomatic HIV is associated with a QALY of 0.73. A healthy MSM is assumed to have a QALY equal to 1, and being dead is associated with a QALY of 0. The QALYs are presented in table 5.

Table 5: QALYs for different health states

Health state	Disutility	QALY (1-disutility)
Healthy	0	1
Asymptomatic HIV, on ART	0,08	0,92
Symptomatic HIV	0,27	0,73

4.5 Relative risk reduction

The consensus seems to be amongst professionals that work in the field that the adherence to PrEP in Norway among MSM is high. The recommendation from the Norwegian directorate of health also argued that one should expect a high efficacy for high adherence in their analysis, which is consistent with the current research. As a consequence it has been assumed an efficacy of 86%, equal to what is found in Proud and IPERGAY for our model [13, 18, 39, 40]. However, there has been additionally performed sensitivity analysis in order to control the robustness of this assumption.

4.6 Costs

Health care costs associated with HIV and PrEP are largely concentrated around visits at the outpatient clinic, medical costs for tests, vaccines and pharmaceuticals, in addition to hospital costs if there is some kind of HIV related admission to a hospital. The costs used in order to perform a CUA has been gathered from looking at the pathway for treating HIV patients and gathering costs in accordance to the Norwegian Doctors Association (NoDA) guidelines for prevention and treatment of HIV. Drug costs was estimated from data provided by the Norwegian prescription registry, where the costs for ART was gathered through estimating the mean costs for the 10 most prescribed antiretroviral drugs used in treatment for HIV. The ten drugs were chosen through the report on antiviral therapy use in Norway (RAVN). Direct medical costs from outpatient visits and hospital treatment has been gathered from the HIV-related DRG-codes. The costs for ART is assumed to be the yearly mean cost of the ten most prescribed antiretroviral therapies used in relation to HIV in 2017. The cost of ART is

assumed to be 71 562 NOK. The HIV pathway and the PrEP-pathway is different resulting in different yearly costs from outpatient visits. See table 6 and 7.

Table 6: DRG-weights and estimated costs

DRG	Name of DRG	DRG-weight	Cost in NOK (DRG-weight * DRG)
489	HIV with considerable HIV-related illness	4,431	192 429 NOK
490	HIV with or without bi-diagnosis	2,226	96 671 NOK
	Mean cost hospital admissions	3,3285	144 550 NOK
9180	Policlinic consultation concerning infectious- and parasite-diseases without significant procedures	0,032	1 390 NOK
* 1 DRG =	43 428 NOK		

Table 7: Estimated yearly costs for PrEP and HIV

PrEP	Outpatient visits	Costs
Before startup	1	1390 NOK
First month	1	1390 NOK
Yearly Control	4	5560 NOK
Cost of Truvada		27900 NOK
Total yearly costs, year 1		36240 NOK
Total yearly costs, all preceding years		33460 NOK
HIV+		
First consultancy	1	1390 NOK
Yearly controls	2	2780 NOK
Yearly cost of ART		71562 NOK
Total yearly costs, year 1		75732 NOK
Total yearly costs, all preceding years		74342 NOK

4.7 Willingness to pay

A willingness to pay-threshold has been estimated from expected loss of life quality and the expected survival, utilizing the absolute shortfall-approach as recommended by the Magnusson-group. The expected disutility from acquiring HIV is 0.08, and the time of survival is expected to be 45 years, ending when the patient is 80 years old, resulting in a absolute shortfall of 3.6, as given by Eq. 4. This puts HIV in group 1, where the threshold is suggested to be 275 000 NOK.

4.8 Population

The estimate that has been utilized for the total MSM-population is 47 500 [25]. However, we're not looking at the cost-effectiveness for the total MSM-population, but the groups within the population that are at high risk of acquiring HIV. Therefore, the population size used when estimating the pEVPI has been set at a 1000 individuals for each prevalence rate.

5 Results

5.1 Costs and effects of treatment over time

The expected deterministic total health care costs and effect from not providing PrEP compared to offering PrEP to MSM for three different incidence rates is presented in table 8. In the table both the undiscounted and discounted costs and QALYs is observed for different points in time. The general trend is that the initial costs from providing PrEP is larger than not providing PrEP, and then the costs associated with not providing PrEP starts to close in over time. For a 1.8% incidence rate we observe that both the undiscounted and discounted costs associated with providing PrEP is larger than not providing PrEP for all points in time. For a HIV incidence rate of 3% undiscounted cost from providing PrEP is larger until the 25 year mark, where the costs from not providing PrEP is larger compared to providing PrEP. The provision of PrEP is still more costly in terms of discounted costs for this prevalence rate. For a prevalence rate of 5.2% the undiscounted costs are almost equal after 15 years and the discounted costs from not providing PrEP is larger after 25 years. Furthermore, one can observe that the amount of QALYs gained is always larger from providing PrEP both in terms of discounted and undiscounted effect for all points in time.

Table 8: Effects and costs over time for three HIV incidence rates

HIV incidence rate		No PrEP		PrEP	
1.8%	Duration of intervention	Costs	QALYs	Costs	QALYs
	5 years	16 851 NOK	4.97	173 479 NOK	4.98
		(14 810 NOK)	(4.51)	(159 155 NOK)	(4.52)
	15 years	71 734 NOK	14.79	181 178 NOK	14.86
		(52 162 NOK)	(11.19)	(164 394 NOK)	(11.24)
	25 years	124 657 NOK	24.37	188 601 NOK	24.50
		(76 515 NOK)	(15.60)	(167 810 NOK)	(15.68)
	45 years	211 890 NOK	40.89	249 670 NOK	41.16
		(99 770 NOK)	(19.98)	(171 072 NOK)	(20.09)
HIV incidence rate					
3.0%	5 years	27 722 NOK	4.95	174 428 NOK	4.98
		(24 371 NOK)	(4.50)	(159 981 NOK)	(4.52)
	15 years	117 554 NOK	14.74	187 226 NOK	14.85
		(85 508 NOK)	(11.16)	(168 691 NOK)	(11.24)
	25 years	204 178 NOK	24.28	199 567 NOK	24.48
		(125 370 NOK)	(15.54)	(174 370 NOK)	(15.67)
	45 years	346 961 NOK	40.69	219 908 NOK	41.13
		(163 433 NOK)	(19.89)	(179 793 NOK)	(20.08)
HIV incidence rate					
5.2%	5 years	46 919 NOK	4.93	176 157 NOK	4.98
		(41 268 NOK)	(4.48)	(161 489 NOK)	(4.52)
	15 years	197 537 NOK	14.65	198 238 NOK	14.84
		(143 773 NOK)	(11.09)	(176 516 NOK)	(11.23)
	25 years	342 775 NOK	24.11	219 530 NOK	24.46
		(210 608 NOK)	(15.44)	(186 314 NOK)	(15.65)
	45 years	582 174 NOK	40.34	254 625 NOK	41.08
		(274 428 NOK)	(19.75)	(195 670 NOK)	(20.05)

** Undiscounted (Discounted)*

5.2 Cost-utility analysis

The result from the deterministic cost-effectiveness analysis has been summarized in table 9.

Table 9: Cost-utility analysis for different prevalence rates

Prevalence rate	Treatment strategy	Total costs	Total QALYs	Incr. costs	Incr. QALY	ICER
1.8%	No PrEP	91 075 NOK	19.988	-	-	-
	PrEP	129 876 NOK	20.095	38 801 NOK	0.107	362 050 NOK
3.0%	No PrEP	161 853 NOK	19.899	-	-	-
	PrEP	171 188 NOK	20.082	9 335 NOK	0.183	51 014 NOK
5.2%	No PrEP	281 388 NOK	19.741	-	-	-
	PrEP	188 374 NOK	20.057	-93 013 NOK	0.316	-293 935 NOK

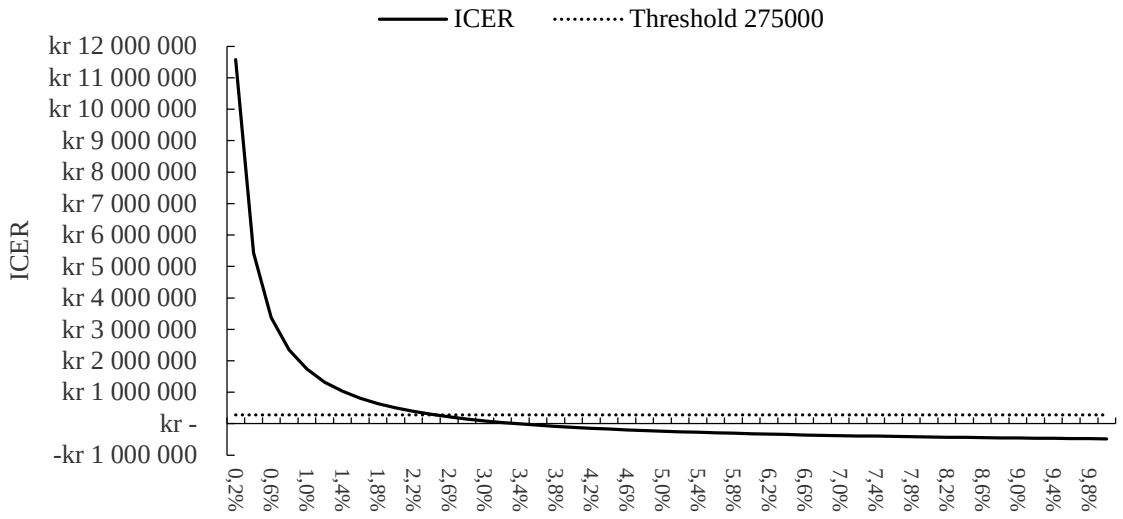
The table illustrates the discounted half-cycle corrected costs, QALY and the ICER from the deterministic cost-effectiveness analysis for all four prevalence rates. The deterministic analysis illustrates how the provision of PrEP ranges from not being CE for the given WTP-threshold (275 000 NOK) for a yearly incidence rate of 1.8%, to being CE for a yearly incidence-rate of 3% and cost-saving for a yearly incidence rate of 5.2%.

5.3 Deterministic sensitivity analysis

It was performed one-way sensitivity analyses for the cost of ART, Truvada, outpatient visits and hospital admissions, in addition to changes in HIV prevalence and relative risk reduction from PrEP. The Y-axis indicates the ICER, and the X-axis reflects the input-variable that is being observed. For all the variables, except incidence rates, the graphs are presented for three different prevalence rates, 1.8 %, 3 % and 5.2 %. The reporting of results from the sensitivity analysis is not to be taken as a quantitative indication that should inform the ultimate decision for the question at hand. Rather, the deterministic sensitivity analysis is created in order to inform the effect a range of values for a given set of parameters has on the output on the model.

Figure 2 shows the effect from changes in HIV incidence in the high risk period.

Figure 2: Sensitivity analysis for changes in HIV prevalence for high risk MSM



The figure illustrates the effect of changing the incidence rates of HIV in the population. A wide range of incidence rates has been chosen in order to show the full effect of changing incidence rates on the model output. The graph start out on the left side with a very high ICER for an incidence rate equal to that to that of the estimated MSM population. Here the ICER is just above 11 million NOK for per QALY. However, the ICER is reduced exponentially for relatively small decreases in incidence rates, and it intersects the WTP-threshold at an incidence rate larger than 2.7 %. The decreasing trend continues beyond the WTP and shows how the ICER will become negative for incidence rate greater than 3.9% indicating that PrEP can be cost-saving.

Figure 3 shows the effect from changes in costs on ART.

Figure 3: Sensitivity analysis for changes in cost of Antiretroviral therapy

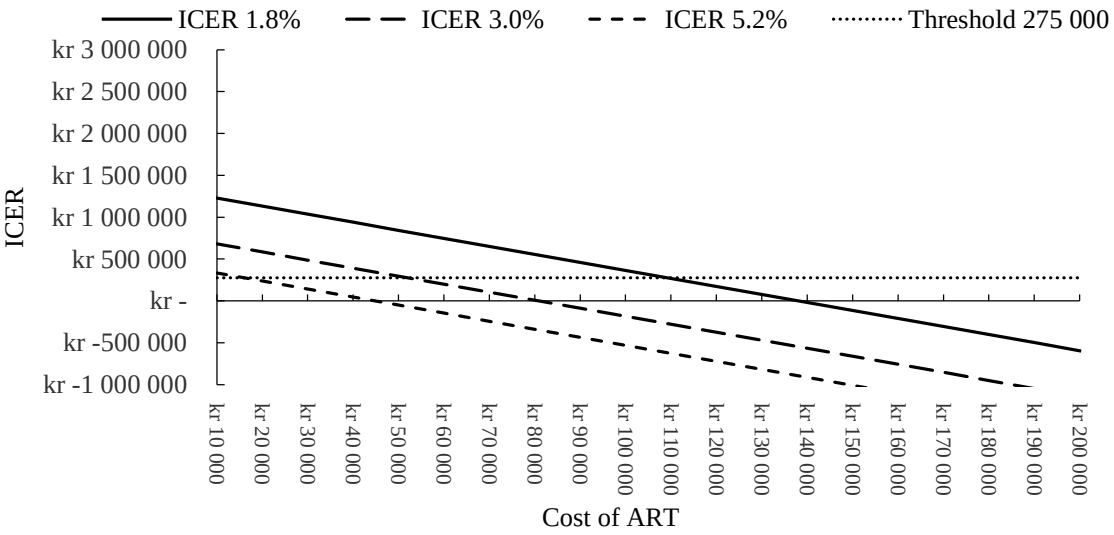


Figure 3 illustrates how changes in the yearly cost of antiretroviral therapy affects the ICER in the model for three different incidence rates. The figure illustrates for all three incidence rates that changes in ART-costs creates a constant negative decreasing slope where the output of the model ranges from not being cost-effective to being cost-effective. For an incidence rate of 1.8% a cost of ART larger than 110 000 NOK indicates that PrEP has the potential of being cost-effective, and for cost if ART larger than 135 000 NOK PrEP has the potential of being cost saving. For an incidence rate of 3% PrEP would be cost-effective for yearly costs of ART equal to 60 000 NOK and cost saving for costs just above 80 000 NOK. For an incidence rate of 5.2 % the yearly cost of ART could be as low as 10 000 and PrEP would still be cost-effective. At this incidence-rate level PrEP becomes cost-saving at ART-costs higher than 45 000 NOK.

Figure 4 shows the effect of changes in the yearly cost of Truvada on the ICER.

Figure 4: Sensitivity analysis for changes in costs of Truvada,

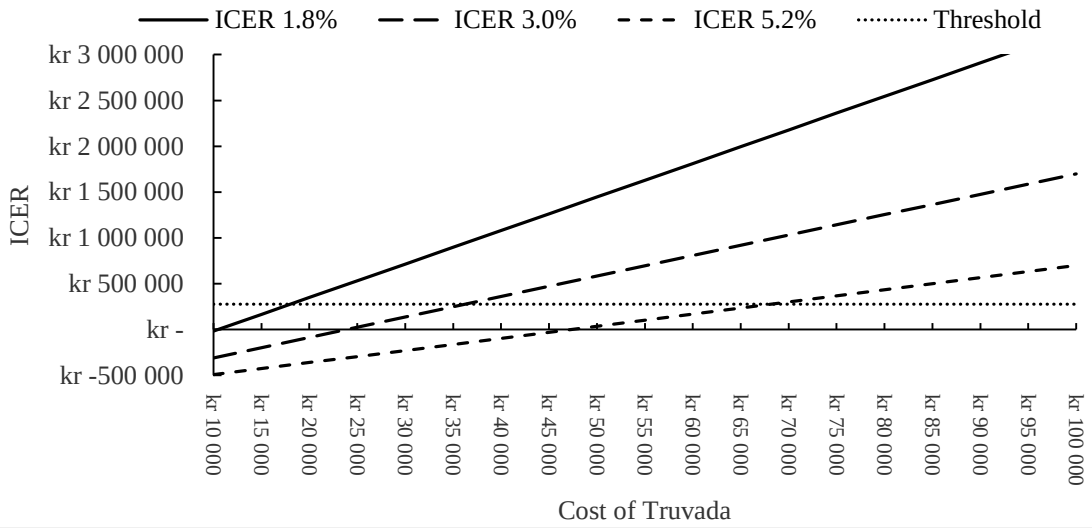


Figure 4 illustrates how a change in cost of Truvada affects the ICER for three different incidence rates. Here the graph indicates an increasingly larger ICER for increases in the cost of Truvada, but at a decreasing rate for higher prevalence rates. For an incidence rate of 1.8% the provision of PrEP stops being cost-effective when the price for Truvada increases above 20 000 NOK. For an incidence rate of 3% the provision of PrEP is cost saving for yearly cost of Truvada below 22 000 NOK and is cost-effective for costs between 22 000 and 35 000 NOK. For an incidence rate of 5.2% the provision of PrEP is cost saving for Truvada-costs around 45 000 NOK and cost-effective for costs between 45 000 and 70 000 NOK.

The effect from changes in disutility from living with HIV is presented in figure 5

Figure 5: Sensitivity analysis of changes in disutility from living with HIV

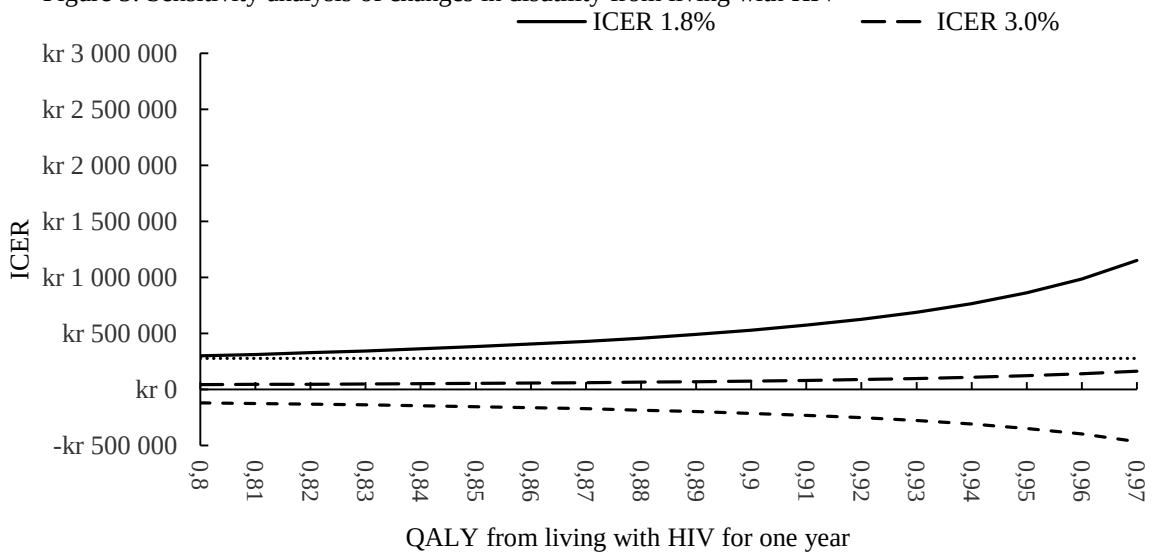


Figure 5 illustrates how the disutility from living with HIV amplifies the effects in the cost-utility analysis. The ICER is increased when the incremental costs between the two interventions are positive, and decreased when the incremental costs are negative. However, relatively large changes in disutility do not change the outcome of the model dramatically for any of the incidence rates.

The effect from changes in risk reduction from PrEP is presented in figure 6.

Figure 6: Sensitivity analysis for changes in relative risk reduction from PrEP

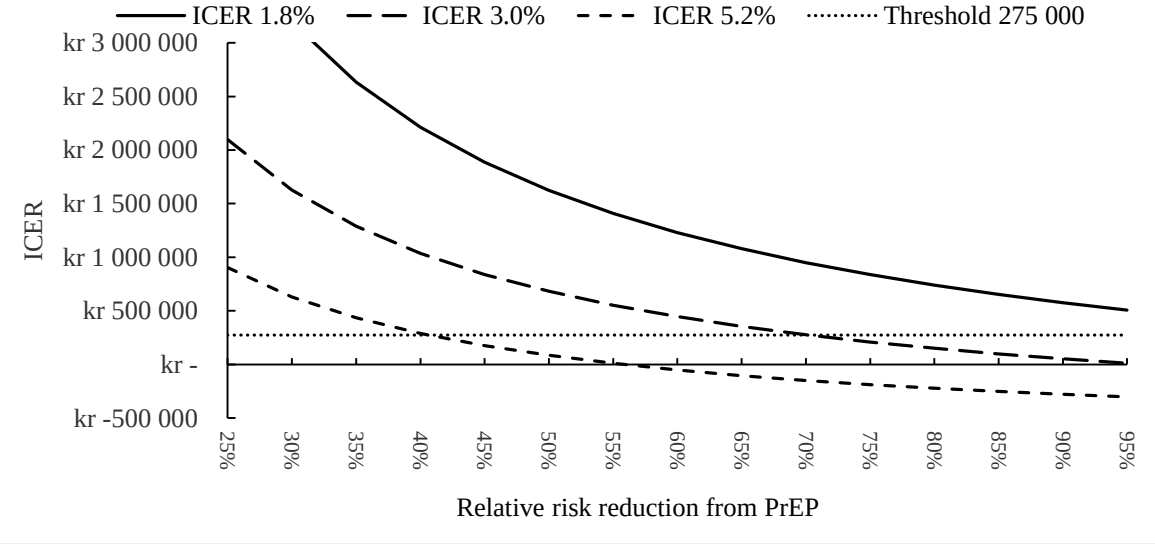


Figure 6 illustrates how changes in the efficacy of PrEP, here expressed as the relative risk reduction, affects the ICER in the model for three different incidence rates. The general trend is a slope that is decreasing but at a falling rate for higher efficacy over all three incidence rates. For an incidence rate of 1.8% the graph never crosses the WTP-threshold and stops at an ICER equal of 500 700 NOK for a reduction in incidences by 35%. For an incidence rate of 3% the provision of PrEP becomes cost-effective for an efficacy of 70%, and stops at an ICER of 11 000 NOK for an efficacy of 95%. For an incidence rate of 5.2% the provision of PrEP becomes cost-effective for an efficacy of 40%, and cost saving for an efficacy just below 60%.with the lowest ICER being just under -300 000 NOK.

Figure 7 illustrates the effects of changes in outpatient visits costs

Figure 7: Sensititivity analysis of changes in costs from outpatient visits

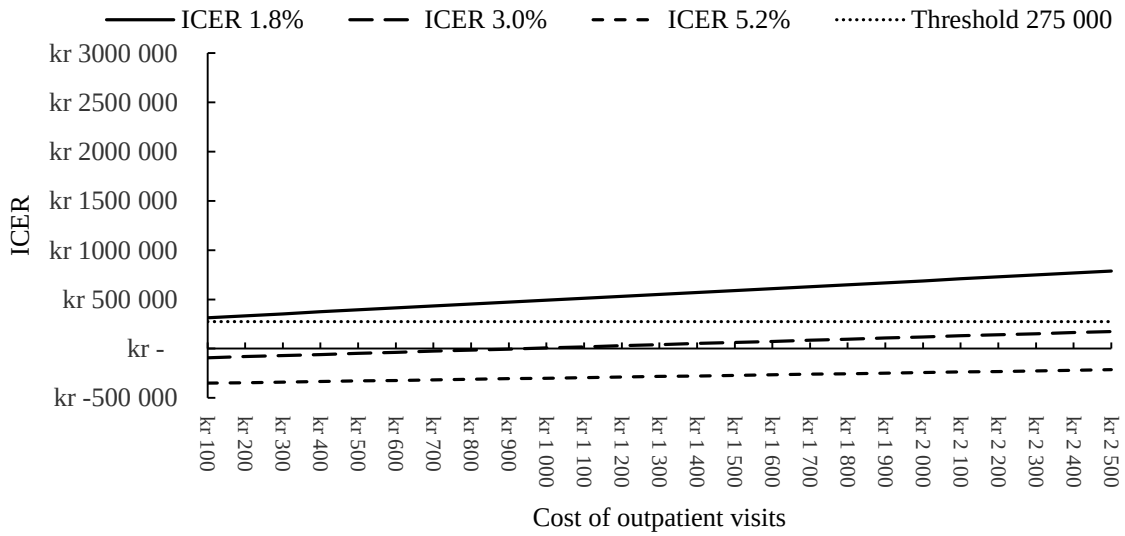
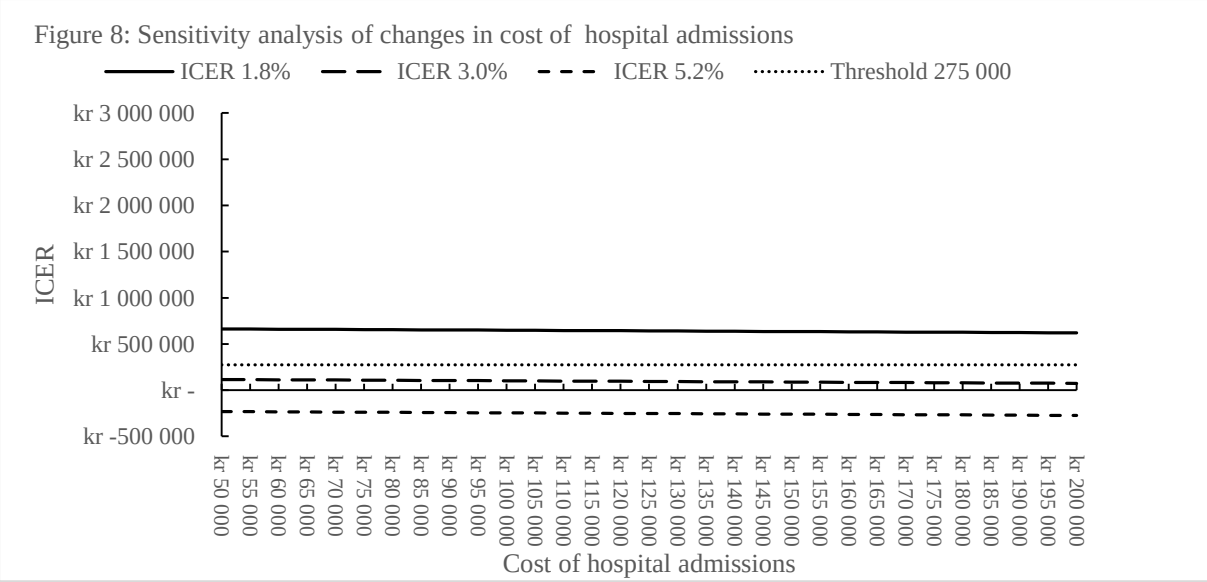


Figure 7 illustrates how changes in yearly costs from outpatient visits affects the ICER. The slope is increasing creating a larger ICER for higher costs related to hospital admissions. However, the slope is not very steep, and only large changes in outpatient related costs affects the output in terms of whether or not the result is deemed effective in relation to the WTP threshold. For an incidence rate of 1.8% and a cost of 100 NOK per outpatient visit an ICER of 334 000 NOK is observed. The ICER then continues to increase for increases in costs for outpatient visits. For an incidence rate of 3% and a cost of 100 NOK per outpatient visit a negative ICER equal to -92 000 NOK is observed, which indicate that the provision of PrEP might be cost-saving for very low outpatient costs. The ICER becomes positive for costs just under 1 000 NOK, and increases but never to the point where the provision of PrEP exceeds

the WTP. For an incidence rate of 5.2% is we see that the ICER is negative and has a value of -350 000 NOK for a cost 100 NOK per outpatient visit. The ICER increases for increases in costs per outpatient visit, but never to the point where the ICER becomes positive

Figure 8 illustrates the effects of changes in cost of hospital admission



In figure 8 the ICER is observed for changes in yearly costs for hospital admissions. The ICER is sloping negatively but very little for large changes in costs. It is further observed that the slope shifts downwards for increases in incidence rates, indicating that the ICER to a very little extent is affected by changes in hospital costs.

5.4 Probabilistic sensitivity analysis

The cost-effectiveness planes from the CUAs are presented in figure 9a-c.

Figure 9 a: Cost efficiency plane, HIV incidence rate 1.8%

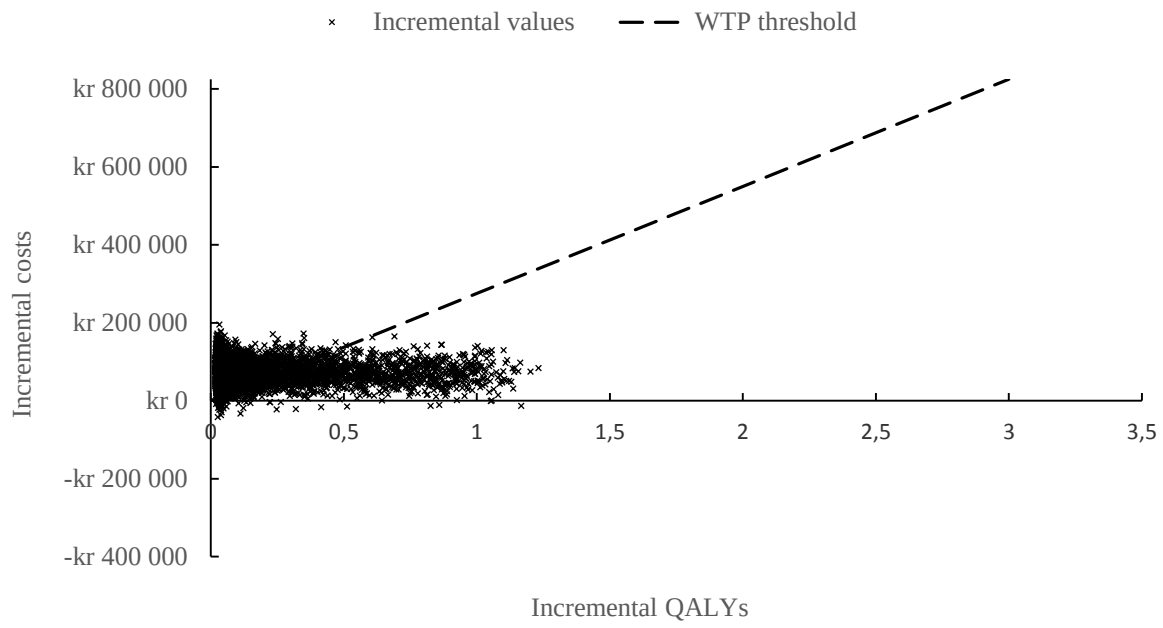


Figure 9 b: Cost efficiency plane, HIV incidence rate 3%

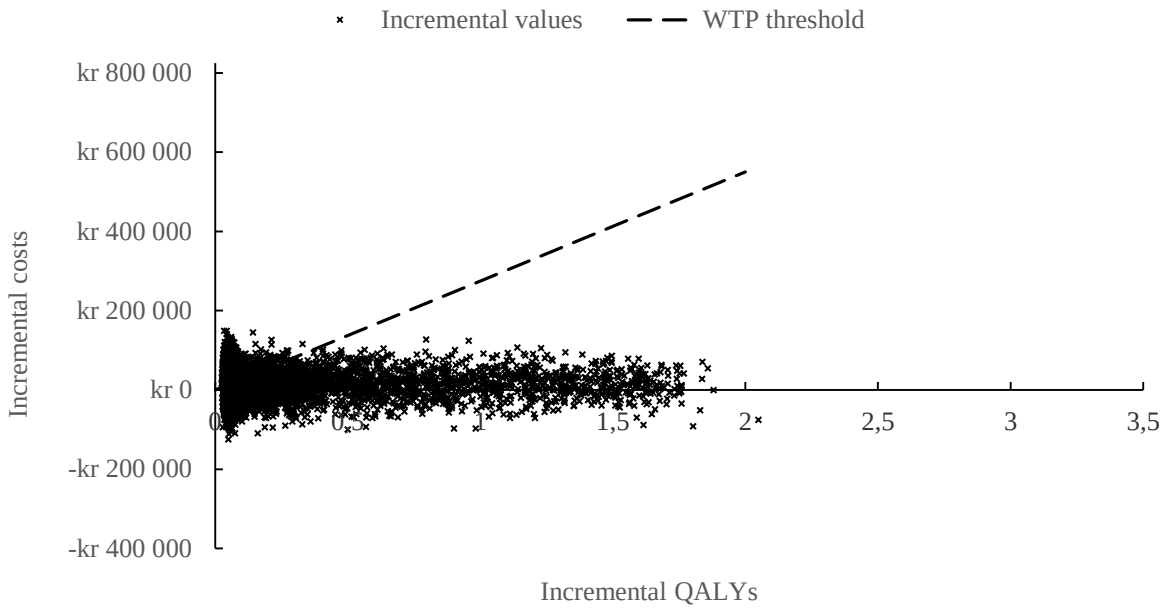
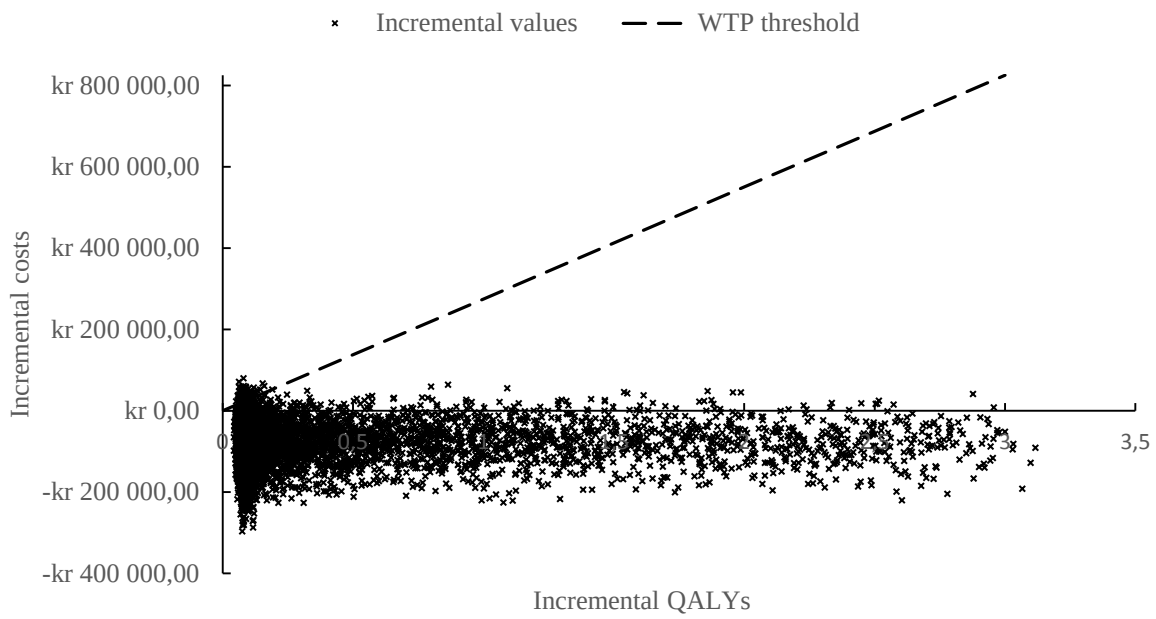


Figure 9 c: Cost efficiency plane, HIV incidence rate 5.2%

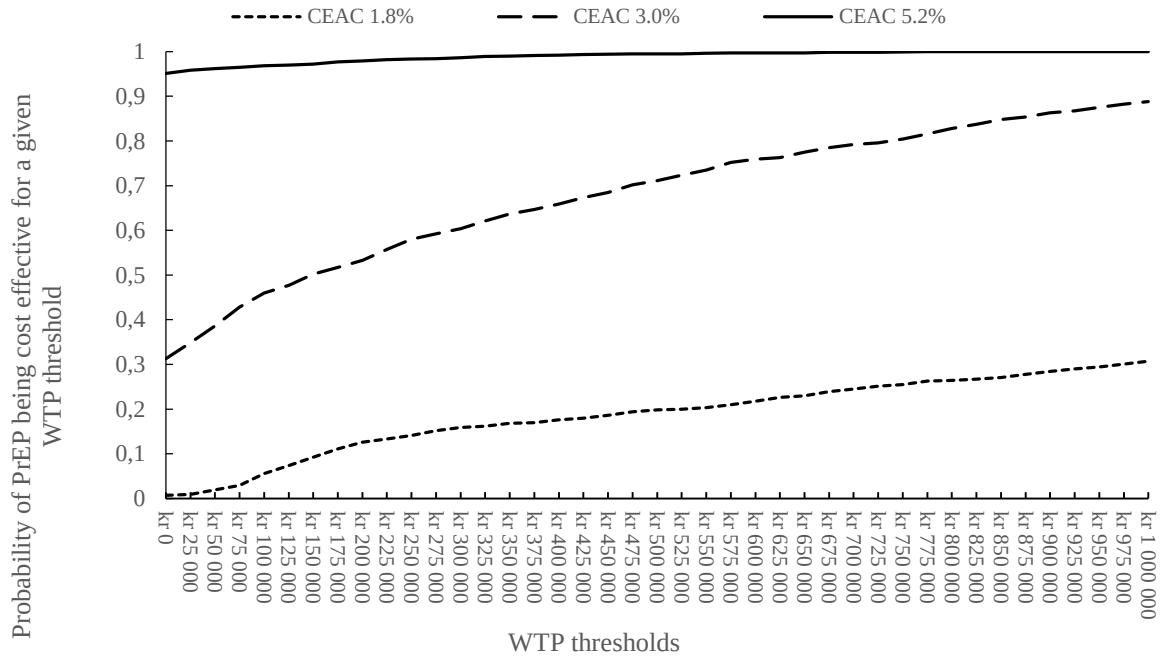


The cost-effectiveness plane is constructed with the incremental effects on the x-axis and the incremental costs on the y-axis. As there is no negative incremental effects, our figures only show the north-east and south-east quadrant. A simulation that places in the northeast quadrant indicates that the intervention is both more expensive, but also more effective than the comparator. In this case the intervention has a potential to be cost-effective depending on the WTP of the provider. Similarly, a simulation that places in the southeast quadrant indicates that the intervention is cheaper and more effective than the comparator for that simulation. If that is the case the comparator is dominated, and should (most likely) be implemented. Our cost-effectiveness planes show the distribution from 10 000 Monte Carlo simulations for three different yearly HIV incidence rates, and the willingness to pay (WTP), which has been gathered from the absolute shortfall approach and is set at 275 000 per QALY. All simulations are placed in either the northeast or southeast quadrants. All simulation-points placed below the WTP-threshold is considered cost-effective, and all observations placed in the south-east quadrant is considered cost-saving. For an incidence rate equal to 1.8% more or less half of the simulations are below and above the WTP-threshold indicating that there is a lot of uncertainty relating to whether or not PrEP ought to be provided to a cohort with this incidence rate. For an incidence rate of 3% per year we observe that a larger portion of the simulations are below the WTP and some are in the southeast quadrant indicating that the intervention in some cases is cost-saving. For a prevalence equal

to 5.2% we observe that most of the simulations are below the WTP threshold, and that a considerable amount is in the southeast quadrant, indicating that the intervention in most cases will be cost-saving.

A CEAC has been constructed for each incidence rate used in the CUA in order to better illustrate the likelihood of PrEP being cost-efficient for a given threshold. See figure 10.

Figure 10: CEAC for each yearly HIV incidence rate



The CEACs represents the probability of PrEP being cost-effective for a given threshold. Here the CEAC suggests that to offer PrEP for a incidence rate of 1.8% will be cost-effective in only 15% of the cases for a WTP threshold of 275 000 NOK. For a threshold of 825 000 PrEP will be CE in 26% of the cases for the same incidence rate. For an incidence rate of 3% PrEP will be cost-effective in 60% of the cases for the sett WTP of 275 000. For the highest possible WTP of 825 000 PrEP would CE be in 83% of the cases. For the highest incidence rate of 5.2% the provision of PrEP would be cost-effective in 95% of the cases if the WTP was equal to zero. For WTP of 275 000 NOK the provision of PrEP is CE in 98% of the cases, and limits towards 1 for all thresholds larger than 275 000 NOK.

5.5 EVPI

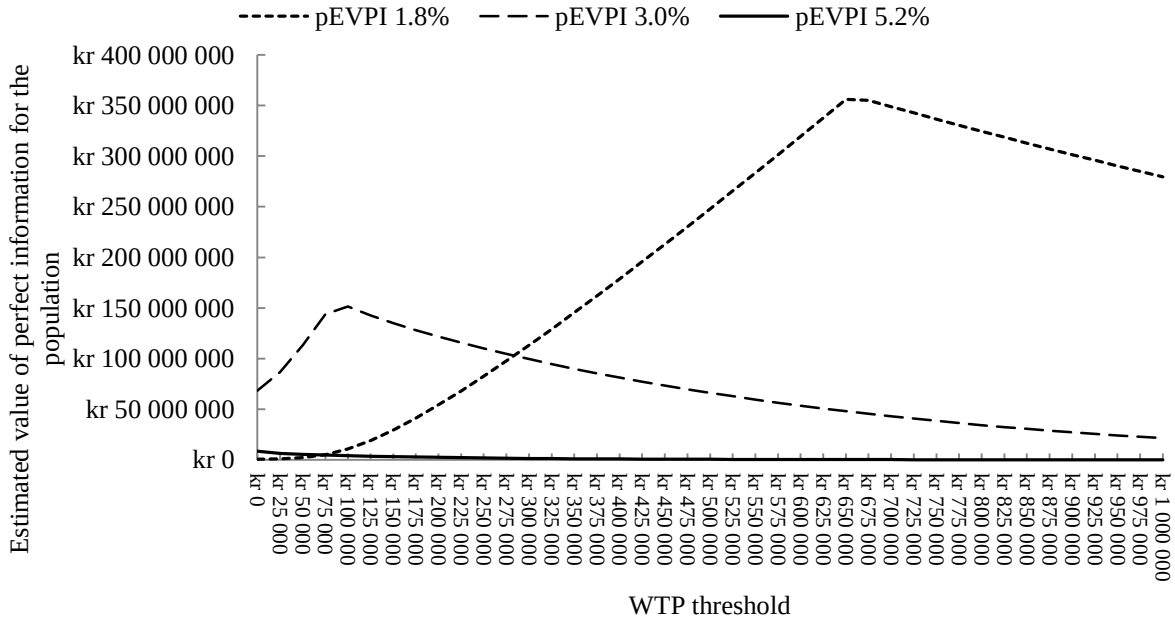
The EVPI expresses the individual uncertainty associated with the decision of providing or not providing PrEP in monetary terms. The individual EVPI is given in figure x. For WTP of

275 000 an individual EVPI of 10 711 NOK, 11 477 NOK and 170 NOK is observed for incidence rates of 1.8%, 3.0% and 5.2%. A low EVPI for an incidence rate of 5.2% is observed which indicates that there is little uncertainty of the intervention being cost-effective even at very low thresholds. For the other two incidence rates the EVPI increases towards a maximum value where the uncertainty surrounding the decision is highest, namely where the ICER is equal the WTP-threshold.

5.6 pEVPI

Where the expected value of information at the individual level informs about the potential loss in monetary terms from making the wrong decision, the estimated value of perfect information for the population should in theory express the potential costs associated with the uncertainty for all patients. However, there is to our knowledge no registry data on the MSM-population that could give an indication of the number of individuals that are in high risk of acquiring HIV. As a consequence we've utilized a hypothetical population size of a 1 000 individuals in each incidence rate group. The pEVPI does here signify the upper limit of the value on the research that would remove all uncertainty from the decision, given a population of 1 000 individuals and a technology lifetime of 10 years. The pEVPI for the three incidence rates are given in figure 11:

Figure 11: Estimated value of perfect information for the population, for three HIV incidence rates



The pEVPI for the given threshold is estimated to be 97 million NOK, 104 million NOK and 1.5 million NOK for incidence rates of respectively 1.8%, 3.0% and 5.2%.

6 Discussion

This thesis increases the available evidence about the cost-effectiveness of PrEP in a Norwegian setting considerably, as there never before has been performed a cost-effectiveness analysis on the subject. The goal of this these has been to provide a better understanding and enable decision makers to make more informed decisions under uncertainty.

6.1 Main findings

The thesis have found that the provision of PrEP to MSM that are at a high risk of acquiring HIV can be cost-efficient if the risk is sufficiently high. The deterministic ICER is however above the WTP at a yearly HIV-incidence rate of 1.8%, deeming it not cost-efficient. For an incidence rate of 3.0%, the ICER is below the WTP-threshold, making PrEP potentially cost-efficient. When observing an incidence rate of 5.2% the ICER is negative, indicating that PrEP can be cost-saving. There is a direct relationship between the time spent and incidence rate when looking at the potential of realizing cost-savings. For an incidence rate of 5.2% undiscounted costs are expected to be larger from not providing PrEP after 15 years, and within 25 years for discounted costs. For an incidence rate of 3% the undiscounted costs are expected to be larger from not providing PrEP after 25 years compared to expected costs from providing PrEP. Costs are however never expected to be lower from providing PrEP for this incidence rate when looking at the discounted costs.

The uncertainty within the model is explored in through the deterministic sensitivity analyses, and they showed that the model is sensitive for large changes in costs of drugs, outpatient visits, the efficacy of Truvada, and prevalence rates. The results are however robust for small (+/- 5%) changes in the parameters.

The results of the PSA indicate that the provision of PrEP to individuals with an expected incidence rate of 5.2% was cost-effective for almost all simulations for our chosen WTP. For incidence rates of 3.0% and 1.8% the provision of PrEP would be cost-effective in respectively 60% and 16% of all simulations.

The pEVPI illustrates the differences in uncertainty for the different incidence rates, and gives us the value from perfect information, which would be the maximum value from further

research. The pEVPI shows the effect from choosing the optimal treatment for each patient every time in terms of selecting the treatment that produces the highest NMB. For our incidence rates of 1.8%, 3.0% and 5.2% the value of information is respectively 97 million NOK, 104 million NOK and 1.5 million NOK for a WTP-threshold of 275 000, highlighting the large difference in uncertainty for our findings.

6.2 Previous research

There has been performed several cost-effectiveness analysis for the provision of PrEP in north-America and Europe, but this is to our knowledge the first CUA of PrEP that has been performed in a Norwegian setting [12-14, 41-46]. The studies that has been looked at concludes to a varying degree that PrEP ought to reduce incidences of HIV, but that the cost-effectiveness largely is dependent on central factors such as the cost of PrEP and ART, the expected level of adherence, the degree one could expect risk compensation, the prevalence of HIV and the WTP within the health system. The results are also largely dependent on the chosen time horizon.

There has in addition been performed several systematic reviews concerning the cost-effectiveness of PrEP. A systematic review performed by Cambiano in 2015 concluded that PrEP could be anything from cost saving to having an ICER of 1 292 982 NOK (160 000$ in 2015 converted to 2018 NOK) per QALY gained for MSM in North America. Cambiano points out that the studies with the least favorable ICERs used static models, which does not take into account secondary transmissions, and that even these models found PrEP to be cost-saving for a efficacy of PrEP equal 92 % (corresponding to a high level of adherence), and a high prevalence of HIV [47]

6.3 Discussion of results

The results of this thesis are in line with previously performed economic evaluations, illustrating how the cost efficiency of PrEP-provision is largely dependent on factors such as costs, incidence rate and efficacy. The results in this thesis indicate that an incidence rate of 5.2%, which was suggested as a potential cut-off point in terms of what constitutes being “at high risk of acquiring HIV” by the NDH in 2016, was reasonable. This statement can be argued as the provision of PrEP to this cohort is expected to be cost-effective for our chosen

threshold 98% percent of the time with very low value of information associated with the result. For the incidence rates of 3 %, and 1.8 %, PrEP is expected to be cost efficient 60 % and 16 % of the time. However, the expected value of information is large for each of the lower incidence rates, and as the consequences of making a wrong decision is associated with large costs over time, it is clear that the uncertainty linked to the two lowest incidence rates is sufficiently high to the point where it should be invested in more information before the treatment can be recommended.

It ought to be mentioned that the reporting of the results in this thesis is contingent on the chosen WTP that was estimated utilizing the absolute shortfall approach. This is not necessarily the threshold that will be utilized by the relevant decision makers and a higher WTP would change the degree provision of PrEP could be considered cost-efficient. As shown by the CEAC and pEVPI in figure 10 and 11 the probability of PrEP being cost-effective increases and the value of information decreases for increasing WTPs. For the largest WTP-threshold given by the Magnusson-group of 825 000 NOK per QALY the probability of being cost-effective have increased to 84% and the value of information has decreased to 32 million NOK for individuals with a incidence rate of 3%, which might be a more acceptable probability and cost associated with implementing PrEP for this cohort.

6.4 Limitations

This thesis has several limitations. Some of them are methodical and some of them are related to a lack of data and knowledge related to HIV and the treatment of it.

A static model has been used. As argued by Cambiano, static models does not take into account the prevention of secondary transmission of HIV and might as such present a less favorable ICER, as the full effect of a PrEP rollout might be underestimated.

The thesis is also looking at the decision question from a health care-perspective. This is largely because of the fact that all costs associated with HIV and PrEP is fully reimbursed so most of the economic burden falls on the health system. The consequence of choosing this perspective is that the individuals cost associated with traveling to and from outpatient visits isn't included in the model. There are more outpatient visits related to the provision of PrEP compared to being HIV positive. Leaving out travel expenses might as a consequence underscore the total costs associated with PrEP-provision. The consequence of this is that the

ICER created from a health care perspective might be more favorable to the provision of PrEP compared to the societal perspective.

Risk compensation has been focused on a lot in the economic evaluation-literature concerning PrEP. The consequences of risk compensation is argued to be that the saved costs associated with the provision of PrEP might be offset by higher costs related to other STDs that are prevalent in communities where the risk of HIV is high. Another factor that are mentioned is that the presence of an STD might increase the probability of acquiring HIV, in turn reducing the efficacy of PrEP.

Another factor that isn't included in the model is the potential long term effects of being on ART which is suspected to potentially lead to an increased chance of comorbidities such as cardiovascular diseases, cancer and osteoporosis. These diseases would in turn decrease QoL and increase mortality rates, which then most likely would create a more beneficial ICER in favor of PrEP. However, there are no available data on these effects, and it would increase the complexity of the model quite a bit, and have for these reasons been left out.

The thesis has only examined the cost-efficiency of daily and not event-driven PrEP. If it is assumed that event-driven PrEP has the same efficacy as daily PrEP, then it is also likely that PrEP could be cost-effective for lower incidence rates as well.

7 Conclusion

HIV as a disease has since the discovery of ART in the 90's gone from being a terminal disease to a largely manageable but chronic condition. Research does however indicate that QoL is from living with HIV is reduced as a consequence of social stigma, poorer sexual health and comorbidities from long-term use of ART [5]. In the recommendation from NDH it was concluded that PrEP should be provided to those that are at a high risk of acquiring HIV as an additional tool in an already existing toolbox where available information, easy access to condoms and testing for STDs and TASP are the central components.

Even with its limitations, this CE has shown that PrEP has the potential of being cost-effective for individuals with a high risk of acquiring HIV for the chosen threshold. However, there is a need of further research where an individual driven, dynamic model that are better suited to take into account all epidemiological factors that are in play when evaluating the provision of PrEP and its potential effects on HIV-transmission in Norway in order to more precisely determine where the cut-off ought to be made at an individual level.

The low pEVPI and high CEAC does show that the provision of PrEP ought to available for individuals that have an expected yearly HIV-incidence rate of 5.2% and above for our WTP. For individuals with a yearly incidence rate of 3% the PSA illustrates how the provision of PrEP will be cost-effective 60% of the time. However, the expected value from more information is very high for the relevant WTP, and further research is therefore recommended for incidence rates of 3% and below.

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