Is treating the healthy an effective use of resources?

A cost-effectiveness study of pre-exposure prophylaxis in the prevention of HIV among MSM in Norway

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Summary

Background: Human Immunodeficiency Virus (HIV) is an incurable viral disease commonly transmitted sexually via bodily fluids such as blood and semen. Decades before, receiving a HIV diagnosis meant a literal death sentence, but now HIV-infected individuals living in resource rich countries can expect to live a long and healthy life for all intents and purposes. To ensure this, however, health systems must provide extremely costly life-long ARV treatment. Moreover, the presence of the disease—while no longer a “death sentence”—is connected to increased incidence of other non-HIV related diseases that may negatively impact the lifespan of seropositive individuals. Additionally, before treatment is initiated, infected individuals experience significantly reduced health related quality of life (HRQoL) as they transition across the various disease-associated stages. The development of cost-effective prevention methods will therefore save large sums of money incurred under the treatment of HIV, and result in a diminished population-wide loss of health. This thesis is a study of the introduction of pre-exposure prophylaxis (PrEP), a new prevention tool specifically targeted towards HIV-prone groups, to the Norwegian market.

Aim: Truvada, the only drug to receive market approval for a prevention indication against HIV, has been granted market access in the United States, France, and Australia. The purpose of this thesis is to explore the comparative cost-effectiveness of Truvada in preventing HIV transmission over a thirty-year period among men who have sex with men (MSM) residing in Norway; a resource-rich country with comparatively low HIV incidence. Two different scenarios involving access to Truvada are explored: 1.) status quo (i.e. no PrEP); 2.) immediate approval of PrEP and subsequent 25% uptake of PrEP among targeted MSM classified as being at high risk.

Methods: A model developed by Long and colleagues to estimate the cost-effectiveness of different HIV prevention methods among intravenous drug users was adapted to estimate both HIV transmission among MSM residing in Norway, and the cost-effectiveness of PrEP vs. a status quo scenario in which PrEP was not available. The model, developed in Excel, is dynamic in nature and compartmentalized according to the various health states associated with HIV disease transmission susceptibility, disease progression, diagnosis and lastly treatment. All states include costs and a health-determined quality of life. Important model parameters
regarding sexual behavior used in the modeling of HIV transmission were estimated from statistical analysis of data gathered from respondents of the Norwegian-specific European MSM Internet Survey (EMIS). The differences in number of new infections over a thirty-year period, as well as the costs and effects (i.e. life years, health related quality of life) accrued under both scenarios were estimated. To assess the uncertainty of the various model parameters and its effect on the results, a probabilistic sensitivity analysis (PSA) was conducted, employing a Monte Carlo second order simulation within Excel.

Results: An estimated 1100 HIV infections will be prevented over a 30-year period if approximately 25-30% of high-activity MSM is treated with PrEP. By preventing so many HIV infections, an estimated 2 300 QALYs are saved/gained. These gains however come at a cost of 12.1 billion NOK when compared to a status quo scenario, as 69 persons are required to receive PrEP treatment in order to prevent one new infection.

Discussion: Time constraints necessitated the adoption of numerous assumptions that, if incorrect, would augment the model’s inaccuracy, thus potentially leading to the wrong decision being taken. While the assumptions provided for rapid construction, the model stands to eventually be improved by examining its incompleteness so as to eliminate the more serious limitations. Given the complexities of accurate parameter estimation and inherent gaps in our knowledge and data systems, model calibration is of substantial importance. Recalibration to a Norwegian context is likely necessary in the future. Nevertheless, the model’s predictive capability has been validated.

Conclusion: When considering costs and potential negative health effects inherent to PrEP, the various cost-effectiveness analysis frameworks applied yielded contradictory estimates, with the CUA approach finding PrEP to be not cost-effective and the CEA approach finding a PrEP scenario to be cost effective. Nevertheless, the review indicates that both setting and target population are decisive “drivers” of cost-effectiveness. More context-specific research including comprehensive costing studies related to HIV and PrEP care in Norway is therefore suggested.
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Abbreviations

AIDS ........................................................................................................... Acquired immune deficiency disease
ART ............................................................................................................. Antiretroviral treatment
ARV .......................................................................................................... Antiretrovirals
CBA ......................................................................................................... Cost-benefit Analysis
CDC .......................................................................................................... Center for Disease Control
CEAC ........................................................................................................ Cost-effectiveness acceptability curve
CE Plane .................................................................................................... Cost-effectiveness plane
CUA ........................................................................................................... Cost-utility analysis
DMC .......................................................................................................... Direct medical costs
DNA .......................................................................................................... Deoxyribose nucleic acid
EMIS .......................................................................................................... European MSM internet survey
EVPI ........................................................................................................... Expected value of perfect information
EVPPI ......................................................................................................... Expected value of partial perfect information
FDA ............................................................................................................ Food and drug agency
FHI ............................................................................................................. Folkehelseinstituttet (Norwegian Public Health Agency)
HAART ....................................................................................................... Highly active antiretroviral therapy
HIV ............................................................................................................. Human immunodeficiency virus
HRQoL ........................................................................................................ Health-related quality of life
ICER ........................................................................................................... Incremental cost-effect ratio
LY ............................................................................................................... Life year
MSM ........................................................................................................... Men who have sex with men
NMA ......................................................................................................... Norwegian Medicines Agency (Legemiddelverket)
NMB .......................................................................................................... Net monetary benefit
NNRTI ....................................................................................................... Non-nucleoside reverse transcriptase inhibitor
NNT ............................................................................................................. Number needed to treat
NOK ........................................................................................................... Norwegian krone
NRTI .......................................................................................................... Nucleoside reverse transcriptase inhibitor
QALY .......................................................................................................... Quality-adjusted life year
PEP ............................................................................................................. Post-exposure prophylaxis
PEVPI ......................................................................................................... Population-level expected value of perfect information
PrEP ............................................................................................................. Pre-exposure prophylaxis
PSA ............................................................................................................. Probabilistic sensitivity analysis
RNA ............................................................................................................. Ribonucleic acid
TrAP ........................................................................................................... Treatment as protection
UIAI ........................................................................................................... Unprotected insertive anal intercourse
URAI ......................................................................................................... Unprotected receptive anal intercourse
WTP ........................................................................................................... Willingness to pay
1 Introduction

Human Immunodeficiency Virus (HIV) is a retrovirus that attacks the body’s CD4+ T cells, macrophages, and dendritic cells vital to the maintenance of a healthy immune defense system designed to fight off infections, cancers, and other morbidities. The virus is communicable, and commonly spread sexually via bodily fluids such as semen, pre-ejaculate, blood, and vaginal fluids. Often after several years of untreated HIV, a person develops acquired immunodeficiency syndrome (AIDS), thus leading to increased susceptibility to opportunistic infections that eventually overpower the body’s immune system completely. Average survival time after infection is ten to thirteen years if HIV goes untreated.

The development of therapeutic options, namely antiretroviral therapy (ART), has seriously improved patient prognosis, though the disease remains incurable. Present combination therapies deliver both a virologic and immunologic response by inhibiting the various phases of the retrovirus’s life and replication cycles (Niskanen Hansen, 2010). For many infected individuals in the developed world, the disease is manageable to such an extent that newly infected persons can expect to live long with little to no diminished long-term health. The development of effective drugs to treat HIV has thus led to a paradigm shift in the understanding of HIV as a chronic illness. Proper management, however, is costly, as it requires not only the combination of three or more different ARV drugs, but also the continued monitoring of biologic indicators that must often be analyzed in a lab setting. Moreover, drug resistance may lead to many of the various classes of ARV drugs becoming ineffective, leaving us with fewer tools for managing HIV infections.

While the overall incidence of HIV in resource-rich countries has remained relatively stable in the past decade, prevalence continues to grow as more and more people live longer with the disease. These infected individuals, as mentioned, incur large costs because successful treatment and management requires the large consumption of medical resources. Additionally, HIV infected individuals experience large decrements in their health related quality of life (HRQoL) before they initiate ART. Even whilst on ART, individuals may experience treatment related side effects and non-HIV related diseases such as diabetes mellitus (Paik et al., 2011), kidney disease (Scherzer et al., 2012) and liver disorders (Price et al, 2010), and cancers (Silverberg et al., 2007), therein leading to suboptimal health and shortened lifespans (Nakagawa et al., 2012). Methods of HIV prevention therefore have the potential to save large sums of financial resources as well as prevent large losses of health. Current methods of pre-
venting the sexual spread of HIV include: condoms and other barrier methods, behavioral counseling, treatment as prevention (TRaP), post-exposure prophylaxis (PEP), and the latest addition to the prevention toolbox, pre-exposure prophylaxis (PrEP). It is this last method and its comparable advantage over the others in preventing new infections that is of interest in this thesis.

PrEP is a medical drug that contains the same antiretroviral agents that are employed in treatment of HIV, but when utilized before an exposure to HIV as chemoprophylaxis, provides protection by preventing the virus from replicating itself. PrEP also has the additional benefit of reducing infectiousness during primary HIV infection (Kersh et al., 2012) in the event of PrEP failure (also referred to as breakthrough infection). Currently there is only one form of PrEP that has received market access, albeit in three countries: the United States, France, and Australia. The drug was developed by Gilead originally as a combination therapy of the antiretrovirals tenofovir and emtricitabine, marketed under the name Truvada. In 2012, the company sought approval for a preventative indication after trials proved the drug’s preventative qualities. As it is the only form of PrEP currently available, Truvada has become synonymous with PrEP. Truvada used as PrEP is at present approved as a daily fixed-dose combination oral ARV medication, though other forms of the drug are currently being investigated. Research investigating the cost-effectiveness of PrEP in preventing HIV infection in endemic areas is lacking (Gomez et al., 2013). Such analyses can assist decision makers in countries such as Norway, where so-called high-risk activity is common yet the incidence and prevalence of HIV infection is relatively low. This thesis attempts to answer the reimbursement question—“does PrEP targeted towards high-activity MSM living in Norway provide good value for money?” To answer the question, several cost-effectiveness analysis frameworks are employed, such as: cost-per-QALY and cost-per-new-infection-averted. Rephrased, the thesis seeks to identify which of the following scenarios is cost-effective: a.) hypothetical scenario that includes a mix of current testing and sexual behavior, and immediate uptake of PrEP among 25% of high-activity MSM residing in Norway, or b.) status-quo scenario in which PrEP is not made available to the MSM target group.

The thesis is structured as follows: background information on HIV is provided in Chapter 2, along with information regarding prevention, diagnostics, and treatment. Additionally, the chapter provides an overview of the theory paramount to economic evaluation and decision analytic modeling as it relates to the frameworks and methods employed in connection to this thesis. In addition to outlining the structure, mechanics and assumptions of the
Markov HIV transmission model employed in assessing PrEP’s cost-effectiveness, Chapter 3 provides a brief explanation of identifying and handling the uncertainty surrounding the model’s outputs. The differential costs and health effects associated with the two scenarios of interest are presented in Chapter 4 along with estimates of model uncertainty. Lastly, both a discussion of the results and key limitations of the model are provided in Chapter 5. Concluding remarks are shared in Chapter 6.
2 Background

2.1 HIV/AIDS

The human immunodeficiency virus is a RNA lentivirus (i.e., virus associated with long latency period) that targets and destroys cells critical to the proper functioning of humans’ immune system, namely macrophages and T cells. Ultimately left untreated, HIV will lead to deadly opportunistic infections (Moore et al., 1996). Two different species of the virus exist in nature: HIV I which is the most common in Europe due to its relatively greater virulence and infectivity, and HIV II which is contained largely in West Africa having failed to spread to other parts of the world given its virologic characteristics (De Cock et al., 1993). The virus ultimately replicates itself in the cells of its host; eventually destroying the latter’s immune system if left untreated. Replication occurs as the virus penetrates a target cell, and converts its viral RNA genome into a double helix DNA molecule using the enzyme reverse transcriptase. The resultant DNA product is then implanted into the target cell’s nucleus and further integrated into its cellular DNA. This process is prone to coding errors, resulting in large numbers of genetic mutations that allow the virus to go undetected by the host’s immune system (Roberts et al., 1988). Eventually, however, the conquered cell begins producing new RNA genomes and virions that are released from the cell to travel freely in the body as they search for new cells to exploit in their further replication.

The various disease stages of HIV have been identified according to its symptoms which are, in turn, related inversely to the infected host’s viral load and CD4 cell count. Health related quality of life, as well as transmission hazards vary across the different stages. Additionally, as HRQoL varies, so too does the individual consumption of health resources. In the model developed as part of the thesis, HIV was stratified into four disease stages according to the Center for Disease Control’s (CDC) disease staging system (Center for Disease Control, 2008). These disease stages are listed below, and are followed by a figure (Figure 1) outlining a typical individual’s transition throughout the stages in absence of treatment.

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1 Mature T helper cells are called CD4+ T cells because they express the surface protein CD4. As type of T cell in the human body, CD4+ serve a vital role in the adaptive immune system as they are essential to B cell antibody class switching, the activation and growth of cytotoxic T cells, and in assisting in the maintenance of macrophages and phagocytes (Thornton et al., 2000).
**Acute Primary Infection** – This initial stage of HIV infection lasts between one and six months after exposure, and is characterized by elevated levels of viral load in the body, leading to a significantly increased risk of transmission (Longini et al., 1989). CD4 cells are used to produce large amounts of the virus in the body, and are destroyed thereafter, thus the amount of CD4 cells in the body may fall sharply. Between 50%-90% of people newly infected with HIV experience symptomatic acute infection (Pilcher et al., 2004; Schacker et al., 1996), in which they suffer extreme flu-like symptoms and extreme discomfort (Tindall & Cooper, 1996).

**Early Asymptomatic Stage** – The host experiences a long latency period after transitioning to this particular disease stage during which the virus, although continually reproducing itself, does so at a much lesser rate (Embretson et al., 1993). Meanwhile, the host has begun to respond to infection by producing CD4 cells, thus driving down the viral load and significantly reducing the host’s infectiousness. During this stage, the virus does not produce clinical symptoms of immune failure so the host experiences very little to no decrease in health. This stage typically lasts for as many as ten years (Longini et al., 1989).

**Symptomatic Stage** – The host eventually develops symptoms as the person’s viral load begins to increase, consequently leading to a fall in CD4 cell count. Symptoms range in severity (Cunningham et al., 1998) but typically involve infections and bacterial/fungal diseases that the body would normally be able to fend off, were the immune system not compromised (Mayer et al., 2007).

**Late Stage (AIDS)** – This particular stage has for many years been defined according to the level of CD4 cells in the host’s body. Conforming to the CDC’s definition, a person progresses to late stage infection when their CD4 level falls below 200 cells/μl. Once a person’s CD4 cell count drops below this threshold, they are considered to no longer have HIV, but have progressed to AIDS. Without treatment, people who progress to AIDS typically survive no more than three years (Lemp et al., 1990) because they are at extremely high risk for contracting (multiple) opportunistic illness(es). Individuals in the “late” stage are also more infectious than those in either early or symptomatic stages (Hollingsworth et al., 2008).
2.1.1 Epidemiology

As of 2014, over 5600 people living in Norway had been diagnosed with HIV (Folkehelseinstituttet, 2014). It is estimated that an additional 800-900 people residing in the country were infected, yet unaware of their status (Hamers & Phillips, 2008). As witnessed in neighboring European countries, the rate of HIV infection in Norway has remained relatively stable during the last decade (Sullivan et al., 2009). In certain particular demographic groups, however, the disease is on the rise. Among men who have sex with men residing in Norway (MSM), there has been observed a tripling of infections within the last decade, with 2014 witnessing the most infections per year on record. While this group makes up a small percentage of the Norwegian population (estimated 3.5%), they account for nearly four of ten infections (Folkehelseinstituttet, 2015). Median age at diagnosis among HIV infected MSM is between 30 and 40 years of age (Folkehelseinstituttet, 2015). Previously, treatment was delayed until CD4 cell count fell below 350 cells/μl, however, recent research has proven that treatment outcomes are drastically improved when treatment is initiated directly after diagnosis (Grinsztejn et al., 2014). A person with a high CD4 count at diagnosis who begins treatment shortly after being diagnosed can expect to live a nearly normal life span (Samji et al., 2014).
though treatment failure is likely to occur at least once (Mocroft et al., 2005). Each therapeu-
tic failure poses health risk to the infected individual as well as increased transmission risk to
the individual’s sexual partners (Deeks et al., 2000).

2.1.2 Risk Factors

Any form of behavior that puts individuals at risk of coming in contact with bodily
fluids known to transport the virus can be labeled a risk factor. Most often, the virus is tran-
spored via blood and secretions from the body’s sexual organs (e.g. semen, vaginal and anal
fluids); therefore needle sharing during injection drug use, and unprotected sexual intercourse
are well established risk factors for contracting HIV (Darrow et al., 1987). Evidence suggests
that anal intercourse is more risky than vaginal sex (Baggaley et al., 2010). It is hypothesized
that the absorption properties of the surface lining of the anus are responsible for this diffe-
rence in transmission risk. Very few intravenous drug users are infected each year in Norway,
and comprise only 11 percent of total HIV infections (Folkehelseinstituttet, 2014). HIV inci-
dence in Norway has dropped significantly in this subgroup largely thanks to successful nee-
dle and syringe exchange programs (Amundsen, 2006). In 2014, injection drug users made up
only seven of the 249 diagnosed HIV cases in that year (Folkehelseinstituttet, 2014). Sexually
transmitted infections (STIs) often lead to sores and secretions of fluid and puss, therefore
increasing the likelihood of contracting as well as further transmitting HIV (Ward & Rönn,
2010). Additionally, it was found that uncircumcised men had an increased risk of heterosex-
ual transmission of HIV (Auvert et al., 2005).

2.1.3 Diagnostics

Several testing and screening technologies of wet samples (typically blood) have been
developed to detect HIV’s presence in the human body. Previous diagnostic tests relied solely
on the detection of the body’s own antibodies produced in an attempt to fight off the virus.
However, these methods proved unable to detect the virus within a so-called “window period”
that lasts up to three months after infection (Busch et al., 1995). This failure leads to numer-
ous false negatives because the body has not produced enough antibodies for the tests to de-
tect. To improve diagnostic sensitivity, a new technology related to the detection of the p24 protein antigen\(^2\) of the HIV virion was adopted. Currently both antibody and antigen-based diagnostic technologies are bundled into a combination test founded upon enzyme immune assay technology (ELISA). According to Norwegian guidelines, a Western Blot test must be conducted in the event of a reactive combination test (Lundby et al., 2014). This form of test is a more expensive technique for detecting specific antibodies that involves several steps (van der Groen et al., 1991). In the last decade, rapid tests have been developed and can detect HIV I and II antibodies and/or antigens. An individual undergoing testing can therefore receive results in a matter of seconds. These tests are less sensitive because they utilize a completely different method of detection (immunochromatography), and may even give false positive responses (Klarkowski et al., 2009). Norwegian authorities therefore require that a combination (EIA) test is taken simultaneously with a rapid test (Folkehelseinstituttet, 2010). While inexpensive and generally accurate, these common HIV diagnostic tests are often interpreted in a laboratory setting and require the collection and proper shipping of human samples to the lab locations. In Norway, over a quarter of all diagnostic blood tests are analyzed at Oslo Universitetssykehus because other smaller hospitals and clinics do not have the capacity (Lundby et al., 2014).

2.1.4 Treatment Options

Zidovudine, a nucleoside reverse transcriptase inhibitor (NRTI) was developed and approved by the United States Food and Drug Administration (FDA) in 1987, becoming the first ever effective therapy against HIV. The drug was initially prescribed as a monotherapy, but was combined with other subsequent NRTIs so as to increase treatment effect and combat drug resistance. These combinations eventually proved ineffective in suppressing the virus over a long period of time (Larder et al., 1989). By the mid 1990’s, however, a new form of highly active ART (HAART) was developed in which two NRTIs and a protease inhibitor were combined. This new therapy drastically reduced death and hospitalization rates, and increased survival (Hammer et al., 1996). The arsenal to combat HIV has since grown from the

\(^2\) An antigen is a molecule (commonly a protein) that incites an immunologic response such as the creation of antibodies (Antigen, U.S. National Library of Medicine)
initial NRTI class to include three other classes (NNRTIs, integrase inhibitors, and protease inhibitors):

*NRTIs* – prevent proper sequencing of DNA chains made during reverse transcription, thereby preventing further viral reproduction. NRTIs block the incorporation of other nucleosides by acting as a competitive substrate inhibitor during the natural process of mitochondrial DNA synthesis (Niskanen Hansen, 2010). This can lead to high levels of lactate in the body resulting in lactic acidosis, as well as neuropathy (i.e. dysfunction of the nerves), myopathy (disease of the muscles) and lipoatrophy (i.e. loss of fat tissue or redistribution of fat).

*NNRTIs* – While NRTIs act as chain terminators blocking both access to the active site for viral but also DNA synthesis, NNRTIs (non-nucleoside reverse transcriptase inhibitors) bind directly to the reverse transcriptase enzyme of the viral RNA molecule (Niskanen Hansen, 2010). NNRTIs are associated with minimized side effects and toxicity because they permit host cell DNA synthesis while NRTIs do not (Kontorinis & Dietrich, 2003).

*Integrase inhibitors* – This drug class inhibits the proper function of the integrase enzyme necessary for integrating viral DNA into the DNA of the host’s infected cells. While integrase inhibitors have been observed to be the best tolerated, treatment use is associated with increased creatine kinase levels and myopathy (Monteiro et al., 2013).

*Protease inhibitor* – during the final stage of the viral reproductive cycle, new HIV-1 virions are bundled into two HIV envelope glycoproteins that are eventually cleaved, a process regulated by protease, from the Golgi complex of the infected host cell and released to further infect other cells (Jaskolski et al., 1991). Inhibited protease fails to properly produce mature virions, therefore the cleaved viral particles are often defective and therefore non-infectious (Kohl et al., 1988). Protease inhibitors are often prescribed with the drug ritonavir, leading to several drug-drug interactions (Malaty & Kuper, 1999). Moreover, this drug class is associated with increased risk of lipoatrophy, elevated levels of triglycerides and risk of heart attack (Rhew et al., 2003).
Figure 2 below illustrates how each class of ARV drug affects the development cycle of the HIV virus. Current clinical guidelines in Norway recommend a first line treatment comprising of two NRTIs and an integrase inhibitor (Norsk Forening for Infeksjonsmedisin, 2016).

Figure 2. HIV development cycle and attack point of available ARV drug families (Source: Helse Fonna, 2013).

2.1.5 Prevention Methods

Infected individuals with HIV ultimately experience great losses in health if treatment is delayed, and once treated, they may experience further suboptimal health due to the available treatments’ toxicities. Moreover, infected persons with HIV are responsible for large health care expenditures related to diagnosis, care, and prevention of further spread of the disease. Prevention methods are therefore paramount to free up health resources for other therapeutic areas, and prevent significant losses of health attributable to HIV infection. HIV diagnosis surveillance data collected in Norway suggest that currently available preventative methods are not adequate in preventing HIV transmission amongst MSM. Attention to alternative strategies for controlling the spread of HIV must therefore be paid. Below is a list of currently available technologies employed to prevent the transmission of HIV.
2.1.5.1 Condoms

Consistent use of latex condoms has been proven effective in the primary prevention of HIV infection. Condoms ultimately serve as a barrier, preventing the exchange of virus containing bodily fluids between an infected individual and his/her sexual partner. Several HIV seroconversion studies among heterosexual partners suggest ultimately that consistent condom use can prevent between 90-95% of would-be-infections (Pinkerton & Abramson, 1997). It is assumed that condoms are equally effective in preventing HIV infection between male same-sex partners. Since the late 1980s, large amounts of resources have been devoted to the promotion of condom use as a form of protection against HIV infection. In 2016, alone the Norwegian government suggested 5.5 million NOK be earmarked to the procurement of condoms and other sexual health programs (Helse og Omsorgsdepartementet, 2016). Despite being readily available, and inexpensive, EMIS survey data indicate that condoms are often not used consistently in Norway (Folkehelseinstituttet, 2013).

2.1.5.2 HIV Testing

When people become aware of their status, they alter their behavior (Marks et al., 2005). Moreover, those testing positive are quickly linked to care and initiate drug treatment which greatly reduces their infectivity (see “Treatment as Prevention” below). Therefore, increasing the magnitude and frequency of testing among a population can ultimately prevent numerous infections. A survey of MSM residing in Norway indicated that over a third never received the result of an HIV test (Folkehelseinstituttet, 2013). Currently HIV tests are available free of charge to MSM living in Norway, and are provided both during consultation with a GP as well as at hospitals and clinics. Further outreach has involved mobile testing sites.

2.1.5.3 Treatment as Prevention (TrAP)

Antiretroviral treatment ultimately lowers the amount of the virus in the body by targeting various viral reproduction mechanisms (Niskanen Hansen, 2010). This leads to a decrease in the infectiousness of the individual. Typically after 24 weeks of successful treatment, a person
achieves viral suppression (i.e. <50 copies/mL) and is therefore practically noninfectious (Smith et al., 2004). The key takeaway from observational studies of serodiscordant couples with the infected partner responding to ART is that wider, earlier initiation of treatment reduces population-level incidence of HIV (Reynolds et al., 2011).

2.1.5.4 Post-exposure Prophylaxis (PEP)

Chemoprophylaxis is an established primary prevention strategy for protecting uninfected persons before, during or after a window of exposure time to a particular pathogen (Desai, 2008). The idea then to prescribe ARVs to healthy patients is not a novel one. Prophylaxis ARV-use specifically within HIV prevention is well documented in preventing mother-to-child HIV infection as well as infection due to occupational exposures to HIV (Desai, 2008). PEP involves the use of HIV treating drugs to prevent infection shortly after an individual is exposed to HIV. As mentioned, antiretrovirals reduce the risk of infection by preventing viral reproduction. PEP is prescribed for a period of four weeks and must be initiated no later than 48–72 hours after exposure (Norsk Forening for Infeksjonsmedisin, 2016). Previously PEP was used to prevent occupational exposures in Norway, but since 2013, the Norwegian Institute of Public Health (FHI) has promoted the technology towards MSM in the hopes of preventing sexual exposures. Although a 2010 survey of Norwegian MSM (Folkehelseinstituttet, 2013) indicated that a third (32%) had knowledge of PEP and its use in preventing HIV, the number of instances PEP is prescribed per year in Norway is unknown. The dubious extent to which PEP prevents HIV infection in Norway compounded by Hansen’s findings, which indicate that many prescribed PEP after a sexual exposure discontinue the treatment before completing the 28 day treatment regimen, often to avoid severe side effects (Hansen, 2014). Widespread interruption in PEP treatment is likely to augment the risk of future resistance against ARV drugs.

2.1.6 Pre-exposure Prophylaxis (PrEP)

In 2012, the pharmaceutical company Gilead Sciences, Inc. sought and gained approval from the U.S. regulatory authorities to market Truvada, a combination ARV therapy consist-
ing of two NRTIs (tenofovir and emtricitabine) for a preventative indication (i.e. marketed towards HIV negative individuals). Although Truvada’s preventative effect is recognized, based on rather incongruent cost-effectiveness study results (Molina et al., 2013) largely attributable to the treatment’s high sticker price, regulatory authorities are unwilling to grant market access for the preventative indication. Estimated cost per QALY figures were found to range from below $50 000 to upwards of $500 000 or more (Juusola, 2013), yet the overwhelming majority of models found Truvada to not be cost-effective on average when using a decision-rule threshold value of willingness to pay. Interestingly, nearly all of the models consulted explored cost-effectiveness in a very specific population, “high risk” MSM, so their findings apply just to this population. No further subpopulations within “high risk” men were incorporated into the models, and how the men were defined as “high risk” often depended on somewhat arbitrary cut-offs of continuous variables (e.g. number of sexual partners in past month).

Critics of PrEP are not only opposed to the high cost, but also fear drug resistance and an increase in more risky behavior. Several leaders in HIV/AIDS advocacy have come out labeling Truvada as a “party drug” (Belluz, 2014). Their concerns primarily stem from the fear that the drug will lead to risk compensation whereby Truvada induces promiscuity and unsafe sex, both of which may have extreme health and cost ramifications. While theoretically people using PrEP might feel protected against HIV and therefore be less prone to use condoms and have more sexual partners (Molina et al., 2013), leading trials for PrEP found no evidence of increased risky behavior among participants placed on PrEP (McCormack et al., 2016). The real-world validity of this finding, however, is “likely to be a consequence of the closed counselling that participants involved in those trials received,” (Molina et al., 2013). Moreover, the fact that participants in the placebo trials were ignorant to whether they were receiving active drugs or not may have made them more “receptive” to counseling (Molina et al., 2013). While Truvada and other forms of PrEP have not received approval from the Norwegian Medicines Agency (NMA), infectious disease specialists working at Oslo Universitetssykehus have allegedly prescribed Truvada to HIV negative individuals\(^3\).

Generic versions of Truvada are also available for purchase from various websites at significantly lower prices (approximately 85% less than Truvada), some of which do not re-

\(^3\) Taken off the record during a qualitative interview with individuals engaged in the Norwegian PrEP debate.
quire customers to upload prescriptions (I Want PrEP Now, 2016). The Norwegian authorities’ unwillingness to reimburse has led to the creation of a strong advocacy movement. PrEP proponents argue that continued investment in traditional treatments and interventions currently implemented come at a cost (Richter et al., 1999). Brandeau et al. echoes this concern in their discussion on diminishing return of expenditure with respect to incremental risk reduction of HIV. Brandeau and colleagues (2009) find that a programme or intervention funded at a certain level ultimately reaches a maximum effect, giving the example of a counselling intervention’s effect plateauing after having reached all individuals willing to change their behaviour (Brandeau et al., 2009). Ultimately, advocates of PrEP are seeking to convey to the authorities that they must expand their treatment portfolios because the available prevention solutions are lacking, and that there exists an intervention mix that collectively provides “the most benefit for a given budget” (Richter et al., 1999).

2.2 Economic Evaluation with Markov Models

The course of an epidemic depends on the force of infection denoted by R_0 (also called the reproductive number). According to Baussano and colleagues (2014), this force is ultimately a function of the rate of contact (c) between susceptible and infected individuals (referred throughout the thesis as seronegatives and seropositives, respectively), the probability of transmission per contact (p), and the duration of infectiousness (d). The product R_0, thus conveys the average number of secondary cases produced by one seropositive.

Equation 1.

\[ R_0 = c \times p \times d \]

Interventions are intended to drive the reproductive number down by either decreasing: contact rates, the probability of transmission, or the duration of the illness. PrEP advocates acknowledge that the drug has the potential to decrease the probability of HIV transmission, and in combination with other prevention strategies, may cause HIV to enter a die-out phase where \( R_0 < 1 \). They claim that the technology is not reaching those who need it, and pur-
port that significant numbers of MSM and other risk groups stand to benefit from market approval (Molina et al., 2013).

This thesis attempts to quantify the level of health forgone in Norway from delaying approval and reimbursement of Truvada with a prophylactic indication. In doing so, the findings presented can aid decision makers in maximising health, and assessing the amount of financial resources potentially freed up were Truvada to be granted approval as PrEP, therein improving budgetary allocation. Optimal allocation is dependent upon the relative added benefit inherent to a treatment over its comparator. To quantify PrEP’s added value in preventing HIV infection in Norway, a series of economic evaluations employing different techniques was conducted. Drummond and colleagues define economic evaluations as, “the comparative analysis of alternative courses of action in terms of both their costs and consequences,” (Drummond et. al, 2005).

2.2.1 Cost Utility Analysis

The primary form of economic analysis employed was cost-utility analysis (CUA): an analysis based upon the comparative differences of costs and health effects between a treatment of interest and its comparator(s). Ultimately the incremental difference in costs is divided by the incremental difference in effects in order to generate the incremental cost-effect ratio (ICER), interpreted as the cost for one additional unit of effect (see Equation 2). In this particular situation, the costs and preventative effects of two different scenarios were compared: a so-called “PrEP” scenario, in which 25% of “high-risk” HIV-negative MSM begin taking a once-daily form of oral PrEP, and a baseline status quo scenario under which current forms of prevention excluding PrEP were considered.

Equation 2.

\[
ICER = \frac{Cost_{PrEP} - Cost_{status quo}}{QALY_{PrEP} - QALY_{status quo}}
\]
In the analyses presented later in the thesis, effects are quantified in life years gained (LYG) and quality-adjusted life years (QALYs). While the former measures the number of life years lived by each individual, the latter “attempts to value benefits of health care” in a common numeraire by combining the impact of increased longevity with quality of life (Brazier et al., 2007). Costs associated with the different scenarios are calculated in Norwegian kroner (NOK), and are related to the costs of both implementing the prevention technology of interest (PrEP) as well as the costs associated with the burden of HIV illness. Costs and effects are considered over a thirty-year time period (time horizon), according to a healthcare perspective, and are discounted at a rate suggested by the NMA. The length of the time horizon ultimately must be long enough to capture all relevant outcomes (events) and resource consumption related to the decision.

The perspective assumed by researchers in conducting the decision analysis greatly impacts the analysis’ results. A healthcare perspective only assumes the direct costs and benefits of the program to be implemented, and ignores both its indirect and intangible costs and benefits. While it is acknowledged that the societal (production) loss attributed to HIV is large and therefore relevant (Hanvelt et al., 1994), it was not considered. Were an extra-welfarist perspective to be assumed, benefits such as increased productive output attributable to improved health would be considered in weighing a reimbursement/access decision. The discounting of costs and effects accounts ultimately for the decision-maker’s time preference (Drummond et al., 2005). An interest rate is used to compute the costs and effects of treatments into present values to reflect the rate at which “the decision maker is willing to trade present for future consumption,” (Brazier et al., 2007). Negative rates of between three and five percent are often applied in economic analyses of health related programmes and technologies, as decision makers are typically unwilling to forgo current consumption unless promised gains of 103-105% on their investment. In addition to the cost-utility analysis, a cost-benefit analysis is provided in order to place monetary value on the health benefits of a certain scenario over another. This is accomplished by applying a willingness to pay threshold so as to estimate the net monetary benefit (NMB) of each treatment (scenario). The treatment with the highest NMB is considered to be the best treatment option.
2.2.2 Cost-Effectiveness Analysis

Lastly, a cost-effectiveness analysis is presented, providing the cost per effect ratio, with all effects being quantified in natural units (e.g. number of infections). In this example of PrEP vs. status quo scenarios, the effects are quantified in both life years and infections averted. From the latter, the number needed to treat to avoid one new infection is derived. Currently there exist no randomly controlled trial data on HIV transmission amongst MSM receiving PrEP in Norway. Moreover, there exists no national surveillance data on the health resource consumption of HIV infected MSM living in Norway. A conceptual deterministic Markov model was therefore created to understand the current consumption of health care resources the health loss due to HIV infection, and potential health/monetary gains and costs associated with making PrEP available to a target group of MSM assessed as high risk.

2.2.3 Modeling PrEP

Models are simplified representations of reality, allowing a complex system to be reduced to its essential elements (Caro et. al, 2012). As such, they are powerful public health tools used in informing policy makers tasked with designing optimal intervention strategies. To distinguish the essential from the superfluous, it is imperative to analyze and understand both how the disease progresses and affects individuals, and how it impacts health expenditures before electing a model structure. Ultimately, a Markov model was elected to estimate PrEP’s impact on HIV transmission, detection and progression as well as expenditures, because its structure is suited best to handle the modelling of options with a large number of potential outcomes (Briggs et. al, 2006). The deterministic compartmental model was developed according to a state transition framework in which inhabitants of the model flow throughout the various health states during discrete time steps (cycles) of fixed duration. The model reflects a social contact structure with respect to sexual activity grouping, a key feature of infectious disease modelling related to the representation of a sexual network. The intervention is targeted towards strongly connected nodes (i.e. high activity group), though there is strong variation in the number of contacts within this group. Figure 3 demonstrates the interactions between the individual nodes of a network, which differentiate according to connec-
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tivity (e.g. sexual activity). It is theorized that targeting “high” nodes rather than “random” nodes will lead to a greater treatment effect (Liljeros et al., 2001).

Figure 3. Example of effective targeting of nodes within a social network (Source: Strogatz, 2001).

In accordance with established epidemiologic disease model structures, every inhabitant at each cycle occupies just one MSM sexual activity group and one immune (susceptible) or disease (infected) state. Infection may be transmitted among individuals within the population upon adequate exposure to HIV. Upon infection, individuals progress through each of several infected states. Disease mortality and mortality due to causes unrelated to HIV were also simulated. Ultimately, costs and effects (QALYs) were incorporated into the model by applying associated mean values of each to the different states. Expected values of costs and effects are calculated by taking the sum of each across the states, and weighting according to the time the patient is expected to be in each state (Briggs et. al, 2006). The number of cycles that each individual spends in the different states is determined from the interaction of model parameters randomly chosen from their appropriate distributions. As transmission is a stochastic process, standard departmental epidemiologic models are seldom perfectly predictive because they divide the population into homogenous groups and apply average rates rather than modelling each individual node in a network system and the links between them (Morris, 1993). Rare events captured in the ranges of the model’s inputs may have a large effect on the outputs, so median rather than mean estimates of costs and effects are of more interest (Punyacharoensin et al., 2016).
2.2.4 Evaluating Uncertainty

Much of the data informing parameter estimates used in the model (e.g. probability of an event, mean cost, mean utility) were obtained from research conducted outside of Norway, and therefore may not be transferable to a Norwegian context. Furthermore, while parameter estimates reflect expected values observed in a population, they were derived from limited information (Briggs et al., 2006), often from studies of population samples that more often than not failed to report variances for these estimates. When samples are not representative of the population, a biased estimate arises. To understand the precision with which the input parameters were estimated, understood otherwise as the level of parameter uncertainty, a probabilistic sensitivity analysis (PSA) was conducted. Uncertainty surrounding the results of an analysis ultimately implies the possibility of an incorrect decision being made, which further imposes a cost (understood as benefits forgone). By quantifying the level of parameter uncertainty inherent to a model, economic evaluators can relay this information to the decision-maker and convey how this form of uncertainty further translates into decision uncertainty (i.e. the probability that a given decision is the correct one (Briggs et al., 2006)). Moreover, the results of probabilistic decision models convert uncertainty estimates into information about the value of “optimal design” of future research, as the collection of additional evidence is likely to reduce uncertainty (Briggs et al., 2006).

2.2.4.1 Probabilistic Sensitivity Analysis

Conducting a PSA entails assigning a probability distribution to each parameter estimate. The plausible range of parameter estimates is dependent on the variance specifications used, and the choice of distribution employed to model estimate variation. Ultimately, distributions are narrower when the mean estimate of a parameter is more certain, and broader when the mean value is less certain. The second stage of a PSA involves a technique called Monte Carlo simulation. This process ultimately varies each of the model’s parameter estimates simultaneously across their determined probability distributions. To do this, parameter estimate values are randomly drawn from assigned probability distributions a specified number of times (iterations). The outputs of the model are logged after each iteration, thus produc-
ing a “large set of expected costs and effects that reflect the combined parameter uncertainty in the model,” (Drummond et al., 2005). Incremental costs and effects generated from each iteration are then plotted onto a cost-effectiveness plane (CE plane) consisting of four separate quadrants (see Figure 4 below).

**Figure 4. The Cost-effectiveness (CE) plane divided into quadrants relating to comparative cost-effectiveness of a treatment versus its competitor.**

The plotted joint density distribution of ICER estimates are then summarized by the cost-effectiveness acceptability curve (CEAC). Ultimately, the CEAC communicates the level of uncertainty surrounding the cost-effectiveness of mutually exclusive treatment options for a range of thresholds for cost-effectiveness (Briggs et al., 2006). To construct the CEAC, the incremental cost and effect ratios for each simulation are transferred into net monetary benefits. By rearranging the algebraic formulation of the decision rule for cost-effectiveness analysis, ICERs can be converted into net monetary benefits in which both costs and effects are measured in monetary units. While it is possible to derive a CEAC from calculated ICERs, it has proven easier to do so using net benefits because ICERs are less informative (Briggs et al., 2006). A ratio in which a treatment has decreased costs has the same sign as a ratio in which a treatment has decreased effects, yet these ratios lie in different quadrants of the CE plane. Negative ICERs lying in the NW quadrant of the CE plane are qualitatively different from negative ICERs in the SE quadrant because they favor two different treatments. Taking averages or rank-ordering the ICERs is therefore flawed. To move away from the inherent issues of ratios, costs and effects are placed on a single scale.
2.2.4.2 *The Value of Information*

Uncertainty exacts a cost because it represents the risk that a decision is wrong. Often, decisions are difficult to reverse so when an incorrect decision is made, society suffers a cost. In the economic evaluation of healthcare technologies, this loss is manifested either as a level of health forgone, or as a failure to save financial resources, or both. While much information surrounding deterministic and parametric parameter uncertainty can be generated in conducting the aforementioned analyses, they both ultimately ignore the “consequences of not selecting the ‘true’ preferred alternative,” (McCullagh et al., 2012). One method of ascribing value to these consequences and, in turn, to their reduction is the Expected Value of Perfect Information (EVPI) approach. The EVPI attaches a value to the simultaneous elimination of parameter uncertainty, and is determined directly from the PSA results. As seen from another perspective, EVPI ascribes value to the creation of additional information used to better inform parameter estimates. The EVPI is thus understood as a measure of the maximum expected return on further research, therefore the decision to acquire more research “involves balancing the cost of acquiring more information with its value,” (Briggs et al., 2006).

While the EVPI reflects the expected value of perfect information at the individual/patient level, the “overall value of perfect information surrounding a healthcare policy decision depends on the number of times that the decision is faced over the lifetime of a technology,” (McCullagh et al., 2012). This population-level EVPI (PEVPI) is thus a function of the “incidence of the decision”: the number of people a decision is expected to impact as well as the amount of time a decision/technology is relevant. Ultimately, both the EVPI and PEVPI estimate the value of the magnitude of uncertainty, and in doing so, the value of future research. Eliminating all parameter uncertainty, however, is unrealistic, so future research must be prioritized. The previous two methods do not lend themselves to this prioritization of research because they do not identify those parameters or parameter groups that cause the greatest uncertainty. An extension method, the Expected Value of Partial Perfect Information (EVPI) method, is therefore applied. In its application, the difference is taken between the expected value of a decision based on current information and the expected value of a decision made with perfect information on selected parameters. All three methods were applied to the simulation results of the PSA so as to inform decision makers of the potential benefit in delaying a decision and collecting more information.
3 Methods

3.1 Decision Analytic Model

As mentioned in the previous chapter, decision analytic modeling allows for an evaluative comparison in the “flow [of possible consequences] from a set of alternative options,” (Briggs et al., 2006). Moreover, modeling allows for the incorporation of uncertainty around its own input parameters related to costs and effects. A model developed by Long and colleagues (see Long et al., 2006) to estimate the cost-effectiveness of different HIV prevention strategies among IDUs was adapted to estimate both HIV transmission among MSM residing in Norway, and the cost-effectiveness of PrEP vs. a status quo scenario in which PrEP was not available. The model, developed in Excel, is dynamic in nature and compartmentalized according to the various health states associated with HIV disease transmission susceptibility, disease progression, diagnosis and lastly treatment. During a model cycle, individuals populating the model either transition to another state or remain put. Costs and a health-determined quality of life are applied to each stage. A schematic flow diagram of the model is provided in Figure 5 below.

Figure 5. Structure of compartmental deterministic PrEP HIV prevention model.
3.1.1 Model Structure

Markov models can be used to represent stochastic processes that evolve over time, by dividing the disease in different mutually exclusive health states (Briggs et al., 2006). The percentage of the cohort in each state (the Markov trace) is determined at each cycle. Health states should be chosen to represent the underlying biological process of the disease in question (Sculpher et al., 2000). The model pictured above was used to estimate the flow of both HIV susceptible and HIV infected MSM residing in Norway over a thirty-year time horizon as denoted by the 519 three-week cycles. The model is comprised of 23 states, as well as the additional absorbing state “death” (not pictured in model). The boxes in the diagram represent these states. Individuals of the model are either susceptible (not infected) or infected (living with HIV), and belong to either “low” or “high” sexual risk groups, indicated by the subscripts $Y_i$ and $X_i$, respectively. Individuals, however, move between the two activity groups (at rate $S_i$; see Table 3) throughout the entirety of the time horizon. Those infected with HIV are distributed according to their CD4 cell count into the different CDC defined HIV infected states mentioned earlier in Chapter 2. Seropositive individuals are either aware (diagnosed or receiving treatment) or unaware (undiagnosed) of their positive serostatus. Only those who have received a diagnosis may begin treatment. Susceptibles may only move within the following three states: low activity susceptible, high activity susceptible, and susceptible receiving PrEP (available only to high activity susceptibles). To simulate the baseline status quo scenario, the three states regarding PrEP treatment ($X_{11}, X_{12},$ and $X_{13}$ pictured in Figure 5 on the preceding page) as well as parameters related to PrEP treatment are excluded from the model.

According to the literature, the choice of cycle length should be driven by what is known about the underlying disease processes and be the minimum interval over which pathology and/or symptoms in patients is expected to alter (Drummond et al., 2005). A cycle length of three weeks was chosen to model both HIV transmission and the preventative effect of PrEP. It is expected that only one transition per individual will take place in this short time frame. While a person may seroconvert (transition) after just one sexual act with a seropositive partner, a length of three weeks was elected largely because a true serconverter undergoing diagnostic testing is likely to receive a positive result. Moreover, it was observed that at a
time step of three weeks, very few people had seroconverted (often between four and six individuals). Lastly, a large number of time-steps would be computationally demanding. A half-cycle correction was integrated into the calculation of model outputs in order to account for the fact that individuals may transition at any point during the three weeks (e.g. directly after the start of the cycle, right before the cycle, and any time in between). The half-cycle correction ultimately identifies the number of model inhabitants in the various states at the exact middle of each cycle (Sonnenberg & Beck, 1993).

A full description of the modeling process and an overview of its assumptions are provided in the following sections.

3.1.2 Model Assumptions

- The model is a deterministic population-based model (i.e. models the entire MSM population of Norway between ages 15 and 66)
- Markov Assumptions (3)
  - Homogeneity at the state level
  - “First-Order Markov” assumption: regardless of an individuals’ history (time spent in previous states), the same transition probability is applied equally to all individuals in a state
  - Transition rates are constant
- Infection of susceptible MSM occurs only via anal intercourse in a sexual partnership with another male
- A partnership involves both partners partaking in receptive and insertive anal sex (i.e. both are “versatile”)
- Partnership mixing occurs randomly, apart from sexual activity grouping
- PrEP leads to risk compensation (increased number of sex partners and frequency of condomless sex)
- Side effects and adverse events related to PrEP no longer occur after PrEP cessation
- All individuals with diagnosed breakthrough infection immediately discontinue PrEP

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Once treated, seropositive individuals remain in the treatment stage until removed from the model (aged out, dead)

- Individuals can transition between activity groups at all stages
- No HIV infection that occurs outside Norway is included except for establishing the number of seropositives living in Norway to populate the first cycle of the Markov trace
- No differentiation by geographic area was included in the model

3.1.3 Model Input Parameters

Model parameters controlling the movement of individuals across the Markov states are listed in Table 3. The majority of parameters were extracted from relevant literature and other HIV modeling studies. References to these sources are therefore also provided in Table 3. Important input parameters regarding sexual behavior used in the modeling of HIV transmission were estimated from statistical analysis of data gathered from respondents of the European MSM Internet Survey (EMIS) residing in Norway. The creators of the EMIS intended for its results to be used in providing input for making improvements in present and future HIV preventative work among MSM. The dataset containing statistical survey response data was split in two according to the definition of the two sexual activity risk groups. The model parameters estimated from the dataset are: average number of sex partners, condom use rates, HIV prevalence, and odds ratios for HIV testing. The software packages STATA and SPSS were used in the statistical analysis of the survey data, specifically to evaluate both measures of center and distribution of parameters, and to run statistical tests of difference (e.g. two sample t tests) between the two sexual activity groups (low vs. high). Survey data was also used in assessing the relative size of the two sexual risk groups in the Norwegian MSM population.

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3.1.4 Model Specifications and Flow

Ultimately, the model’s parameters combine to govern the number of individuals in each compartment as a function of model cycles (i.e. time). This is achieved by solving a linked system of ordinary differential equations to trace the movement of susceptible and HIV infected MSM. The full set of equations is listed in the Appendix.

3.1.4.1 Population Size

The size of the MSM population aged 15-66 and living in Norway was derived from statistics published by Statistics Norway. The model’s lower age limit was defined according to survey data taken from Norwegian MSM, which revealed that the majority did not sexually debut before the age of 15 (Folkehelseinstituttet, 2002; Folkehelseinstituttet, 2013). Due to a lack of data concerning the age at which MSM living in Norway stop being sexually active, the upper limit was assumed. It was estimated that 3,471,000 people living in Norway were between the ages of 16 and 66; with half of that amount assumed to be men. To understand what proportion of these men engage in sex with other men, a 2002 report published by the Norwegian Public Health Institute (FHI) was consulted. The institute collected data on the sexual habits of 10,000 people between the ages of 18 and 49. Nearly four percent (3.8%) of male respondents reported having had sex with a person of the same sex within the last year. With these pieces of information, a crude estimate of 61 000 was suggested for the total size of the MSM population aged 15-66. This estimated population size was further stratified by sexual activity level and HIV serostatus.

Inhabitants of the model were assigned to one of two sexual activity risk groups—“low” and “high”—at rates obtained from the Norwegian-specific results of the European MSM Internet Survey (EMIS). The risk groups were defined according to number of annual sexual partners, and were based solely on the condition that the proportion of each risk group must be greater than 25% of the general MSM population so as to satisfy the internal and external demand for sexual partners from both groups (Pynyacharoensin et al., 2016). To ensure appropriate group size, a cut-off point of one male sexual partner in the last year was chosen to define the low-activity risk group. Consequently, individuals were required to have had two or more annual male partners in order to be considered as being at high-activity risk.
Analysis of data taken from the EMIS survey indicate that 31% of respondents would fall into the low-activity risk group, while 69% would be assigned to the high-activity group (Folkehelseinstituttet, 2013). These proportions were applied to the MSM model population.

Stratification according to serostatus was conducted based on data published by FHI, which indicated that over 1 800 MSM had received an HIV diagnosis since 1984. It was assumed that approximately 3.5% of MSM living in Norway have received an HIV diagnosis. According to estimates suggested by Hamers and Phillips (2008), an additional 15% of this figure was assumed to be infected, but unaware of their positive serostatus. Three-quarters of those diagnosed were assumed to be receiving ART. Estimates of the distribution of undiagnosed HIV infected MSM across the various disease stages were derived from a British nationwide population study of HIV incidence in MSM (MRC Biostatistics Unit, 2013). The distribution of diagnosed HIV infected MSM was estimated from the EMIS survey (Folkehelseinstituttet, 2013). Data from the EMIS survey revealed a difference in HIV prevalence between the high-activity (3.5%) and low activity (2.8%) groups (Folkehelseinstituttet, 2013). A multiplicative factor of 1.2 was thus applied in the model in order to account for differences in HIV prevalence between the two sexual activity risk groups.

3.1.4.2 Rate of Aging/Maturation ($\alpha$)

The annual rate of aging out of the population is equal to the proportion of individuals at the maximum age in the model: 66 years. As the age range of the inhabitants of the model is nearly 50 years, it was assumed that each year of age represents 2% of the model\(^5\). This assumption was corroborated by the EMIS survey data which indicated that 1.72% of respondents were in the age group 60-64 years (Folkehelseinstituttet, 2013). A maturation rate of 2% was therefore used. This rate also includes those who exit the model because they have stopped having sex with male partners.

\(^5\) It is likely, however, that those on the two extreme ends of the age scale make up less than 2% of the model’s population because they have either not yet begun to have sex or have died/stopped having sex.
3.1.4.3 Population Growth Rate ($V_i$)

It was assumed that the size of the model population grew at a faster rate than the entire Norwegian population, as sexual habit data indicate that an increasingly larger proportion of the population partakes in sex with same-sex partners. In 1987, it was reported that 1.5% of men had had sex with another male in the last year, whereas by 2002 this proportion had grown to 3.8% (Folkehelseinstituttet, 2002). Interestingly, a British survey conducted by YouGov UK found that 23% of respondents did not self-identify as exclusively heterosexual, suggesting that bisexuality is increasingly more common in our society (YouGov, 2015). Ultimately, an annual growth rate of 3% was included in the model.

3.1.4.4 Mortality Rate ($\mu_i$)

The baseline mortality rate for HIV negative MSM was obtained from mortality data provided by Statistics Norway (Statistik sentralbyrå, 2015). It was assumed that HIV negative MSM would have the same mortality as persons aged 15 to 66 of the general population, thus a rate of 0.3% was adopted. Evidence increasingly suggests that HIV infection itself increases risk for clinical conditions such as non-AIDS cancers, renal and liver disease, and cardiovascular diseases (Marin et al., 2012). Maman and colleagues observed a higher mortality among patients receiving ART, of the order of 1.5. For treatment naïve HIV positive MSM, mortality increased at a factor of as great as 2.56 that of HIV negatives (Maman et. al, 2012). Evidence presented by Nakagawa and colleagues further substantiates the differentiation of mortality rates, reporting that HIV positive individuals die seven years earlier than their seronegative counterparts (Nakagawa et al., 2012). In line with these findings, annual mortality for HIV positives on ART was assessed at 0.45% and 0.62% for treatment naïve seropositives. The mortality rate for individuals with late stage HIV used in the model was derived from register data from Denmark, Sweden and Norway (Helleberg et al., 2013). On average, between one and two percent of individuals with a CD4 count below 200 cells/μl die annually, thus a rate of 1.5% was included in the model.
3.1.4.5  HIV Transmission

In this model, HIV transmission may only occur through intercourse. Sexual HIV transmission is dependent upon the infected partner’s disease stage, as well as the riskiness of the partnership. Neither the effects of circumcision nor the presence of STI infection were included, though evidence suggests circumcision may reduce and STIs may increase risk of HIV infection (Auvert et al., 2005). Only seronegative individuals are susceptible to HIV infection. Conversely, only susceptible individuals are at risk for seroconverting. Transmission probabilities were calculated per partnership rather than per act\(^6\). It is assumed that all sexual partnerships result from random mixing, such that neither age, sexual role/preference, nor serological status determine the partnership formation. The model, however, allows for preferential mixing among the two different activity groups. The probability that the partnership will result in sexual transmission of HIV from an infected individual in compartment \(j\) and a susceptible individual in compartment \(i\) is calculated as:

\[
\beta_{i,j}^{r}(t) = P_i^r * M_{i,j}^r(t) * \sigma_{i,j} \quad (i = X_1, X_{11}, Y_1; j = X_2, ..., X_{10}, X_{12}, X_{13}, Y_2, ..., Y_{10}; r = H, L)
\]

The term \(\beta_{i,j}^{r}(t)\) represents the force of infection (FOI), which is a function of the number of infectious individuals at a given point in time, the contact function and the transmission coefficients. The average annual number of risky partnerships that could lead to the infection of a susceptible individual in compartment \(i\) is given as \(P_i^r\). A risky partnership is either one that does not involve consistent condom use (referred to as “high risk”) or one that involves either improper use or use of an ineffective condom (referred to as “low risk”). These partnerships are indexed by \(r = H, L\). \(P_i\) represents the average number of sexual partnerships per year for an individual in a given compartment \(i\). Estimation of this parameter was obtained from the EMIS dataset (Folkehelseinstituttet, 2013).

\(^6\) Modelling demonstrated that it would require unreasonably low numbers of anal intercourse HIV exposures per partnership to reconcile the summary per-act and per-partner estimates, suggesting considerable variability in anal intercourse infectiousness between and within partnerships over time (Baggaley et al., 2010).
\textbf{Equation 4}

\[ P_i^H = p_i \times (1 - d_i) \quad (i = X_1, ..., X_{13}, Y_1, ..., Y_{10}) \]

\textbf{Equation 5}

\[ P_i^L = p_i \times d_i \times (1 - ce) \quad (i = X_1, ..., X_{13}, Y_1, ..., Y_{10}) \]

The proportion of sexual partnerships that involve consistent condom use is represented by \( d_i \). Estimates for this particular parameter were derived from the EMIS survey dataset (Folkehelseinstituttet, 2013). Condom efficacy in reducing transmission of HIV amongst MSM was obtained from meta-analysis estimates of efficacy observed in heterosexual partnerships (Pinkerton & Abramson, 1997) and is represented by the letters \( ce \).

The likelihood that an individual in compartment \( i \) has a risky sexual partnership of type \( r \) with an individual in compartment \( j \) at time \( t \) is denoted as \( M_{ij}^r(t) \). This probability is therefore impacted by the number of individuals in each compartment, the level of mixing between the two sexual activity groups, as well as the risk taking behavior of the individuals inhabiting those compartments. Due to selective mixing by sexual activity group, \( M_{ij}^r(t) \) is calculated in four different ways:

Partnership of individual in compartment \( i \) belonging to the high sexual activity group and an individual in compartment \( j \) also belonging to the high activity group:

\textbf{Equation 6}

\[ M_{ij}^r(t) = G_i \left[ \frac{X_j(t)P_j^r}{\sum_{h=X_1}^{X_{13}} X_h(t)P_h^r} \right] \quad (i = X_1, ..., X_{13}; j = X_1 ... X_{13}; r = H, L) \]

The term within the brackets represents the total number of risky sexual partnerships by members of compartment \( j \) divided by the total number of risky sexual partnerships of all individuals in the high activity group.

Partnership of individual in compartment \( i \) of high activity group with individual in compartment \( j \) of low activity group:
Equation 7

\[ M^r_{ij}(t) = (1 - G_i) \left[ \frac{X_j(t)P^r_j}{\sum_{n=1}^{10} X_n(t)P^r_n} \right] \quad (i = X_1, ..., X_{13}; j = Y_1, ..., Y_{10}; r = H, L) \]

Partnership of individual in compartment \( i \) of low activity group with individual in compartment \( j \) of high activity group:

Equation 8

\[ M^r_{ij}(t) = \left[ \frac{\sum_{n=1}^{13} (1 - G_n)X_n(t)P^r_n}{\sum_{n=1}^{10} X_n(t)P^r_n} \right] * \left[ \frac{X_j(t)P^r_j}{\sum_{n=1}^{13} X_n(t)P^r_n} \right] \quad (i = y_1, ..., y_{10}; j = x_1, ..., x_{13}; r = H, L) \]

Partnership between individual in compartment \( i \) of low activity group with individual in compartment \( j \) of low activity group:

Equation 9

\[ M^r_{ij}(t) = \left[ 1 - \frac{\sum_{n=1}^{13} (1 - G_n)X_n(t)P^r_n}{\sum_{n=1}^{10} X_n(t)P^r_n} \right] * \left[ \frac{X_j(t)P^r_j}{\sum_{n=1}^{10} X_n(t)P^r_n} \right] \quad (i = y_1, ..., y_{10}; j = x_1, ..., x_{13}; r = H, L) \]

The last two equations represent conditional probabilities, and can be understood as the likelihood of having a risky sexual partnership with an individual from compartment \( j \) given that the sexual partnership from that particular activity group occurs.

The risk of transmission per sexual partnership between an individual in compartment \( i \) and an individual in compartment \( j \) is denoted by \( \sigma_{i,j} \). The transmission rate varies across CD4 count levels and therefore changes according to disease progression and treatment status. The baseline probability of HIV transmission per male same-sex partnership between an individual in the symptomatic stage and another susceptible male was assessed by Baggaley and colleagues as being 7.9%. This estimate is based on the assumption of a mix of unprotected insertive anal intercourse (UIAI) and unprotected receptive anal intercourse (URAI). From this rate, other transmission probabilities were further calculated. Boily et al. estimate that infectiousness decreases by a factor of 2.45 for each log10 copies/mL decrease in viral load.

\[ \text{An insertive partner is proven to be at less risk of contracting HIV than a receptive partner.} \]
(Boily, 2009), therefore the likelihood of transmission between a susceptible individual and an individual with early stage HIV was found to be less than half that of symptomatic HIV.

Additionally, Boily and colleagues estimated primary and late phase HIV infectiousness to be 9.4, and 7.3 times greater than asymptomatic HIV (Boily, 2009). As the majority of people initiating ART began treatment whilst in the symptomatic phase, the transmission rate for MSM receiving treatment was assessed as being nearly 1/20th of the transmission rate of the symptomatic phase. Surveillance data was used to derive this estimate, indicating that approximately 94% of those receiving treatment are virally suppressed (Norsk kvalitetsregister for hiv, 2015). The use of PrEP and its effect on preventing transmission was incorporated into the model as a coefficient to be multiplied by the parameter $\sigma_{i,j}$. If PrEP were to have an effectiveness of 86%, then its effect would in turn reduce $\sigma_{i,j}$ by a factor equal to the complement of PrEP’s effectiveness i.e. $\sigma_{i,j} \times (1 - 0.86)$. In the event of breakthrough infection whilst on PrEP, all newly seroconverted individuals in the primary infection stage will have a lower level of infectiousness than what is normally observed in seroconverts in the primary infection stage. Undiagnosed breakthrough seroconverts taking PrEP were assumed to have their infectiousness reduced by half, while those diagnosed were assumed to have their infectiousness reduced by approximately 13% (Garcia-Lerma et al., 2008). This is due to the assumption that diagnosed breakthrough seroconverts would immediately stop taking PrEP.

3.1.4.6 Disease Progression Rate ($\gamma_i$)

Infected individuals transition to a more advanced disease stage (i.e. a lower CD4 count) as long as they remain treatment naïve. The disease progression rate is analogous to the inverse of the mean duration of that particular stage. The acute primary phase lasts on average 2.9 months (Hollingsworth et. al, 2008), though it may last up to 6 months. Estimates for duration of disease in the other various disease stages were obtained from a modeling study conducted in the UK (MRC Biostatistics Unit, 2012). These derived disease stage durations are displayed in Table 1 on the next page.
Table 1. Duration of each CDC defined HIV disease stage

<table>
<thead>
<tr>
<th>HIV Stage</th>
<th>Length of time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Primary Infection</td>
<td>2.90</td>
</tr>
<tr>
<td>Early stage</td>
<td>67.27</td>
</tr>
<tr>
<td>Symtomatic stage</td>
<td>23.92</td>
</tr>
<tr>
<td>Late stage (AIDS)</td>
<td>20.12</td>
</tr>
</tbody>
</table>

3.1.4.7 Diagnosis Rate ($\varphi_i$)

The diagnosis rate controls the one directional flow of MSM moving from undiagnosed to diagnosed stages at time $t$. The flow is one directional as one cannot return to undiagnosed. A baseline probability of diagnosis was derived from taking the inverse of the average time from infection to diagnosis. In a recent Dutch study, van Sighem and colleagues found that the average time passed between infection and diagnosis for MSM was 2.6 years (90% confidence interval, 2.2-3.1), thus resulting in an annual probability of diagnosis of 38.5%. The majority of MSM in this study were diagnosed while in the symptomatic stage (van Sighem et al., 2015), so this diagnosis rate was applied to the symptomatic HIV state in the model. Increments and decrements were applied to this baseline depending on disease stage and sexual activity group. Those with more advanced stages have a greater probability of diagnosis because symptoms worsen, whereas those with early stages would have a lesser probability of diagnosis. A (either positive or negative) change in 10% was applied to the baseline diagnosis rate for each additional change in disease stage. High activity MSM were assumed to have a 10% higher diagnosis rate than low activity MSM because EMIS data shows the former group is more likely to test for HIV than the latter (Folkehelseinstituttet, 2013). According to the survey data, 45.8% of the low activity group had never tested for HIV, while 28.3% of the high activity group had never tested for HIV. Combined, the two activity groups have an unweighted average annual diagnosis rate 33%, which is slightly less than the baseline estimate of 38.5%, but within the 90% confidence interval presented by van
Sighem et. al. This discrepancy is realistically minimal, given that there are more MSM in the high activity group than the low activity group.

It is assumed that 100% of individuals experiencing breakthrough infection whilst on PrEP receive a diagnosis within three months of being infected. This assumption was made because all individuals receiving PrEP are assumed to undergo mandatory HIV testing every 3 months in order to continue receiving PrEP and to prevent development of drug resistance.

Lastly, in order to reflect the findings of Marks et al., it was assumed that a proportion of MSM switch to the other sexual activity group (at rate $S_i$) or reduce their number of partners by 30% after being diagnosed with HIV.

3.1.4.8 Treatment Rate ($\omega ; \tau_i$)

Only high activity individuals can begin PrEP treatment. It is likely that only a percentage of those eligible for PrEP treatment will elect pre-prophylactic treatment. PrEP initiation occurs at a constant rate ($\omega$) after the passage of the first two cycles. A different rate is used in the first cycle to represent the level of initial PrEP uptake. Individuals may stop PrEP at the start of each new cycle, either because they are no longer eligible due to change in sexual activity, or because they wish to discontinue treatment for other reasons (e.g. poor adherence, side effects). The PrEP cessation rate (not associated with sexual activity level reclassification) is represented by the symbol $\pi$.

Only after being diagnosed with HIV, can one begin first-line ARV treatment. Both the rate of diagnosis and the rate of initiating treatment ($\tau_i$) are strongly related to an individual’s disease stage. Although HIV infection may be diagnosed while the individual is in the primary infection stage, it was assumed that treatment would not be initiated until the individual had progressed to the early stage. Treatment initiation rates in general should be directly related to national treatment guidelines. In 2013, the Norwegian Association of Infectious Medicine retracted its previous recommendation that patients wait to initiate treatment until a certain CD4 count was reached, suggesting instead that treatment begin as soon as possible so as to improve the health outcome of the patient and prevent further spread of infection (Norsk Forening for Infeksjonsmedisin, 2015). In practice, however, there are still many diagnosed
patients who either personally choose to delay treatment or are not directly offered immediate initiation of treatment (Hansen, 2014). The rates used in the model were obtained from British guidelines published in 2008 (Gazzard et. al, 2008) and are listed in Table 2.

**Table 2. Treatment initiation rates according to disease stage (annual probability of initiating treatment)**

<table>
<thead>
<tr>
<th>HIV Stage</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early stage</td>
<td>0.91</td>
</tr>
<tr>
<td>Symptomatic stage</td>
<td>3.04</td>
</tr>
<tr>
<td>Late stage (AIDS)</td>
<td>3.08</td>
</tr>
</tbody>
</table>

While the guidelines listed equal rates for symptomatic and late stages, the rate of treatment initiated for individuals in the symptomatic stage used in the model was decreased by a factor of 20%. This was done to reflect certain peoples’ personal desire to delay treatment, and also health professionals’ reluctance to recommend treatment if they presume the individual in question is unlikely to adhere to the prescribed regimen.
Table 3. Estimates of parameters controlling movement throughout the various Markov states

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Value</th>
<th>Standard Error</th>
<th>Distrib.</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Growth rate</td>
<td>$\xi$</td>
<td>0.03</td>
<td>0.0005206</td>
<td>Normal</td>
<td>Assumed</td>
</tr>
<tr>
<td>Maturation rate</td>
<td>$\omega$</td>
<td>0.02</td>
<td>0.0000204</td>
<td>Normal</td>
<td>EMIS 2010 data</td>
</tr>
<tr>
<td>Mortality rate</td>
<td>$\mu$</td>
<td>0.0099</td>
<td>0.0005130</td>
<td>Normal</td>
<td>Statistics Norway</td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td>0.0062</td>
<td>0.0000547</td>
<td>Normal</td>
<td>Memarzadeh et al., 2012</td>
</tr>
<tr>
<td>Late stage</td>
<td></td>
<td>0.0130</td>
<td>0.0007623</td>
<td>Normal</td>
<td>Memarzadeh et al., 2012</td>
</tr>
<tr>
<td>ART</td>
<td></td>
<td>0.0045</td>
<td>0.0001550</td>
<td>Normal</td>
<td>Hellersberg et al., 2013</td>
</tr>
<tr>
<td>Annual rate of change from low activity to high</td>
<td></td>
<td>0.15</td>
<td>0.0006</td>
<td>Normal</td>
<td>Assumed</td>
</tr>
<tr>
<td>Annual rate of change from high activity to low</td>
<td></td>
<td>0.10</td>
<td>0.0040</td>
<td>Normal</td>
<td>Assumed</td>
</tr>
<tr>
<td>Transmission Parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual nr. sexual partnership contacts (high)</td>
<td>$p_{HI}$</td>
<td>0.21</td>
<td>0.0170</td>
<td>Gamma</td>
<td>EMIS 2010 data</td>
</tr>
<tr>
<td>Annual nr. sexual partnership contacts (low)</td>
<td>$p_{LO}$</td>
<td>0.69</td>
<td>0.1000</td>
<td>Beta</td>
<td>EMIS 2010 data</td>
</tr>
<tr>
<td>Percent increase in partnership contacts (due to PrEP)</td>
<td></td>
<td>1.15</td>
<td>0.1000</td>
<td>Beta</td>
<td>Assumed</td>
</tr>
<tr>
<td>Percent decrease in partnership contacts (due to diagnosis)</td>
<td></td>
<td>0.75</td>
<td>0.1000</td>
<td>Gamma</td>
<td>Assumed</td>
</tr>
<tr>
<td>Percent increase in condom usage rate (due to PrEP)</td>
<td></td>
<td>0.10</td>
<td>0.0050</td>
<td>Beta</td>
<td>Assumed</td>
</tr>
<tr>
<td>Percent decrease in condom usage (due to diagnosis)</td>
<td></td>
<td>0.30</td>
<td>0.1000</td>
<td>Beta</td>
<td>Assumed</td>
</tr>
<tr>
<td>Percent reduction in contacts (due to ART initiation)</td>
<td></td>
<td>0.10</td>
<td>0.0006</td>
<td>Beta</td>
<td>Assumed</td>
</tr>
<tr>
<td>condom effectiveness</td>
<td>$\nu$</td>
<td>0.90</td>
<td>0.0459</td>
<td>Beta</td>
<td>Pinkerton &amp; Anastos, 2007</td>
</tr>
<tr>
<td>Diagnostics Parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to diagnosis (years) primary stage</td>
<td>$\theta_p$</td>
<td>0.303</td>
<td>0.0008</td>
<td>Beta</td>
<td>Bailey</td>
</tr>
<tr>
<td>Time to diagnosis (years) primary stage undiagnosed PrEP breakthrough infection</td>
<td>$\theta_{PI}$</td>
<td>0.152</td>
<td>0.0007</td>
<td>Beta</td>
<td>Garcia-Lerma et al., 2008</td>
</tr>
<tr>
<td>Time to diagnosis (years) primary stage diagnosed PrEP breakthrough infection</td>
<td>$\theta_{PD}$</td>
<td>0.265</td>
<td>0.0007</td>
<td>Beta</td>
<td>Garcia-Lerma et al., 2009</td>
</tr>
<tr>
<td>Time to diagnosis (years) early stage</td>
<td>$\theta_e$</td>
<td>0.002</td>
<td>0.0005</td>
<td>Beta</td>
<td>Bailey</td>
</tr>
<tr>
<td>Time to diagnosis (years) symptomatic stage</td>
<td>$\theta_s$</td>
<td>0.079</td>
<td>0.0005</td>
<td>Beta</td>
<td>Baggaley, 2010</td>
</tr>
<tr>
<td>Time to diagnosis (years) late stage</td>
<td>$\theta_l$</td>
<td>0.234</td>
<td>0.0005</td>
<td>Beta</td>
<td>Bailey</td>
</tr>
<tr>
<td>Treatment Parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial uptake of PrEP</td>
<td>$r$</td>
<td>0.25</td>
<td></td>
<td>Fixed</td>
<td></td>
</tr>
<tr>
<td>Annual PrEP cessation rate not related to change in activity group</td>
<td>$\nu_r$</td>
<td>0.11</td>
<td>0.000408</td>
<td>Normal</td>
<td>Assumed</td>
</tr>
<tr>
<td>Annual rate of initiating PrEP after initial uptake</td>
<td>$\nu_w$</td>
<td>0.10</td>
<td>0.000504</td>
<td>Normal</td>
<td>Assumed</td>
</tr>
<tr>
<td>Annual ART initiation rate</td>
<td>$\tau$</td>
<td>0.91</td>
<td>0.1000</td>
<td>Beta</td>
<td>Assumed</td>
</tr>
<tr>
<td>Disease Progression Parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual rate of progression to next stage Early to Symptomatic</td>
<td>$\tau_{ES}$</td>
<td>4.1170</td>
<td>0.0333</td>
<td>Normal</td>
<td>Hollingsworth et al., 2008</td>
</tr>
<tr>
<td>Early to Symptomatic</td>
<td>$\tau_{ES}$</td>
<td>0.13139</td>
<td>0.0047</td>
<td>Normal</td>
<td>Binrel et al., 2012</td>
</tr>
<tr>
<td>Symptomatic to Late</td>
<td>$\tau_{SL}$</td>
<td>0.0464</td>
<td>0.0025</td>
<td>Normal</td>
<td>Binrel et al., 2013</td>
</tr>
</tbody>
</table>

3.1.5 Model Outputs

The differences in number of new infections over a thirty-year period, as well as the costs and effects (i.e. life years, health related quality of life) accrued under both scenarios were estimated. The number of HIV infections averted was computed by taking the difference in new infections occurring at each cycle and over the entire time horizon between each scenario (baseline status quo, and the 25% PrEP strategy). To calculate life years gained, model inhabitants who had not yet transitioned to the death state (i.e. were still living) were summed and divided by number of inhabitants at beginning of the cycle.
Additionally, the number needed to treat to prevent one new infection (NNT) was calculated to further reflect PrEP’s comparative cost-effectiveness. The NNT gives a mean number of individuals among whom, if they were treated with PrEP, exactly one would benefit from not contracting HIV. This value is derived by calculating the event rates of the different scenarios. Under this framework, infections are events, and non-events are represented as the number of susceptibles inhabiting the model at the end of the thirty-year time horizon. The formula below illustrates explicitly how the NNT is derived. Table 4 follows with an explanation of the formula’s inputs.

\[
NNT = \frac{1}{(EE/ES) - (CE/CS)}
\]

Table 4. Deriving the inputs required to calculate NNT

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nr. of events</td>
<td>(EE)</td>
<td>(CE)</td>
</tr>
<tr>
<td>Nr. of non-events</td>
<td>(EN)</td>
<td>(CN)</td>
</tr>
<tr>
<td>Total</td>
<td>(ES)</td>
<td>(CS)</td>
</tr>
</tbody>
</table>

3.1.6 Costs

Total costs were computed and indexed in Norwegian kroner (NOK) for the year 2015. Price and cost data not in kroner were first indexed to 2015 prices in their original currency and then converted into kroner using the average of the 2015 conversion rate between the original currency and the Norwegian krone. All costs were later discounted at an annual rate of 4% as recommended by the Norwegian Medicines Agency (NMA) in their guidelines.
Costs were divided into direct-medical costs, one-off diagnostic and upstart costs, and treatment costs.

3.1.6.1 Direct Medical Costs (DMC)

Direct medical costs are understood as the summation of costs arising from outpatient and dayward visits, as well as from overnight stays in the hospital. Additionally, screening, monitoring and testing service consumption, as well as medical drug consumption factor into direct medical costs for all HIV infected individuals and individuals taking PrEP.

3.1.6.1.1 DMC: Susceptible

Data published by Statistics Norway was used to calculate the costs HIV negative MSM incur per cycle. According to the agency’s published figures, Norwegian adult men on average visited their general practitioner 2.4 times per year (Statistisk sentralbyrå, 2014). A quarter visited a dayward at least once, while over one-third (35%) were hospitalized for an average of four days. It was assumed that susceptible MSM of all ages had the same level of health care consumption as the general adult male population. Costs for each visit/stay were derived from various sources, and are found in Table 5. Ultimately, the direct medical cost applied to this group did not account for prescription drug consumption. A cycle cost of 692 NOK was used in modelling direct medical costs for susceptible individuals not receiving PrEP.

3.1.6.1.2 DMC: Susceptible on PrEP

Direct medical costs for users of PrEP were calculated according to current CDC clinical guidelines which outline the monitoring of PrEP users (U.S. Public Health Service, 2014). According to these guidelines, individuals prescribed PrEP are expected to meet quarterly with their general practitioner in order to undergo testing for HIV and other STIs, as well as discuss their personal behavior and situation. New information gathered in these discussions may impact the prescriber’s decision to continue refilling the patient’s prescription. The CDC guidelines further outline that individuals must have their renal function assessed at least bi-
annually, which typically entails urine and creatine analysis. In addition to these monitoring costs associated with PrEP use, seronegative individuals prescribed PrEP are assumed to have the same resource consumption as other susceptibles. However, the number of GP visits used in the costing exercise for individuals prescribed PrEP did not exceed the four visits already considered in calculating the monitoring costs mentioned above (thereby ignoring the 2.4 visits typical of the susceptible male population). A total cycle cost of 739 NOK was used to model the direct medical costs of individuals in this particular state of the model.

Table 5. Direct medical costs incurred by HIV susceptible men

<table>
<thead>
<tr>
<th>Service</th>
<th>Nr of units</th>
<th>Unit price</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultation with GP</td>
<td>4</td>
<td>218</td>
<td>872</td>
</tr>
<tr>
<td>Filling of prescription</td>
<td>4</td>
<td>55</td>
<td>220</td>
</tr>
<tr>
<td>HIV testing</td>
<td>4</td>
<td>18</td>
<td>72</td>
</tr>
<tr>
<td>Urine/creatine analysis</td>
<td>2</td>
<td>79</td>
<td>158</td>
</tr>
<tr>
<td>Dayward visit</td>
<td>0.25</td>
<td>730</td>
<td>183</td>
</tr>
<tr>
<td>Inpatient day *</td>
<td>1.4</td>
<td>8069</td>
<td>11297</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>12801</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Service</th>
<th>Nr of units</th>
<th>Unit price</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultation with GP</td>
<td>2.4</td>
<td>218</td>
<td>523</td>
</tr>
<tr>
<td>Dayward visit</td>
<td>0.25</td>
<td>730</td>
<td>183</td>
</tr>
<tr>
<td>Inpatient day *</td>
<td>1.4</td>
<td>8069</td>
<td>11297</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>12002</td>
</tr>
</tbody>
</table>

*inpatient day unit = % of population who experience hospitalization annually multiplied by the average length of stay; i.e. 1.4 units = 0.35 * 4

3.1.6.1.3 DMC: Seropositive (undiagnosed and treatment naïve)

Direct medical costs related to outpatient, dayward, and hospital services consumption among HIV positive MSM were obtained from figures presented by Beck and colleagues (2011). The tariffs applied in the model are based on the annual consumption of health resources required throughout the national HIV clinical care pathway, namely: use of health care services (e.g. outpatient visits, inpatient days at hospital, and dayward visits), and non ARV drugs. According to Beck and colleagues’ findings, ART naïve seropositive patients’ consumption of health resources varies according to CD4 count. Seropositive individuals with CD4 count above 200 cells/μl consumed 60% less resources than those with a count below 200 cells/μl (81 632 NOK annually compared to 31 013 NOK). It was assumed that HIV positive MSM living in Norway have an identical consumption of medical resources, therefore
consumption rates were multiplied by costs of such services within Norway, and “other drug costs” were converted into Norwegian kroner. For simplification purposes and for lack of data, it was further assumed that undiagnosed HIV infected MSM incurred the same direct medical costs as their diagnosed counterparts. Ultimately, cycle costs of 1 789 NOK and 4 710 NOK were applied to treatment naïve persons (both diagnosed and undiagnosed) with a count above 200 cells/μl and a count below 200 cells/μl, respectively (see Table 6).

### 3.1.6.1.4 DMC (seropositive receiving ART)

The average direct medical cost for seropositive individuals receiving treatment was also derived the same British study (Beck et al., 2011). Health care costs were again found to vary according to CD4 count. The annual cost for persons with a CD4 count above 200 was estimated to be 44 741 NOK, and 75 786 NOK for persons with a CD4 count below 200. According to Norwegian register data, 94% of persons on ART are stable and are responding to treatment (SOURCE). It was therefore assumed that 94% of persons on ART have a CD4 count above 200 cells/μl, and that six percent have a count less than 200 cells/μl. In applying these proportions, a weighted direct medical cycle cost of 2 689 NOK was applied for each individual receiving ART.

**Table 6. Annual direct medical costs related to treatment of HIV**

<table>
<thead>
<tr>
<th>Service</th>
<th>ART naïve CD4&lt;200</th>
<th>CD4&gt;200</th>
<th>Receiving ART CD4&lt;200 (6%)</th>
<th>CD4&gt;200 (94%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient days (hospital)</td>
<td>2.76 visits (22 270 NOK)</td>
<td>0.41 visits (3 308 NOK)</td>
<td>2.94 visits (23 723 NOK)</td>
<td>1.38 visits (11 135 NOK)</td>
</tr>
<tr>
<td>Outpatient visits (GP)</td>
<td>8.32 visits (1 814 NOK)</td>
<td>6.22 visits (1 355 NOK)</td>
<td>7.88 visits (1 718 NOK)</td>
<td>7.12 visits (1 552 NOK)</td>
</tr>
<tr>
<td>Dayward visits (emergency)</td>
<td>0.77 visits (562 NOK)</td>
<td>0.41 (299 NOK)</td>
<td>1.23 visits (898 NOK)</td>
<td>0.82 visits (599 NOK)</td>
</tr>
<tr>
<td>Tests &amp; Procedures</td>
<td>11 402 NOK</td>
<td>461 (6849 NOK)</td>
<td>9 786 NOK</td>
<td>7 133 NOK</td>
</tr>
<tr>
<td>Other drug costs</td>
<td>45 584 NOK</td>
<td>19 201 NOK</td>
<td>39 661 NOK</td>
<td>24 322 NOK</td>
</tr>
<tr>
<td>Total cost</td>
<td>81 632 NOK</td>
<td>31 013 NOK</td>
<td>75 786 NOK</td>
<td>44 741 NOK</td>
</tr>
</tbody>
</table>
3.1.6.2 One-time Costs

3.1.6.2.1 One-off initial cost of PrEP treatment and immediate follow-up

An initiation cost of 765 NOK is accrued by all seronegative individuals wishing to start PrEP, and was calculated according to the current FDA guidelines regarding patient uptake to PrEP treatment. The following must be completed before an individual begins taking PrEP: a.) the individuals’ kidney function must be assessed at baseline b.) the individual is tested for Hepatitis B and given a vaccine if not yet inoculated (not included in costing) c.) the individual is tested for HIV and other STIs d.) the individual receives structured guidance related to his sexual activity and continued use of prophylactic barrier methods (i.e. condoms). Ultimately, the cost of initiating PrEP includes two visits with the individual’s GP.

Table 7

<table>
<thead>
<tr>
<th>Service</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP consultation (2 visits)</td>
<td>436 NOK</td>
</tr>
<tr>
<td>Prescription filling</td>
<td>55 NOK</td>
</tr>
<tr>
<td>Structured guidance regarding sexual health</td>
<td>150 NOK</td>
</tr>
<tr>
<td>Urine &amp; creatine analysis</td>
<td>86 NOK</td>
</tr>
<tr>
<td>HIV and STI testing</td>
<td>38 NOK</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>765 NOK</strong></td>
</tr>
</tbody>
</table>

3.1.6.2.2 One-off initial cost of HIV diagnosis

A one-off cost (4 163 NOK) of HIV infection was applied to each new infection per cycle to reflect the consumption and cost of diagnostic resources and follow-up directly after
diagnosis. A breakdown of the costs is found in Table 8 below. In many cases, multiple tests and examinations are undergone and assessed in order so as to assure that the individual has in fact seroconverted, therefore the one-off proxy cost for diagnostic services may be far greater. According to data published by the molecular biological laboratory at Oslo Universitetssykehus, additional HIV antibody and DNA provirus PCR tests were used 10% and 50% of the time (Bakken Kran, 2014). It was therefore assumed that ten percent of HIV diagnoses incurred a cost for HIV antibody testing, and 50% of HIV diagnoses incurred a cost for DNA provirus PCR testing.

Table 8. The consumption of resources in diagnosing a single HIV infection and its related cost

<table>
<thead>
<tr>
<th>Activity</th>
<th>Cost [NOK]</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultation with GP</td>
<td>218</td>
<td>Helse&amp;konomiforvaltningen, 2012</td>
</tr>
<tr>
<td>Psychosocial meeting with infected and family/partner</td>
<td>200</td>
<td>Legeforeningen, 2016</td>
</tr>
<tr>
<td>Guidance meeting related to sexual activity</td>
<td>150</td>
<td>Legeforeningen, 2016</td>
</tr>
<tr>
<td>Cost related to informing patient of infection</td>
<td>64</td>
<td>Legeforeningen, 2016</td>
</tr>
<tr>
<td>Infection tracing</td>
<td>1100</td>
<td>Folkhalsomyndigheten, 2016</td>
</tr>
<tr>
<td>Shipment of test samples</td>
<td>250</td>
<td>Legeforeningen, 2016</td>
</tr>
<tr>
<td>ELISA combination test</td>
<td>26</td>
<td>Helse og Omsorgsdepartementet 2016</td>
</tr>
<tr>
<td>Western Blot confirmation test</td>
<td>297</td>
<td>Helse og Omsorgsdepartementet 2016</td>
</tr>
<tr>
<td>Resistance Testing</td>
<td>1036</td>
<td>Helse og Omsorgsdepartementet 2016</td>
</tr>
<tr>
<td>CD4 count</td>
<td>26</td>
<td>Helse og Omsorgsdepartementet 2016</td>
</tr>
<tr>
<td>Viral load count</td>
<td>767</td>
<td>Helse og Omsorgsdepartementet 2016</td>
</tr>
<tr>
<td>ELISA antibody test (10%)</td>
<td>2,2</td>
<td>Helse og Omsorgsdepartementet 2016</td>
</tr>
<tr>
<td>DNA Provirus PCR test (50% of diagnoses)</td>
<td>26,5</td>
<td>Helse og Omsorgsdepartementet 2016</td>
</tr>
</tbody>
</table>

Total Cost 4163

3.1.6.3 Treatment Costs

Estimates of the prescription drug costs associated with PrEP usage among seronegative susceptibles and ART among seropositive individuals were taken from the 2016 Norwegian clinical guidelines for follow-up and treatment of HIV infection (Norsk Forening for Infeksjonsmedisin, 2016). The price listings of various ARV drugs are listed in Figure 6 on the following page.
### 3.1.6.3.1 Cycle cost of ART

While many ARV drugs of various classes have gained entry to the Norwegian market, the medical community in Norway has decided that initial therapy should consist of two nucleoside reverse transcriptase inhibitors (NRTI) and one integrase inhibitor (Norsk Forenig for Infeksjonsmedisin, 2016). The two NRTIs are often bundled into a combination therapy. Truvada (the marketed name of PrEP) is the preferred NRTI combination, thus its monthly sticker price (see Figure 6) was used to calculate the standard cycle cost for ART (3 857 NOK).
NOK). This cycle price for the combination therapy was added to the cycle price of the integrase inhibitor to derive a total ART cycle price. Dolutegravir was chosen as the standard integrase inhibitor because it is relatively cheaper (500 NOK per month less according the prices published in clinical guidelines; see Norsk Forening for Infeksjonsmedisin, 2016) than the other option in its class (raltegravir), though the latter is associated with less adverse events. A total cycle cost of 7,986 NOK was used in the model.

3.1.6.3.2 Cycle cost of PrEP

The cost of Truvada listed above (3,857 NOK) was used in calculating the cost of PrEP. To represent the impact of generic drug entry on PrEP prices, a multiplier of 0.33 was applied to the price of Truvada (i.e. 33% of original price ≈ 1,272 NOK). While Truvada is the only form of PrEP currently used in the global market for a preventative indication, it is possible that other drugs will receive approval for this particular indication in the future, and that generic forms will be made available.

3.1.6.4 Cost of Adverse Events

Adverse events were assumed to occur as long as the patient was receiving PrEP treatment, and would cease after treatment was stopped. Costs associated with adverse events linked to PrEP were calculated per cycle using the following formula:

Equation 11

\[ c_{cycle} = p_{adverse \text{ event}} \times r_{hospitalization} \times \mu_{hospitalization} \times \mu_{days \ in \ hospital} \]

The first term \(c_{cycle}\) represents the average cost related to adverse events occurring per cycle. The total costs of adverse events are computed by summing the costs per individual adverse event. The probabilities of occurrence for the various adverse events \(p_{adverse \text{ event}}\) were obtained largely from two sources: the iPERGAY pilot study conducted in France and Canada (Molina et al., 2015) and an American study published by Liu and colleagues (2011). To be incorporated into the model, the published probabilities were further adjusted to the
model’s cycle length of three weeks. Adjustments were made according to the following three steps:

1. Convert probabilities into rates ($r$) with $r = -\ln(1 - p)$
2. Multiply the rates by the following quotient: $\frac{\text{length of trial (in weeks)}}{\text{cycle length (in weeks)}}$
3. Convert rates back into probabilities ($p$) with $p = 1 - \exp(-r)$

Hospitalization rates ($r_{hospitalization}$) for these events were not available, so an arbitrary rates were applied. A rate of 10% was applied to adverse events apart from fractures and diminished kidney function (generally observed as proximal-tubular dysfunction caused by high concentrations of creatine), to which a hospitalization rate of 25% was applied. The national average cost of a day spent in hospital was estimated to be between 5 000 NOK – 11 000 NOK (Hospitalet AS, 2012). To generate the average cost per stay, an estimate of 8 069 NOK (Hospitalet AS, 2012) was applied to the estimate of average number of days spent in hospital ($\mu_{days \ in \ hospital}$) for each adverse event. This last figure was obtained from a 2006 Health Care Utilization Project (HCUP) report which recorded length of stay data at American hospitals for various principal diagnoses (Health Care Utilization Project, 2006).

Ultimately, a cost per cycle related to adverse events was estimated to be 128 NOK (see Table 9 below). This cost was applied to each individual receiving PrEP treatment.

**Table 9. Calculation of the cost of adverse events per cycle**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Probability reported in study</th>
<th>Prob. Hospitalization</th>
<th>Cost per inpatient day (NOK)</th>
<th>Length of stay (days)</th>
<th>Cost per hospitalization (NOK)</th>
<th>Rate per cycle</th>
<th>Probability per cycle</th>
<th>Cost Per cycle (NOK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysfunction of the kidneys</td>
<td>0.017</td>
<td>0.25</td>
<td>8069</td>
<td>4.1</td>
<td>8270.725</td>
<td>0.000491591</td>
<td>0.00049147</td>
<td>4</td>
</tr>
<tr>
<td>Loss of bone mass</td>
<td>0.13</td>
<td>0.1</td>
<td>8069</td>
<td>3.6</td>
<td>2964.84</td>
<td>0.01466235</td>
<td>0.01400093</td>
<td>33</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.08</td>
<td>0.1</td>
<td>8069</td>
<td>3.2</td>
<td>2562.08</td>
<td>0.03515835</td>
<td>0.03515639</td>
<td>13</td>
</tr>
<tr>
<td>Arthritis/polyarthralgia</td>
<td>0.1</td>
<td>0.1</td>
<td>8069</td>
<td>3.2</td>
<td>2562.08</td>
<td>0.03515835</td>
<td>0.03515639</td>
<td>13</td>
</tr>
<tr>
<td>Lipodystrophy</td>
<td>0.08</td>
<td>0.1</td>
<td>8069</td>
<td>4.2</td>
<td>3368.98</td>
<td>0.02072508</td>
<td>0.02072508</td>
<td>16</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>0.07</td>
<td>0.1</td>
<td>8069</td>
<td>2.9</td>
<td>2348.01</td>
<td>0.03944758</td>
<td>0.03944758</td>
<td>10</td>
</tr>
<tr>
<td>Gastrointestinal problems</td>
<td>0.02</td>
<td>0.1</td>
<td>8069</td>
<td>5.5</td>
<td>4637.35</td>
<td>0.07820561</td>
<td>0.07820561</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.04</td>
<td>0.1</td>
<td>8069</td>
<td>4.32</td>
<td>3485.908</td>
<td>0.03251781</td>
<td>0.03251781</td>
<td>9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.02</td>
<td>0.1</td>
<td>8069</td>
<td>3.2</td>
<td>2562.08</td>
<td>0.03515835</td>
<td>0.03515639</td>
<td>13</td>
</tr>
<tr>
<td>Bone fracture</td>
<td>0.0217</td>
<td>0.25</td>
<td>8069</td>
<td>5.4</td>
<td>10931.15</td>
<td>0.01828484</td>
<td>0.01828484</td>
<td>20</td>
</tr>
</tbody>
</table>

128 NOK
3.1.6.5 Cost of Death

Resources consumed in the last month of life have been used in economic analyses of health technologies to represent the cost per death of an individual. These costs are associated with the consumption of medical resources as well as hospice resources. Moger and colleagues estimated the cost of death to be approximately 50,000 NOK (Moger et al. 2010). As death occurs at different times according to which scenario is being modelled, costs are incurred at different points in time. Therefore, discounting leads to differential costs of death for both scenarios.

3.1.7 Health Related Quality of Life

The associated HRQoL for each of the various states of the model were obtained from the literature. Search terms used in the literature review included: HIV/AIDS utilities, health related quality of life, utility decrements, and disutility. Both Google Scholar and the University of Oslo’s library database were used to obtain articles relating to utilities. Ultimately, one article (Tengs & Lin, 2002) was consulted for the estimation of the majority of the health state utilities.

3.1.7.1 Health State Utilities

Tengs and Lin (2002) conducted a meta-analysis of utility estimates according to the following CD4 count-related health states: early (asymptomatic; CD4 > 350 cells/μl), symptomatic (350 cells/μl > CD4 >200 cells/μl), and late (CD4 < 200 cells/μl). These estimations were drawn from 25 articles reporting 74 utilities elicited from 1956 respondents using a variation of methods. The respondent group consisted of both seropositive and seronegative individuals, the latter made up of experts (e.g. clinicians, medical authors) who had not experienced HIV/AIDS themselves. Tengs and Lin ultimately created a meta-regression, hierarchical linear model in order to obtain a pooled estimate for three specific stages of HIV infection. Ultimately, only pooled utilities elicited from patients using the time tradeoff method (using scales ranging from death to perfect health) were incorporated in the modeling of PrEP. These estimates are reported in Table 10.
A utility estimate of the acute primary stage of HIV was derived also from the literature. The probability of a newly seroconverted individual experiencing symptomatic acute HIV infection illness is between 50-90% (Schacker et al., 1996; Lodi et al., 2013). A probability of 66% was assumed for the modeling of PrEP. The disutility associated with acute symptomatic HIV infection illness is assumed to be equal to the disutility experienced in the symptomatic HIV stage (disutility of 0.22). Therefore the primary infection stage in the PrEP model was estimated to have a health state utility 0.854, or $1-(0.66 \times 0.22)$.

Salomon and colleagues (2012) estimated that seropositives receiving antiretroviral treatment had a disutility of 0.053 (95% confidence interval: 0.034 - 0.079). The decrement estimate acknowledges and accounts for utility decrements related to toxicities and other adverse events related to ARVs, as well as potential decrements in health that occurred after infection and prior to initiation of treatment. This estimate was used to derive a health state utility value of 0.947 for individuals receiving ART.

It is likely that some individuals in the model experience an AIDS-related illness. The occurrence of such an illness leads to a further decrement in an HIV infected individual’s health utility. The Global Burden of Disease Study (see Salomon et al., 2010) estimates this decrement to be approximately -0.547 QALYs, regardless of number of AIDS-related illnesses inflicting the infected individual. Mocroft and colleagues ultimately observed that both persons with lower and higher CD4 counts may experience such an illness (Mocroft et al., 2013). To account for these findings, both the probability of an AIDS-related illness occurring and the associated decrement were applied to the health state utility estimates of the different diseased states obtained from Tengs & Lin. Adjusted health state utility estimates are presented on the next page in Table 10. It is estimated that six percent of individuals with a CD4 count between 200 and 350 develop an AIDS-related illness (Mocroft et al., 2013). For individuals with a CD4 count between 50 and 200 cells, the probability of having developed an AIDS-related illness is approximately 25% (90% confidence interval: 21-60%). It was assumed that persons with a CD4 count greater than 350 would not experience an AIDS-related disutility.
3.1.7.2 **Decrement Related to PrEP Adverse Events**

A disutility related to the adverse events experienced by individuals taking PrEP was calculated according to the same data used in calculation of the related cost of PrEP’s adverse events. The formula below was applied in calculating disutility experienced during PrEP treatment. The total disutility per cycle is the sum of all the probability-weighted (per cycle) decrements for each associated adverse event.

**Equation 12**

\[
d_{totalU_{cycle}} = \sum P_{cycle}(adverse\ event) \times dU_{adverse\ event}
\]

According to the input estimates presented in Table 5, an expected disutility per cycle of 0.002 is experienced by all MSM receiving PrEP treatment. The disutilities for the different adverse events is provided in Table 11 on the following page.
Table 11. Disutilities attributed to adverse events whilst taking PrEP

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Disutility</th>
<th>Probability</th>
<th>Probability per cycle</th>
<th>Disutility per cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney dysfunction</td>
<td>0.150</td>
<td>0.017</td>
<td>0.000404147</td>
<td>7.37013E-05</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.076</td>
<td>0.08</td>
<td>0.005116197</td>
<td>0.000388811</td>
</tr>
<tr>
<td>Arthralgia/polyarth</td>
<td>0.069</td>
<td>0.1</td>
<td>0.004833071</td>
<td>0.000396882</td>
</tr>
<tr>
<td>Lipodystrophy</td>
<td>0.130</td>
<td>0.08</td>
<td>0.004741442</td>
<td>0.000612838</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0.038</td>
<td>0.07</td>
<td>0.00463598</td>
<td>0.00059617</td>
</tr>
<tr>
<td>Gastrointestinal prol</td>
<td>0.090</td>
<td>0.01</td>
<td>0.006267765</td>
<td>5.04088E-05</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.047</td>
<td>0.04</td>
<td>0.005285279</td>
<td>0.00041943</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.076</td>
<td>0.02</td>
<td>0.00257087</td>
<td>9.53196E-05</td>
</tr>
<tr>
<td>Bone fracture</td>
<td>0.040</td>
<td>0.0017</td>
<td>0.001823219</td>
<td>7.29288E-05</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>0.002032608</td>
<td></td>
</tr>
</tbody>
</table>

3.2 Quantifying Uncertainty

3.2.1 Deterministic Multiway (“Scenario”) Analysis

A so-called multiway “scenario” analysis was conducted to explore the relative cost-effectiveness of PrEP according to a “best-case” scenario in which PrEP resulted in no decrement to individuals’ HRQoL, caused no adverse event related direct medical costs, was priced at 12% of the current sticker price, did not lead to risk compensation (i.e. no increase in sex partners and frequency of condomless sex), was 95% effective, and costs and effects were discounted at differential rates of four and two percent, respectively.

3.2.2 Probabilistic Sensitivity Analysis

Conducting a PSA entails first estimating the variance of the mean parameter estimate, and then assigning a probability distribution to each parameter estimate. To explore this particular model’s inherent uncertainty, a Monte Carlo simulation involving 10,000 iterations was performed. The incremental costs and effects generated from each iteration were plotted onto a CE plane. Table 3 presents the variance specifications (per parameter estimate) as well as the probability distribution-parameter pairings made for each parameter that is inputted in solution of differential equations. Standard errors for costs were assumed to be 50% of the mean parameter estimate. A short justification for each pairing is listed below:

Costs—gamma distributions are commonly used in economic analyses of health care costs due to their asymptotic properties for non-negative outcomes (Liu et al.,
The distribution of costs is often skewed right by outliers, and is bounded by zero as negative costs are not possible.

Utilities—beta distributions have been applied to PSA in utilities because utility values are often bounded by 0 and 1 (related to death and perfect health, respectively).

Number of sex partners—a gamma distribution was used for convenience, though an Australian study indicates that a log normal (Gaussian) distribution is best suited in approximating the distribution of number of sex partners (Kault, 1996).

Transmission probabilities—the event of contracting HIV via sexual transmission is a binomial event (i.e. either occurs or does not); the beta distribution is a conjugate to the binomial distribution and is a natural choice for representing uncertainty within a probability parameter (Briggs et al., 2006).

Diagnostic Probability—the probability of being diagnosed is related inversely to the length of time from infection to diagnosis. There are many who do not test themselves, and there are others who test themselves regularly. Moreover, each person infected with HIV will eventually receive a diagnosis. A gamma distribution was used.

Diagnostic Probability—a beta distribution was used as many HIV infected persons in Norway are connected to care shortly after diagnosis, so there are less outliers.

Demographic estimates—MSM were ultimately divided into a number of categories (susceptible, infected, diagnosed, treated, etc.) so state assignment is multinomial. As there exists little HIV surveillance data in Norway, the size of these categories is unknown. Kessler and colleagues (Kessler et al., 2012) recommend using dirichlet distributions when estimating the uncertainty around so-called “unknown prior” parameters.

To measure the uncertainty surrounding the epicenter of the plotted joint distribution, a parametric method involving the construction of a “confidence box” was employed. The width of
the box represents the 95% uncertainty interval for QALYs gained, and the box’s length represents the 95% uncertainty interval for costs, such that one can be 90% certain (.95 * .95 = .9025) that the true ICER lies within the “boxed” region. This “confidence box” approach assumes the difference in costs is independent of the difference in effects, yet this assumption is highly unlikely because treatments associated with improved quality are often more expensive (e.g. value-based pricing) and require more consumption of resources (Drummond et al., 2005).

An alternative method of describing uncertainty involving the CEAC was used. Each of the 10,000 ICERs was converted into net monetary benefits (in which both costs and effects are measured in monetary units) according to the following formula:

**Equation 13.**

\[ NMT = (\lambda \times \text{QALY}) - \text{cost} \]

The CEAC was generated from the calculated NMBs of each Monte Carlo iteration by altering the WTP threshold (\(\lambda\)) used in the model. A count was taken of the number of iterations in which the NMB of PrEP scenario was greater than the NMB of the status quo scenario. This count determines the proportion of iterations in which the PrEP scenario is acceptable for the given value of \(\lambda\) (Al, 2013). The curve thus communicates the likelihood that a treatment has an associated higher NMB than its comparators (Al, 2013).

### 3.2.3 Estimating the Value of Information

All three methods of estimating the value of information introduced in Chapter 1 were applied to the simulation results of the PSA so as to inform decision makers of the potential benefit in delaying a decision and collecting more information. According to model projections, the MSM population grew by an average of 450 persons each year over the 30-year time horizon. This mean estimate of population growth was used in estimating the PEVPI. A discount rate of four percent was applied to this growth resulting in the per-anum discounted population sizes. Over 30 years, an estimated 1,973,044 individuals are to be impacted by a reimbursement decision regarding PrEP.
4 Results

The system of differential equations was solved in order to obtain the results. A range of outcome measures were then calculated, including HIV prevalence, number of new HIV infections, discounted health costs, and health benefits (QALYs) and incremental cost-effectiveness.

The model ultimately produces an estimate of the number of HIV infections averted over a thirty-year period, were PrEP to receive approval. Model estimations indicate that PrEP is able to immediately reduce the number of infections occurring in each cycle. An immediate uptake of PrEP among 25% of high activity MSM would lead to an estimated decrease in one infection per cycle (see Figure 7). By the end of the 30 years, there is less than one infection occurring per cycle in the PrEP model arm, compared to less than three in the status quo arm.

**Figure 7.** Difference in number of infections occurring per cycle within the different treatment arms of the model

Figure 8 illustrates how PrEP’s power in reducing the number of infections translates into fewer individuals living with HIV (thereby avoiding large lifetime treatment costs). In the status quo scenario, the number of MSM individuals living with HIV infection remains relatively stable, hovering between 2000 and 2500 individuals. By cycle 35 in the PrEP scenario, however, HIV prevalence begins to decrease at a sharp rate such that at the completion of the
30-year time horizon there are approximately 1600 individuals living with HIV as opposed to an approximate 2200 persons in the status quo scenario.

**Figure 8. Difference in number of individuals in diseased states between the PrEP and status quo scenarios**

Ultimately, in the absence of PrEP, it is expected that 1855 new HIV infections will occur amongst the MSM population over the next 30 years. High-activity infected individuals will transmit the lion’s share of infections (1534 new infections ≈ 82.7%) whilst low-activity infected individuals are responsible for the remainder (321 new infections ≈ 17.3%). These estimates are presented in Table 12 on the following page.
Under the status quo scenario, approximately eight of ten new infections (79%) are the result of an undiagnosed seropositive transmitting HIV to a susceptible partner (See Figure 9). Despite there being fewer infected individuals in the acute primary infection stage compared to any other disease state (at any point in time within the model), they account for 28.9% (423 infections) of all infections transmitted by undiagnosed seropositives. Undiagnosed individuals in the early stage of HIV (i.e. the most populated disease state within the model) cause a similar number of infections (432 infections). Together the seropositive individuals inhabiting these two states combine for 46.1% of all infections in the status quo scenario. Approximately 14.5% of all infections under this scenario result from partnerships between seropositive individuals receiving ART and seronegative susceptibles. Nine individuals on average per year contract HIV from partners receiving ARV treatment. Throughout the model, there is an average of 2051 individuals receiving ART at any cycle, so the annual risk of transmitting HIV whilst on ART is between 0.4% and 0.5%. Diagnosed individuals in all disease stages who have not yet initiated ART contribute just six percent of all new infections.

Were PrEP to be made available to high-activity MSM, nearly 60% of infections would be prevented. Under the PrEP scenario, 762 new infections are estimated to arise over 30 years (See Table 13 on the following page). The number of infections transmitted by high-activity individuals is estimated to decrease by 4.1% (78.6%). Of the 596 infections attributable to high-activity seropositives, 11 infections are resultant of breakthrough infections in which an individual, having experienced PrEP failure, transmits the disease to a susceptible. It is estimated that 45 individuals prescribed PrEP will contract HIV.

Table 12. Number of infections explained by sexual activity level of both the susceptible and infected partner (status quo)

<table>
<thead>
<tr>
<th>Group causing infection</th>
<th>Newly contracted infections per group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High activity</td>
</tr>
<tr>
<td>High activity</td>
<td>1227</td>
</tr>
<tr>
<td>Low activity</td>
<td>249</td>
</tr>
<tr>
<td>Total</td>
<td>1476</td>
</tr>
</tbody>
</table>

Table 12. Nr of infections occurring in status quo scenario according to sexual activity level

<table>
<thead>
<tr>
<th>Group causing infection</th>
<th>Newly contracted infections per group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High activity</td>
</tr>
<tr>
<td>High activity</td>
<td>1227</td>
</tr>
<tr>
<td>Low activity</td>
<td>249</td>
</tr>
<tr>
<td>Total</td>
<td>1476</td>
</tr>
</tbody>
</table>
Table 13. Number of infections explained by sexual activity level of both the susceptible and infected partner (PrEP 25%)

<table>
<thead>
<tr>
<th>Group Causing Infection</th>
<th>Infections Per Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High Activity</td>
</tr>
<tr>
<td>High Activity (breakthroughs)</td>
<td>411 (6)</td>
</tr>
<tr>
<td>Low Activity</td>
<td>115</td>
</tr>
<tr>
<td>Total</td>
<td>526</td>
</tr>
</tbody>
</table>

The share of new infections attributable to seropositive partners in undiagnosed disease states decreases by eight percent when PrEP is targeted to high-activity MSM. Infections caused by undiagnosed individuals in the acute primary (122 infections) and early HIV (159 infections) infection stages account for 36.3% of all new infections, representing a decrease of approximately 10%. Individuals who have initiated ART transmit more than one in five new infections (161 infections ≈ 20.9%) under the PrEP scenario (see Figure 9). A total of 59 infections are attributable to diagnosed individuals who have not yet initiated ARV treatment, representing a share of 7.8% of all new infections.

Figure 9. Proportion of infections caused by different groups of HIV seropositives

By the end of the 30-year time horizon, 97.8% and 93.6% of HIV seropositives have received a diagnosis under the assumptions of the PrEP and status quo scenarios, respectively. Of those who have received a diagnosis, 99.3% (PrEP scenario) and 98.3% (status quo scenario) have initiated ARV treatment. Whereas 44 model inhabitants are infected and treatment
naïve in the PrEP arm of the model, approximately 182 inhabitants occupying the baseline status quo arm of the model are unaware of their seropositive status. In the last cycle of the model, 0.662 and 2.77 new infections occur per cycle in the PrEP and status quo arms of the model, respectively (see Figure 7). This would amount to 11-12 new infections per year under the assumptions of the PrEP model arm, and 48 new infections per year under the assumptions of the status quo model arm.

Ultimately, an estimated 1094 new HIV infections over a period of 30 years would be prevented as a result of an initial immediate uptake of PrEP among 25% of the high activity MSM population. This equates to more than 36 infections per year that are averted, a figure corresponding to roughly just over half (58.1%) of new infections occurring each year under the status quo scenario. To understand the diminishing (preventative) return of increased initial PrEP uptake, the model parameter was varied at different levels. The results are presented below in Figure 10. While the level of initial uptake does affect the number of infections prevented, it does not drastically affect the number of susceptibles taking PrEP over the thirty-year period, as the parameters controlling uptake and PrEP cessation assure a stable level of PrEP use. This is evidenced by taking the difference in number of individuals in the PrEP state at the end of the thirty years under the different uptake assumptions: 83 more individuals occupy the PrEP state than when initial uptake is estimated at 75% than when it is estimated at 5%. Lastly, Figure 10 also explores the difference in number of infections averted were PrEP to be 100% effective in preventing sexual transmission of HIV between MSM. Under this scenario, there would be no breakthrough infection, so states $X_{12}$ and $X_{13}$ would remain unoccupied throughout the model.

Figure 10. Number of infections averted at different levels of PrEP effectiveness and initial uptake

![Number of infections averted at various levels of initial PrEP uptake](image)
4.1 CEA Results

The cost of preventing one infection was derived by adding the population costs of each cycle and dividing that figure by the difference in number of infections occurring over 30 years between the two scenarios. A cost of 6.5 million NOK (≈ £893 076) per infection averted was estimated when only discounting costs (and not the infections averted).

Table 14. Cost per infection averted at various discounting rates

<table>
<thead>
<tr>
<th>Time Preference</th>
<th>NOK</th>
<th>UK£</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-discounted</td>
<td>11020558</td>
<td>893076</td>
</tr>
<tr>
<td>Discounted (costs &amp; effects)</td>
<td>11357301</td>
<td>920365</td>
</tr>
<tr>
<td>Discounted Costs only</td>
<td>6504636</td>
<td>527118</td>
</tr>
</tbody>
</table>

Over the 30-year period, the number of individuals needed to treat (NNT) to avoid one new infection was estimated to be 69. Formula inputs for calculating the NNT according to the formula provided in Chapter 3 are listed in the table below.

Table 15. Tabulation of formula inputs for the calculation of NNT

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>Status Quo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nr. of events</td>
<td>762 (EE)</td>
<td>1855 (CE)</td>
</tr>
<tr>
<td>Nr. of non-events</td>
<td>73318 (EN)</td>
<td>72514 (CN)</td>
</tr>
<tr>
<td>Total</td>
<td>74080 (ES)</td>
<td>74369 (CS)</td>
</tr>
</tbody>
</table>
4.2 CUA Results

4.2.1 Deterministic Results

Table 16 presents the deterministic results of the model, expressed as mean costs (NOK), and mean effects (QALYs, LYs) per individual. The original PrEP scenario (25% immediate initial uptake) is associated with an overall higher (discounted) cost for all MSM. Ultimately, the PrEP scenario is associated with an increase of 179,674 NOK per MSM accrued over 30 years. The level of HRQoL among the MSM population is expected to suffer a very minimal decrease (-0.00213 QALYs per individual; undiscouned) under the PrEP scenario, yet this is accompanied by an equally minimal increase in life years (0.00349 LYs per individual; undiscounted). Although PrEP prevents a large number of infections over the time horizon, it is also associated with a minimal decrease in HRQoL due adverse events related to the treatment. Since over several thousands of MSM are modelled to receive PrEP treatment, this minimal decrease applied to each PrEP-treated individual outweighs the QALYs saved in preventing more than 1000 HIV infections.

As cost-utility analysis ignores the increase in life years attributable to PrEP, and focuses solely on the difference in costs and HRQoL, PrEP would not be recommended at any willingness to pay threshold. PrEP is ultimately dominated by the status quo scenario, as it is associated with increased costs and negative effects.

Table 16. Deterministic results of the cost-utility analysis

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Costs</th>
<th>QALY</th>
<th>LY</th>
<th>Costs</th>
<th>QALY</th>
<th>LY</th>
</tr>
</thead>
<tbody>
<tr>
<td>PrEP 25%</td>
<td>695,240</td>
<td>29,087</td>
<td>29,345</td>
<td>41,383</td>
<td>17,235</td>
<td>17,389</td>
</tr>
<tr>
<td>Baseline</td>
<td>515,565</td>
<td>29,089</td>
<td>29,344</td>
<td>30,576</td>
<td>17,237</td>
<td>17,386</td>
</tr>
<tr>
<td>Increment</td>
<td>179,674</td>
<td>-0,021</td>
<td>0,000</td>
<td>10,807</td>
<td>-0,021</td>
<td>0,000</td>
</tr>
<tr>
<td>∆Costs/∆QALY</td>
<td>NOK</td>
<td>NOK</td>
<td>NOK</td>
<td>NOK</td>
<td>NOK</td>
<td>NOK</td>
</tr>
<tr>
<td></td>
<td>843,1193</td>
<td>514,706</td>
<td>514,706</td>
<td>515,48642</td>
<td>611,493,408</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UK £</td>
<td>UK £</td>
<td>UK £</td>
<td>UK £</td>
<td>UK £</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-683,970</td>
<td>416,839</td>
<td>-417,786</td>
<td>495,3761</td>
<td></td>
<td></td>
</tr>
<tr>
<td>∆Costs/∆LYS</td>
<td>NOK</td>
<td>NOK</td>
<td>NOK</td>
<td>NOK</td>
<td>NOK</td>
<td>NOK</td>
</tr>
<tr>
<td></td>
<td>-843,1193</td>
<td>514,706</td>
<td>514,706</td>
<td>515,48642</td>
<td>611,493,408</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UK £</td>
<td>UK £</td>
<td>UK £</td>
<td>UK £</td>
<td>UK £</td>
<td></td>
</tr>
</tbody>
</table>
4.2.2 Uncertainty Analyses

4.2.2.1 Multiway analysis

The multiway uncertainty analysis was conducted by altering the parameters to create an artificial “best case” scenario for PrEP approval. Despite adjusting parameter values and discount rates to create favorable circumstances, the scenario in which PrEP is made available to high-activity MSM residing in Norway was still found to be not cost-effective when using traditionally accepted willingness to pay thresholds. While costs were discounted at four percent and effects at two percent, the cost per QALY was estimated to be \( 5719437 \text{ NOK} \approx £463228 \). This estimate is presented below in Table 17. According to the United Kingdom’s National Institute for Health and Clinical Excellence (NICE) guidelines, treatments should be rejected as being cost-effective if they exceed £20 000 - £30 000 (NICE, 2008).

Table 17. Results from multiway uncertainty analysis

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Costs (NOK)</th>
<th>QALY</th>
<th>LY</th>
<th>Costs (NOK)</th>
<th>QALY</th>
<th>LY</th>
</tr>
</thead>
<tbody>
<tr>
<td>PrEP 25%</td>
<td>588871</td>
<td>29,100</td>
<td>95</td>
<td>351893</td>
<td>22,041</td>
<td>46</td>
</tr>
<tr>
<td>Baseline</td>
<td>515566</td>
<td>29,089</td>
<td>47</td>
<td>305763</td>
<td>22,033</td>
<td>39</td>
</tr>
<tr>
<td>Increment</td>
<td>73305</td>
<td>0,011</td>
<td>48</td>
<td>46130</td>
<td>0,008</td>
<td>26</td>
</tr>
</tbody>
</table>

\[ \Delta \text{Costs/ΔQALYs} \]
\[ \Delta \text{Costs/ΔLYs} \]

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Not Discounted</th>
<th>Discounted</th>
</tr>
</thead>
<tbody>
<tr>
<td>PrEP 25%</td>
<td>517460</td>
<td>16501216</td>
</tr>
<tr>
<td>Baseline</td>
<td>517460</td>
<td>16501216</td>
</tr>
<tr>
<td>Increment</td>
<td>5716233</td>
<td>14577883</td>
</tr>
</tbody>
</table>

4.2.2.2 Probabilistic Sensitivity Analysis

The results (median incremental costs and effects) of the PSA are provided on the following page in Table 18. Using the median estimates, an ICER of 9.2 million NOK (\( \approx £750 \text{ 000} \)) was estimated.
Table 18. Results from the PSA (using discounted median costs and effects)

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Costs</th>
<th>QALY</th>
<th>LY</th>
<th>ΔCosts/ΔLYs</th>
<th>ΔCosts/ΔQALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>PrEP 25%</td>
<td>416341</td>
<td>29,10095</td>
<td>17,39006</td>
<td>NOK</td>
<td>9196341</td>
</tr>
<tr>
<td>Baseline</td>
<td>310767</td>
<td>29,08947</td>
<td>17,38973</td>
<td>UK £</td>
<td>745246</td>
</tr>
<tr>
<td>Increment</td>
<td>105574</td>
<td>0,01148</td>
<td>0,00033</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Outputs of the probabilistic model—involving a Monte Carlo simulation using the Visual Basic program in Excel—define a distribution of the incremental effects and costs over incremental cost, which are subsequently plotted on the CE plane. The spread of ICERs across the plane reveals the weakness of the deterministic ICER in predicting with certainty PrEP’s comparative cost-effectiveness (see Figure 11 on the following page). Much of the density function appears to straddle the northwest and northeast quadrants indicating that the PrEP scenario is associated with increased costs per person rather than savings, and has a dubious impact on the effects (HRQoL). Interval estimates of the “true” ICER (90% confidence interval related to costs: 4 329 NOK – 173 319 NOK; 90% confidence interval related to effects: -.304 – .308 QALYs) were calculated from the outputs of the Monte Carlo simulation according to the percentile method. The red confidence box rendered in Figure 11 below indicates these results. Interestingly, the upper bound of the cost interval is similar to the incremental cost calculated in the deterministic ICER calculations (179 674 NOK).

Figure 11. Joint distribution of ICER estimates from PSA plotted on the CE plane
The CEAC, as mentioned in the previous section, was derived from a Monte Carlo simulation of the net monetary benefit of the different scenarios. The curves cut the vertical axis at the probability that the intervention under evaluation is cost-saving at different values of willingness to pay. Figure 12 illustrates the behavior of the scenarios’ acceptability curves, indicating that most decision uncertainty occurs when the willingness to pay threshold is set at approximately 25 million NOK. It is at this point where the two curves cross, meaning that each scenario has a 50% probability of being comparatively more cost-effective and a 50% probability of not being cost-effective.

**Figure 12. The CEAC derived from PSA results converted into NMBs**

As the extended CEAC presented in Figure 13 below indicates, the two curves continue almost at a straight line across the x-axis after intersecting one another, with neither of the two curves approaching the boundaries (0, 1) of the y-axis. The behavior of these particular curves has great implications for the value of information assessments.

**Figure 13. Extended CEAC**
4.2.3 Informing Research Priorities

Both the individual and population-level EVPI estimates continuously rise as the threshold increases. EVPI curves have often been observed to rise steadily until peaking at a certain threshold level, before descending negatively as the threshold level moves along the x-axis. This is because the level of uncertainty is very small at low threshold levels, but grows as the threshold increases and the two acceptability curves begin to converge until the threshold is so large that there is little uncertainty as to which treatment is most cost-effective. In the case of PrEP vs. status quo scenarios, however, the EVPI (not shown) is continuously rising towards infinity even though the two acceptability curves do, in fact, cross. Despite intersecting, the slope of each curve is extremely tenuous, with the probabilities that the PrEP and status quo scenarios are cost-effective hovering (regardless of the size of the threshold) at 63.5% and 36.5%, respectively.

Across a wide range of WTP threshold values (ranging from 0 NOK to 375 million NOK), the average individual EVPI is 124.7 million NOK. Ultimately, an estimated 1,973,044 individuals are to be effected (over 30 years) by an approval decision related to PrEP. Double counting does occur from year to year, yet the population estimate is discounted by four percent each year. Applying the individual EVPI value to the population produces an average population-level EVPI (i.e. across the range of threshold levels) of 4.76 trillion NOK. Figure 14 below presents the behavior of the PEVPI curve at various levels of WTP.

Figure 14. PEVPI curve derived from PSA results
Analyses related to expected value of partial perfect information on the model’s parameters revealed that uncertainty about the different state utility estimates drives the total model uncertainty. According to EVPPI estimates, uncertainty connected to utility estimates of the different model states is responsible for 89% of total parameter uncertainty. Results suggest that an average of 8 240 415 NOK (see Figure 15 on the following page) could be invested per person to better understand the different levels of HRQoL experienced when treated with PrEP and when infected with HIV (before and after initiation of ART).

Figure 15. EVPPI by parameter grouping

The other three groups of parameters responsible for model uncertainty are: sexual behavior (9%), transmission probability (2%), and disease progression parameters (0.2%). These estimates are presented below in Figure 16. Ultimately, the different EVPPI estimates do not sum to the estimated EVPI. This is likely due to correlation between the parameters (McCallaugh et al., 2013).
Figure 16. EVPPI for the different parameter groupings as a percentage
5 Discussion

Given the complexities of accurate parameter estimation and inherent gaps in our knowledge and data systems, model calibration is of substantial importance. Recalibration to a Norwegian context is likely necessary in the future. Nevertheless, the model’s predictive capability has been validated. A discussion of its predictive accuracy and limitations follows below.

5.1 Results and Model Validation

The Monte Carlo experiment showed that the deterministic nonlinear differential equations using expected values gave more pessimistic predictions than the probabilistic process. According to median results of the PSA, a baseline of 1880 new HIV infections amongst MSM are estimated to occur over the next 30 years in Norway. Assuming that diagnosed HIV infections represent 85% of all HIV infections amongst MSM, the FHI data from 2010 to 2014 (see Table 19) suggest that an average of 109 MSM residing in Norway are infected each year (both diagnosed and undiagnosed), with approximately 70 of these infections (i.e. 65%) occurring in Norway. Despite future growth of the MSM population, the model’s estimate of 63 new infections per year seems reasonable when compared to the FHI data, given that both diagnosis and treatment initiation rates are likely to improve in the future.

Table 19. HIV infection among MSM 2002-2014 by diagnosis year and location infection took place

<table>
<thead>
<tr>
<th>Smittetår</th>
<th>&lt;05</th>
<th>05</th>
<th>06</th>
<th>07</th>
<th>08</th>
<th>09</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heteroseksuell</td>
<td>1434</td>
<td>134</td>
<td>165</td>
<td>141</td>
<td>184</td>
<td>171</td>
<td>157</td>
<td>155</td>
<td>142</td>
<td>124</td>
<td>130</td>
<td>2937</td>
</tr>
<tr>
<td>- smittet mens basatt i Norge</td>
<td>485</td>
<td>33</td>
<td>42</td>
<td>41</td>
<td>45</td>
<td>44</td>
<td>57</td>
<td>46</td>
<td>46</td>
<td>31</td>
<td>47</td>
<td>918</td>
</tr>
<tr>
<td>- smittet før ankomst Norge</td>
<td>949</td>
<td>101</td>
<td>123</td>
<td>100</td>
<td>138</td>
<td>127</td>
<td>100</td>
<td>109</td>
<td>96</td>
<td>93</td>
<td>83</td>
<td>2019</td>
</tr>
<tr>
<td>Homoseksuell</td>
<td>965</td>
<td>56</td>
<td>90</td>
<td>77</td>
<td>93</td>
<td>88</td>
<td>85</td>
<td>97</td>
<td>76</td>
<td>98</td>
<td>107</td>
<td>1832</td>
</tr>
<tr>
<td>Søktemisbruk</td>
<td>501</td>
<td>20</td>
<td>7</td>
<td>13</td>
<td>12</td>
<td>11</td>
<td>11</td>
<td>10</td>
<td>11</td>
<td>8</td>
<td>7</td>
<td>611</td>
</tr>
<tr>
<td>Via blod-/blodprodukt</td>
<td>46</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>48</td>
</tr>
<tr>
<td>Fra mort til barn</td>
<td>35</td>
<td>5</td>
<td>6</td>
<td>9</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>7</td>
<td>1</td>
<td>3</td>
<td>79</td>
</tr>
<tr>
<td>Annen/ukjent</td>
<td>63</td>
<td>4</td>
<td>9</td>
<td>8</td>
<td>6</td>
<td>9</td>
<td>4</td>
<td>2</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>115</td>
</tr>
<tr>
<td>Total</td>
<td>3044</td>
<td>219</td>
<td>277</td>
<td>248</td>
<td>299</td>
<td>284</td>
<td>258</td>
<td>268</td>
<td>242</td>
<td>234</td>
<td>249</td>
<td>5622</td>
</tr>
</tbody>
</table>

Analysis confirms the potential benefit of including PrEP as a prevention tool in controlling HIV amongst MSM residing in Norway. The initial provision and uptake of PrEP in one of
every four high-activity individuals stands to prevent nearly 1100 infections. Whether this level of initial uptake is achievable remains to be seen. In the United States where PrEP is available, limited awareness, among both health care professionals and lay folk alike, has led to low immediate uptake (Krakower et al., 2012). It must be acknowledged that approval of PrEP would require subsequent investments in outreach and communication activities to augment awareness. Increased interest in PrEP may lead to a big upsurge in MSM coming forward for an HIV test (and possibly other STI testing) since prescription is conditional upon an initial negative HIV test result. This increase in testing is likely to have a positive effect if many come forward whom otherwise would not have undergone testing. Additionally, the 1100 estimated prevented infections are conditional upon a PrEP efficacy level of 86%. Several studies report higher effectiveness rates than the one used in the model, with one study finding PrEP to be 100% effective when individuals adhere to a once-daily dosing regimen at least four to six days a week (Grant et al., 2010). Demonstrated high PrEP adherence would therefore increase the number of infections averted.

While the iPrEX, PROUD and iPERGAY studies have solidified the global acknowledgement of PrEP’s effectiveness, several stakeholders engaged in HIV prevention continue to deny the drug a place in prevention portfolios and budgets, referencing the cost in their justifications for refusing or delaying reimbursement. Though different stakeholders have floated around various PrEP cost estimates, the price used in the model was taken directly from the NMA. The 66 840 NOK a year “sticker price” however is likely to drop significantly in the coming years, as the European patent for Truvada expires in 2018. For this reason, the impact on costs due to market entry of generics was included. According to the step-price model adopted in Norway in 2005, generic competition may enter the market in the same year as the pharmaceutical drug misses its patent protection, given that the generic version delivers the same value (Statens Legemiddelverk, 2016). A 36% cut in the price of the original drug is made at the time of generic entry, with additional cuts in price occurring at six and twelve months after generic entry. All future price cuts are conditional upon Gilead’s revenue from the drug. Table 20 on the following page explains the extent of the cuts in relation to annual earnings.
Table 20. Description of NMA’s step pricing policy

<table>
<thead>
<tr>
<th>Omsetning før generisk konkurranse</th>
<th>1. trinnpriskutt (umiddelbart)</th>
<th>2. trinnpriskutt (etter 6 mnd)</th>
<th>3. trinnpriskutt (tidligst etter 18 mnd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 100 mill. kroner</td>
<td>35 %</td>
<td>59 %</td>
<td>Omsetning &gt; 15 mill. kroner: 69 %</td>
</tr>
<tr>
<td>Over 100 mill. kroner</td>
<td>35 %</td>
<td>81 %</td>
<td>Omsetning &gt; 30 mill. kroner: 88 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Omsetning &gt; 100 mill. kroner: 90 %</td>
</tr>
</tbody>
</table>

Figure 17. Representation of NMA’s step price policy due to introduction of generics as percent of original cost

According to costing regulations imposed by the NMA, the cost of PrEP in Norway could be as low as 10% of the original sticker price of Truvada; a price level which is similar to the one used in the “best case scenario” multiway analysis. Ultimately even at severely reduced prices, the PrEP scenario was not found to be comparatively more cost-effective. This is due to the cost of PrEP itself, the cost of PrEP related adverse events, and costs associated with monitoring for HIV, STIs and kidney and other organ dysfunctions. Other forms of PrEP (e.g. lubricants, rectal douches, oral on-demand tablets, tenofovir-only tablets, injections) are currently being investigated, and may prove more cost-effective than once-daily oral PrEP since they limit use and therein cost of drugs, whilst preventing similar numbers of infection. Ouellet and colleagues found that on-demand PrEP was able to reduce active ingredient intake, thereby leading to less costs (Ouellet, 2015). An American study conducted in Kenya found
that removing the chemorophylactic agent emtricitabine from the PrEP tablet reduced program costs by 39\% (Baeten et al., 2011).

In using a CUA framework involving the application of widely accepted WTP thresholds, once-daily oral PrEP prescribed to MSM with an average of 6.2 annual sex partners was not found to be cost-effective in preventing HIV infection. Although the PrEP scenario is associated with an increase of 0.01148 QALYs for each MSM in the model over the 30-year time horizon, the improved effects are not enough to offset a discounted median increase in health expenditures of 105,574 NOK per individual over the same time period (translating to an annual increase of 6,311 NOK per MSM). While the model suggests PrEP saves a total of 22 lives over the 30-year time horizon by preventing HIV infections, the total number of life years per person saved within the entire MSM population is negligible. The discounted cost for an additional life year is over 611 million NOK.

According to the deterministic results of the model, the PrEP scenario was associated with 2,472 more QALYs accrued over the time horizon than the status quo scenario when equal utilities were assumed between PrEP and non-PrEP using susceptibles. To estimate the number of QALYs gained by one prevented infection, the aforementioned figure of 2,472 QALYS was divided by the number of prevented infections (1,100 infections). This leads to an estimate gain of roughly 2.5 QALYs per prevented infection averted. Research, however suggests that between five and six QALYs are saved per infection averted (Holtgrave et al., 2012; Hutchinson et. al, 2010). This large discrepancy in estimated QALYs saved is likely due in part to the fact that costs and QALYs are ignored once individuals mature out of the model. Additionally, potentially overly optimistic estimates of diagnosis and treatment initiation rates incorporated into the model are presumably to blame as they lead to less time spent in the disease stages than what may actually be observed. Were the incremental QALY estimate to be increased three-fold so as to adjust for the discrepancy discussed above, the new ICER would lie at approximately 3.07 million NOK per QALY, an amount eight times greater than traditional WTP thresholds.

To further explore the cost-effectiveness of PrEP, a CEA framework involving cost per infection averted was employed. According to the CDC, the lifetime treatment cost of an HIV infection can be used as a conservative threshold value for the cost of averting one infection (Ouellet et al., 2015). The non-discounted direct treatment cost of a single HIV infection
as of 2015 was estimated from the model to be 6 569 847 NOK. This lifetime HIV cost estimate assumes that every seropositive individual goes 2.6 years before receiving diagnosis, has a CD4 count above 200 cells/µl when diagnosed, is treatment naïve for 12 cycles before initiating PrEP, and then remains on ARV treatment for 35 years. Ultimately the model estimate corresponds to a figure suggested by Ouellet and colleagues of 5 857 332 NOK (2012\(^8\)), when correcting for inflation due to a weakening Norwegian krone. Similarly, a German study from 2013 found that HIV direct health care costs were approximately 19 103 euros per year (Mostardt et al., 2013). Thirty-five years of treatment is thus associated with an undiscounted cost of approximately 6.15 million NOK. As the discounted cost per new infection averted (not discounted) is roughly 6.55 million NOK, PrEP may be cost-effective in preventing HIV infections depending on the decision maker’s time preference and adopted perspective (e.g. societal perspective, health care “payer” perspective).

An additional method involving NNT was employed in the assessment of PrEP. The NNT estimates the number of persons needed to receive treatment per year to prevent one new infection from arising. Using projections data from the model to calculate event rates between the two scenarios, the overall NNT value over the 30-year time horizon was found to be 69. Interpretation of this estimate suggests that 69 high-activity MSM must be treated with PrEP per year in order to prevent one new HIV occurrence within Norway’s entire MSM population. Chen and Dowdy (2014) derived a similar NNT estimate of 64 (95% confidence interval: 26-176) when PrEP was made available to the general U.S. MSM population (i.e. patients fitting generic population profiles). In the American study, the NNT was never less than 50 in any setting where HIV prevalence was 15% or lower (Chen & Dowdy, 2014). While there exists no golden rule for evaluating treatments based on NNT estimates, the lower the NNT value, the better. The value of 69 suggests a cost of 2.61 million NOK per infection averted. In using this estimate, PrEP is found to be cost-effective as 2.61 million NOK is less than the undiscounted lifetime health care cost of HIV infection derived from the model (6.59 million NOK). Additionally the NNT-related cost-per-averted infection of 2.61 million NOK is less than the undiscounted 4.45 million NOK life-long cost of HIV infection proposed by Nakagawa and colleagues (Nakagawa et al., 2015).

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\(^8\) Originally published in 2012 Canadian dollars.
5.2 Limitations

Models are false representations of reality, constructed from simplifications and incomplete facts, yet the limitations inherent to modeling also allow for convenience and practicality. The quality of a model in capturing reality ultimately depends on its accuracy, convenience, and uniformity (Phillips et. al, 2006). The third, non-exhaustive criterion for a good model deals more with physical models than with abstractions (Phillips et al., 2006), therefore the model’s convenience and accuracy will be of interest in this section. This particular PrEP-HIV transmission model hopefully will prove convenient for decision makers in Norway if and when they are tasked with making a reimbursement decision. Despite a dearth of HIV surveillance data and information regarding sexual/diagnostic behavior of MSM, the model is able to provide an estimation of HIV transmission under a scenario in which PrEP is made available. This accomplishment is attributable to the great number of assumptions and simplifications made, which if incorrect, would diminish the model’s accuracy thereby potentially leading to the wrong decision being taken. While the assumptions provided for rapid construction, the model stands to eventually be improved by examining its incompleteness so as to eliminate the more serious limitations. What follows is a discussion of potential errors incorporated into the model as well as the key assumptions made by the author.

5.2.1 Model Structure

As opposed to an individual-based model in which characteristics of each individual are tracked over time, the model presented ultimately describes HIV transmission in the entire MSM population residing in Norway, thus relying on a technique where population characteristics are averaged together. To validate the technique, three assumptions must be made:

1. The population is homogeneous: populations are nevertheless heterogeneous, with individuals differing with respect to susceptibility and infectiousness, sexual behavior, and treatment response. Very little heterogeneity was incorporated into the model, however, because to do so necessitates a complex model structure. No age or partnership-type (e.g. one-off, long-term) distinction was incorporated into the model, although studies reviewed reported a higher cost-effectiveness benefit for PrEP targeted
at certain age groups and at individuals in concurrent and non-monogamous partnerships (Cambiano et al., 2015).

2. Patient history is ignored: the Markov structure does not account for the time spent in each previous state (i.e. the patients’ history). According to this assumption, whether a person was diagnosed in the late stage or experienced a delay in the initiation of treatment has no impact on future transitions, costs or HRQoL. Ultimately, the same transition probability, costs and HRQoL are applied equally to all individuals occupying the same state. Empirical evidence however refutes this assumption, reporting increased risk of treatment failure, lower levels of HRQoL and higher mortality rates for for individuals who began care in progressed disease states (Lok et al., 2010; Nakagawa et al., 2012).

3. A third assumption related to the model’s Markov structure involves constant transition rates. Rates of transition from one state to the next do not change over time. Rates of diagnosis and treatment initiation have, nevertheless, been increasing piecemeal for decades as testing becomes more widespread and evidence-based guidelines are modified. Less than five years ago it was recommended that individuals wait to initiate treatment until their CD4 cell count drops below 350 cells/µl, yet as of 2013 it is recommended to begin treatment as soon as possible given that the patient is likely to adhere. It is therefore likely that estimates of transition rates and model parameters will change over the 30-year period.

This particular model incorporates a single level of mixing according to sexual activity grouping, and thus disregards any multilevel mixing behavior related to partner’s presumed serostatus, age, race, nationality, etc. In reality, individuals tend to interact with certain groups of individuals at a much higher rate, based solely on characteristics (e.g. age, race, and geographic location). EMIS survey response data, indicates, however that the majority of individuals do not consider a partner’s HIV status before or during sex (Folkehelseinstituttet, 2013).

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9 Insertive and receptive anal sex rates are different for age groups; testing behaviour; number of partners, age of partners
Being a closed, population-based model, the model only estimates infections occurring within Norway. In reality, many MSM residing in Norway are infected abroad. Table 19 indicates that the majority of MSM diagnosed in 2014 reported being exposed to HIV while abroad. Approval of PrEP within Norway may therefore have a greater preventative effect as individuals travel to areas with higher HIV incidence.

Further assumptions regarding maturation flow out of the model, and ARV treatment success were made to maintain a simplified model structure. Individuals maturing out of the model are no longer considered when estimating incremental costs and effects between the two scenarios. Maturation ultimately entails complete future abstinence from sex with other MSM, therefore it is important to estimate out-flow of individuals so as to properly model HIV transmission. While these individuals may have exited the sexual network, they will continue to experience a certain level of quality of life and consume medical resources (thereby incurring costs) until their death. A future inclusion of these costs and HRQoL levels in cost-utility analyses could potentially sway a decision in favor of reimbursing PrEP. Although the inclusion of various treatment success and failure as well as “therapy-line” states was considered when designing the model, a simpler structure involving one treatment state for each activity group was selected. In reality, some individuals must switch to a subsequent line of therapy due to toxicity and or virologic failure. Switching to a new line of treatment is costly, as it requires an assessment of adherence, drug-drug and drug-food interactions, drug tolerability, HIV RNA and CD4 cell count trends, treatment history, and drug-resistance testing (Panel on ARV Guidelines for Adults & Adolescents, 2016). The subsequent second and third-line drugs are also more expensive, so any shift would have considerable financial implications. Moreover, any stop in treatment could entail a drop in HRQoL and increase in transmission risk due to low virologic suppression. A study conducted in the UK found that by the fourth year of treatment, three of four seropositive individuals receiving ART had discontinued at least one drug in their initial regimen (Mocroft et al., 2005). An additional study reported that more than one in ten individuals (12%) receiving ARV treatment had experienced triple class virologic failure (Mocroft et al., 2004), an event that greatly increases their risk of dying (Grover et al., 2008). The risk of drug resistance emergence in persons who experience treatment failure is currently unknown in Norway. Its occurrence is dependent upon the potency of the ARV regimens and individual adherence. The inclusion of PrEP in preventative care may contribute to drug resistance if an individual experiencing breakthrough infec-
tion were to continue taking PrEP, thereby exposing the virus to lower levels of the chemoprophylactic agents than what is required for suppression. Costs of emerging resistance to Truvada and other drugs were not included in the analysis, however. Recent clinical trials, nevertheless, failed to identify instances of drug resistance related to PrEP use (Liegler et al., 2014; Grant et al., 2010), “suggesting that the percentage of emerging drug resistant cases would be negligible” (Grant et al., 2010).

5.2.2 Parameter Estimates

The parameter estimates related to diagnosis and treatment initiation were informed from studies conducted abroad (all in Western Europe) as there exists little surveillance data related to HIV care in Norway. For the better half of the last decade, there has been talk of creating a register for HIV seropositive individuals that could be used not only to improve and bring equity to care, but also in medical and health economics research. A lack of legislation regarding patients’ privacy, however, has prevented these discussions from being realized. Until a register is in place, it will be difficult to estimate with much certainty population estimates related to HIV diagnosis and treatment. Severely limited data related to the MSM sexual network and sexual behavior of MSM necessitated the use of the EMIS survey data in estimating activity group size, and difference in HIV prevalence, number of sex partners, HIV testing, and condom use between the groups. The EMIS was an anonymous, voluntary (self-administered) online survey that was advertised on the main social/dating websites for MSM in Norway (e.g. Gaysir). Follow-up studies found that EMIS respondents throughout the 38 countries participating displayed somewhat higher risk than the general MSM population (Marcus et al., 2012). This would result in over-estimations of number of sex partners and frequency of condomless sex. Furthermore, Internet samples are biased as younger men are over-represented on MSM social/dating websites, and are thus more likely to participate (Marcus et al., 2012).

Though the inhabitants of the model are initially divided into two activity groups, high and low risk is assumed to be transient, changing over time within individuals. It is purely not feasible to correctly estimate the parameter controlling intergroup transitions with a population. Similarly it is extremely difficult to estimate how long a person would continue on PrEP. Associated costs would be much lower if PrEP were to be used as a short-term solution when
risk is highest than if PrEP were to be used continuously for many years. Future research should therefore investigate rates of PrEP use and cessation over the life cycle so as to understand the average length of time spent on PrEP.

Recent findings indicate that PrEP does not promote risk inhibition (McCormack et al., 2014). The studies reporting insignificant risk inhibition were all placebo-based. The findings, therefore, may not translate into real world situations where individuals are aware of the protective qualities of their drug treatments. Risk compensation was ultimately incorporated into the model by associating PrEP use with a 15% increase in number of sex partners and a 10% decrease in condom usage. Interestingly, an increase in sex partners resulted in a higher cost-effectiveness benefit. This is likely to have occurred due to specifications in the model controlling force of infection, which is related to the proportion of sex acts with different groups. PrEP is unlikely to cause individuals not taking PrEP to begin having sex with more people; for purposes of the model, this means that any additional partners PrEP users might have are likely to be other PrEP users. The presence of other STIs, however, was not included in the model. Were risk compensation to take place, it is likely rates of STI infection would be higher among PrEP users, leading to decrements in health-based utility and higher costs related to treatment of STIs.

Patients recruited into the PROUD study, from which the PrEP efficacy rate used in the model was estimated, received behavioral counseling to ensure medication adherence and to combat risk compensation. The protective effect of PrEP against HIV relies greatly on individuals’ drug adherence, and is likely to vary greatly due to personal characteristics and behavior, and also the presence and extent of supplementary support programs.

Within the model, infection of susceptible MSM occurs only via anal intercourse in a sexual partnership with another male. MSM may nevertheless have female sex partners, and/or contract/transmit HIV during oral sex, though this risk of infection is much smaller (Benn et al., 2011). The partnership transmission rate during anal sex used in the model involved the assumption that both partners partake in insertive and receptive anal sex. In reality, however, one partner may only be receptive (passive) while the other may only be insertive.
(active). Norwegian data collected from the EMIS indicate that 19% of high-activity MSM adopt exclusively an insertive role, while 16% are exclusively receptive (Folkehelseinstituttet, 2013). Insertive sex is associated with much lower rates of infection when compared to receptive anal sex, therefore a large number of individuals would have significantly higher/lower risks of contracting HIV depending upon the type of exposure.

Table 21. Assumed HIV transmission rate due to unprotected exposure from known HIV positive not on ART (Source: Benn et al., 2011)

<table>
<thead>
<tr>
<th>Eksponeringstype</th>
<th>Antatt transmisjonsrate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reseptivt analt samleie</td>
<td>1,11 (0,042-3,0)</td>
</tr>
<tr>
<td>Insertivt analt samleie</td>
<td>0,06 (0,06-0,065)</td>
</tr>
<tr>
<td>Reseptivt vaginalt samleie</td>
<td>0,1 (0,004-0,32)</td>
</tr>
<tr>
<td>Insertivt vaginalt samleie</td>
<td>0,082 (0,011-0,38)</td>
</tr>
<tr>
<td>Reseptivt oralsex (fellatie)</td>
<td>0,02</td>
</tr>
<tr>
<td>Insertiv oralsex</td>
<td>0</td>
</tr>
</tbody>
</table>

Per-act transmission probability estimates were not used in the model, due to a lack of sexual behavior data related to length of partnership and frequency of unprotected anal intercourse within the relationship. As Røttingen & Garnett write, “probability theory would assume that there was a per-act transmission probability, and that as the number of sex acts increased then so too would the transmission probability per partnership,” yet several studies attempting to estimate partnership transmission as a function of sex acts have failed to find a straightforward relationship between the two probabilities (Røttingen & Garnett, 2002). The model ultimately assumes that transmission within the partnership either occurs instantaneously or doesn’t occur at all, yet this is not “biologically plausible,” as transmission is a function of the seropositive partner’s infectiousness (highest during acute phase), type of sexual contact, and susceptibility of the seronegative partner (Røttingen & Garnett, 2002).

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10 There was not enough data regarding sexual role in the low-activity group as more than 85% of respondents assigned to the group did not answer question.
5.2.3 Utility Estimates

For individuals receiving ART, their level of HRQoL is likely to be nearly similar to that of seronegative individuals. Before starting treatment, however, seropositive individuals experience large decrements as the disease progresses and symptoms develop. For an asymptomatic individual, even the diagnosis itself may impact his HRQoL, as stigma has historically surrounded the disease (Honinden et al., 2006). Stigma, potential social isolation, and stress may cause psychosocial problems for the newly diagnosed. Stigma is also responsible for fear and angst experienced by seronegatives who are preoccupied with contracting HIV. Individuals may experience a higher HRQoL whilst on PrEP because they experience a sense of protection, quelling their worries. Moreover, PrEP may allow individuals to realize their sexual desires, which in turn can augment utility and satisfaction, though this is likely not to be detected by standard health utility elicitation instruments. Consideration of these effects was, nevertheless, not reflected in the model’s inputs.

A disutility decrement was applied to all seronegative individuals on PrEP (i.e. excluded PrEP users experiencing breakthrough infection). This decrement is related to frequency of severe adverse events. Clinical trial data from PrEP studies reports very little information regarding side effects and hospitalizations. A person might have a negative reaction to PrEP or experience side-effects albeit for just a few days or weeks. In contrast, the majority of studies lasted for less than a year, and are likely not to have captured relevant data related to adverse events that develop over time, such as kidney failure, bone density loss, diabetes, and lipoatrophy. It was assumed that all adverse events would stop after PrEP cessation, though the aforementioned side-effects are likely to be irreversible. In the future, more resources should be spent on trials related to identifying the occurrence and magnitude of these events, and how they affect health care consumption and quality of life.

5.2.4 Cost Estimates

Health care consumption of seropositive individuals living in Norway was assumed to be the same as that reported from British surveillance studies conducted at a number of pilot sites throughout the country. While the UK health system is similarly structured, it is likely that both the level of consumption and price of care in Norway are far from identical. Unfor-
fortunately there is no similar surveillance system in place in Norway to derive costs of care. Consultations with specialists in HIV care may, nevertheless, compensate for this lack of infrastructure, as their expert input can be used in costing and modeling studies.

Documented consumption of resources related to PrEP treatment is severely lacking. Risk estimates of hospitalization due to adverse events were assumed arbitrarily and are therefore not defensible. Length of stay per hospitalization was estimated for each major adverse event using health care utilization data collected in the U.S. American health systems data is likely not to be representative of Norwegian health care consumption, though the two countries have similar expenditures (The World Bank, 2015).

The development of HAART has radically changed the average HIV positive prognosis, yet seropositives are continually forced to confront psychosocial issues connected to the disease as many experience a range of mental health disorders such as anxiety, depression, mood swings, and even organic brain syndromes caused by the virus itself (Catalan et al., 2000). To meet these psychosocial health needs, health care providers have implemented psychological interventions including counseling, cognitive-behavior therapy, stress and anxiety management, as well as psychotherapy (Green et al., 2004). Psychosocial health services were not considered, however, in measuring health care consumption. It is therefore likely that ICER estimates would be more favorable to PrEP were they to be included in the costing of HIV care. To understand the full extent of the cost of HIV care in Norway, future analyses must incorporate the consumption of psychosocial care resources.

Another key limitation to this modeling study is that it does not include savings in treatment and hospitalization due to secondary infections averted. The reproductive number of HIV in Norway had dropped to less than one at the beginning of the new millennium, but has risen to more than one over the last ten years, meaning that each new infected person is expected to infect more than one additional person in their life time. The results of cost-effect and cost-utility analyses considering the benefits in preventing secondary cases would improve PrEP cost-effectiveness.

In choosing a health care payer perspective, social costs due to loss of productivity were excluded from the analysis. Costs such as lost revenue due to absenteeism were not included. Research also suggests that there exists an income revenue and employment gap between the general MSM population and HIV-positive MSM (Dray-Spira et al., 2007). For
some, the effects of HIV on physical and mental function may prevent them from maintaining regular employment, or whilst others may experience that “their work responsibilities compete with their health care needs,” (American Psychological Association, 2013). Moreover, seropositive individuals must miss work to attend outpatient and psychosocial visits potentially taking up hours of their time, and inpatient/emergency care leads to entire work days being missed. Additionally, seropositive individuals might require non-traditional care provided by family and friends which may too, lead to productivity loss. For many regulatory authorities, it would be worthwhile to investigate the comparative loss/gain in productivity associated with access and reimbursement of PrEP.

5.2.5 Discounting

Equal discounting rates were applied to costs and health effects, yet this uniform approach may considerably influence the conclusions drawn from health economic analyses concerning PrEP as costs and benefits occur at different points in time. The application of differential discounting rates (e.g. lower rates for health effects) is common in several countries with established health technology assessment bodies, yet the NMA guidelines state that a uniform rate of four percent be applied. This guideline conflicts with the findings of several researchers, which suggest that constant, differential rates not be used when assessing preventative initiatives such as vaccines as it is fairer from an “intergenerational perspective” (Jit & Mibei, 2015). Furthermore, there is debate over whether discount rates should be applied to QALYs in the first place. Opponents argue that to do so would be an act of double discounting if the instrument used in measuring QALYs incorporates time preference. The utilities used in the model were elicited using the time-tradeoff method, a method that asks time-based questions such that the respondent’s time preference for the effect of the treatment is already captured in the response. To apply discounting would then lead to an incorrect ranking of treatments that violates individuals’ preferences. Nevertheless, in program evaluation, discounting ultimately reflects the time preference of the decision maker and not the patients. If the NMA believes standard discounting procedures would violate their own preference, they would likely adjust the rate.
5.2.6 Sensitivity Analyses

The results of the sensitivity analyses are largely based on the calculation of parameters’ deviations and the choice of probability distributions. The standard errors proved difficult to identify in the literature, so many were derived by taking an arbitrary percentage (e.g. 20%, 50%) of the mean value. Therefore, much uncertainty surrounds these estimates; the results of the PSA and value of information analyses consequentially may not be reliable.
6 Conclusion

Several studies have reported PrEP to be cost-effective in particular settings, specifically among high-risk MSM living in areas with high HIV prevalence. As stakeholders in Norway continue to debate the place of PrEP as a prevention strategy targeted towards MSM, it is imperative that the drug continues be evaluated within a context that reflects Norway’s universal health care setting and low HIV incidence/prevalence. As of the time of this writing, no study has estimated the cost-effectiveness of PrEP in Norway or a similar setting. The model developed in conjunction with the thesis demonstrates that Norway is on track to achieving at least two of the three UNAIDS 90-90-90 goals adopted in 2010 and intended to reduce HIV incidence by 90% before 2030 (UNAIDS, 2014). Model projections suggest that a baseline status quo scenario under which PrEP is not available will only lead to a 44% reduction in incidence by the year 2045. Were PrEP to be included in the prevention repertoire, however, an approximate 90% reduction over a 30-year period would be realized. Ultimately, expanded testing to identify all seropositive MSM and streamlined initiation of ART is likely to yield significant health benefits and cost savings by affecting the dynamics of HIV transmission. Dreams of eradicating the disease within the Norwegian MSM population are lofty, however, unless individuals likely to be exposed to HIV gain access to PrEP.

From a payer perspective, the expected benefits of PrEP may not be worth the associated costs. A PrEP scenario ultimately entails presumably healthy people initiating a treatment that is associated with both adverse events and irreversible side effects, and requires investments in monitoring and screening. When considering these costs and potential negative health effects inherent to PrEP, the various cost-effectiveness analysis frameworks applied yielded contradictory estimates, with the CUA approach finding PrEP to be not cost-effective and the CEA approach finding a PrEP scenario to be cost effective. Nevertheless, the review indicates that both setting and target population are decisive “drivers” of cost-effectiveness. More context-specific research including comprehensive costing studies related to HIV and PrEP care in Norway is therefore suggested. Observations at the individual level made possible through surveillance and creation of registries would contribute greatly to future cost-effectiveness analyses.
References


Center for Disease Control. (2008). Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <18 years (Department of Health 57(RR10);1-8. Atlanta: CDC


Appendix 1: Schematic diagram of the model
Appendix 2: Differential Equations

Change in X1 =

\[ X_1 + ( (N \ast V_{X1}) + (Y_1 \ast S_{Y1}) + (X_{11} \ast \pi) ) - \left( X_1 \ast \left( \mu_{X1} + \alpha + \omega + S_{X1} + \left( \sum_{n=X_2}^{Y_10} \beta_{X1,i}^r \right) \right) \right) \ast \left( \frac{3}{52} \right) \]

Change in Y1 =

\[ Y_1 + ( (N \ast V_{Y1}) + (X_1 \ast S_{X1}) + (X_{11} \ast S_{X11}) ) - \left( Y_1 \ast \left( \mu_{Y1} + \alpha + S_{Y1} + \left( \sum_{n=X_2}^{Y_10} \beta_{Y1,j}^r \right) \right) \right) \ast \left( \frac{3}{52} \right) \]

Change in X11 =

\[ X_{11} + ( (Y_1 \ast S_{Y1}) + (X_1 \ast \omega) ) - (X_{11} \ast \left( \mu_{X11} + \alpha + S_{X11} + \emptyset + \left( \sum_{n=X_2}^{Y_10} \beta_{X11,i}^r \right) \right) ) \ast \left( \frac{3}{52} \right) \]

Change in X2 =

\[ X_2 + ( (X_1 \ast \sum_{n=X_2}^{Y_10} \beta_{X1,i}^r ) \ast (1 - S_{X1} ) ) + \left( Y_1 \ast \sum_{n=X_2}^{Y_10} \beta_{Y1,j}^r \ast S_{Y1} \right) + (X_{11} \ast \sum_{n=X_2}^{Y_10} \beta_{X11,i}^r ) \ast (1 - S_{X11} \right) ) - \left( X_2 \ast \left( \mu_{X2} + \alpha + S_{X2} + \varphi_{X2} + \gamma_{X2} \right) \right) \ast \left( \frac{3}{52} \right) \]

Change in Y2 =

\[ Y_2 + ( \left( Y_1 \ast \sum_{n=X_2}^{Y_10} \beta_{Y1,j}^r \right) \ast (1 - S_{Y1} ) ) + \left( X_1 \ast \sum_{n=X_2}^{Y_10} \beta_{X1,i}^r \right) \ast S_{X1} \right) + (X_{11} \ast \left( \sum_{n=X_2}^{Y_10} \beta_{X11,i}^r \right) \ast S_{X11} \right) \ast \left( \frac{3}{52} \right) \]

Change in X12 =

\[ (X_{12} \ast \left( 1 - (\mu_{X11} + \alpha + \varphi_{X11} \right) ) \ast \left( \frac{3}{52} \right) ) + (X_{11} \ast \left( \sum_{n=X_2}^{Y_10} \beta_{X11,i}^r \right) \ast \left( \frac{3}{52} \right) ) \]

Change in X13 =

\[ (X_{13} \ast \left( 1 - (\mu_{X13} + \alpha + \gamma_{X13} \right) ) \ast \left( \frac{3}{52} \right) ) + (X_{12} \ast \varphi_{X12} \ast \left( \frac{3}{52} \right) ) \]

Change in X3 =

\[ \left( X_{3} \ast \left( 1 - (\mu_{X3} + \alpha + \gamma_{X3} + S_{X3} \right) ) \ast \left( \frac{3}{52} \right) \right) + \left( \left( X_{2} \ast \varphi_{X2} \ast (1 - S_{X2} + S_{X3}^p ) \right) + (Y_2 \ast \varphi_{Y2} \ast (S_{Y2} + S_{Y2}^p ) + (S_{Y3} + S_{Y3} ) \right) \ast \left( \frac{3}{52} \right) \)
Change in \( Y_3 \) =
\[
\left( Y_3 \ast \left( 1 - (\mu_{Y_3} + \alpha + \gamma_{Y_3} + S_{Y_3}) \right) \ast \left( \frac{3}{52} \right) \right) + \left( Y_3 \ast \phi_{Y_3} \ast \left( 1 - (S_{Y_3} + S_{Y_3}^p) \right) \right) + \left( X_2 \ast \phi_{X_2} \ast (S_{X_2} + S_{X_2}^p) \right) + \left( X_3 \ast S_{X_3} \right) \ast \left( \frac{3}{52} \right)
\]

Change in \( X_4 \) =
\[
\left( X_4 \ast \left( 1 - (\mu_{X_4} + \alpha + \phi_{X_4} + \gamma_{X_4} + S_{X_4}) \right) \ast \left( \frac{3}{52} \right) \right) + \left( Y_2 \ast \gamma_{Y_2} \ast S_{Y_2} \right) + \left( Y_4 \ast S_{Y_4} \right) + \left( X_2 \ast \gamma_{X_2} \ast (1 - S_{X_2}) \right) \ast \left( \frac{3}{52} \right)
\]

Change in \( Y_4 \) =
\[
\left( Y_4 \ast \left( 1 - (\mu_{Y_4} + \alpha + \phi_{Y_4} + \gamma_{Y_4} + S_{Y_4}) \right) \ast \left( \frac{3}{52} \right) \right) + \left( X_2 \ast \gamma_{X_2} \ast S_{X_2} \right) + \left( X_4 \ast S_{X_4} \right) + \left( Y_2 \ast \gamma_{Y_2} \ast (1 - S_{Y_2}) \right) \ast \left( \frac{3}{52} \right)
\]

Change in \( X_5 \) =
\[
\left( X_5 \ast \left( 1 - (\mu_{X_5} + \alpha + \gamma_{X_5} + \tau_{X_5} + S_{X_5}) \right) \ast \left( \frac{3}{52} \right) \right) + \left( Y_2 \ast \gamma_{Y_2} \ast S_{Y_2} \right) + \left( X_3 \ast \gamma_{X_3} \ast (1 - S_{X_3}) \right) + \left( Y_5 \ast S_{Y_5} \right) + \left( Y_3 \ast \gamma_{Y_3} \ast S_{Y_3} \right) \ast \left( \frac{3}{52} \right)
\]

Change in \( Y_5 \) =
\[
\left( Y_5 \ast \left( 1 - (\mu_{Y_5} + \alpha + \gamma_{Y_5} + \tau_{Y_5} + S_{Y_5}) \right) \ast \left( \frac{3}{52} \right) \right) + \left( X_3 \ast \gamma_{X_3} \ast (1 - S_{X_3}) \right) + \left( Y_6 \ast S_{Y_6} \right) + \left( Y_4 \ast \gamma_{Y_4} \ast S_{Y_4} \right) + \left( X_5 \ast S_{X_5} \right) \ast \left( \frac{3}{52} \right)
\]

Change in \( X_6 \) =
\[
\left( X_6 \ast \left( 1 - (\mu_{X_6} + \alpha + \phi_{X_6} + \gamma_{X_6} + S_{X_6}) \right) \ast \left( \frac{3}{52} \right) \right) + \left( Y_4 \ast \gamma_{Y_4} \ast (1 - S_{Y_4}) \right) + \left( Y_6 \ast S_{Y_6} \right) \ast \left( \frac{3}{52} \right)
\]

Change in \( Y_6 \) =
\[
\left( Y_6 \ast \left( 1 - (\mu_{Y_6} + \alpha + \phi_{Y_6} + \gamma_{Y_6} + S_{Y_6}) \right) \ast \left( \frac{3}{52} \right) \right) + \left( Y_4 \ast \gamma_{Y_4} \ast (1 - S_{Y_4}) \right) + \left( Y_6 \ast S_{Y_6} \right) + \left( X_4 \ast \gamma_{X_4} \ast S_{X_4} \right) \ast \left( \frac{3}{52} \right)
\]
Change in X7 =
\[
(\chi_7 \times (1 - (\mu_{x_7} + \alpha + \tau_{x_7} + \gamma_{x_7} + S_{x_7})) \times \left(\frac{3}{52}\right) + (X_6 \times \varphi_{x_6} \times (1 - (S_{x_6} + S_{x_6}^\theta))) + (Y_6 \times \varphi_{y_6} \times (S_{y_6} + S_{y_6}^\theta)) + (X_5 \times \gamma_{x_5} \times (1 - S_{x_5})) + (Y_5 \times \gamma_{y_5} \times S_{y_5}) + (Y_7 \times S_{y_7}) \times \left(\frac{3}{52}\right)
\]

Change in Y7 =
\[
(Y_7 \times (1 - (\mu_{y_7} + \alpha + \tau_{y_7} + \gamma_{y_7} + S_{y_7})) \times \left(\frac{3}{52}\right) + (X_6 \times \varphi_{x_6} \times (1 - (S_{x_6} + S_{x_6}^\theta))) + (X_6 \times \varphi_{x_6} \times (S_{y_6} + S_{y_6}^\theta)) + (X_6 \times \gamma_{y_6} \times (1 - S_{y_6})) + (X_5 \times \gamma_{x_5} \times S_{y_5}) + (X_7 \times S_{x_7}) \times \left(\frac{3}{52}\right)
\]

Change in X8 =
\[
(((X_6 \times \gamma_{x_6} \times (1 - S_{x_6})) + (Y_6 \times \varphi_{y_6} \times (S_{y_6} + S_{y_6}^\theta))) \times \left(\frac{3}{52}\right) + (X_6 \times \gamma_{x_6} \times S_{x_6} \times (Y_6 \times S_{y_6})) \times \left(\frac{3}{52}\right)
\]

Change in Y8 =
\[
= Y_6 \times (1 - (\mu_{y_6} + \alpha + \varphi_{y_6} + S_{y_6}) \times \left(\frac{3}{52}\right) + ((X_6 \times \gamma_{y_6} \times (1 - S_{y_6})) + (X_6 \times \gamma_{x_6} \times S_{y_6} \times (Y_6 \times S_{x_6})) \times \left(\frac{3}{52}\right)
\]

Change in X9 =
\[
((X_8 \times (1 - (\mu_{x_9} + \alpha + \tau_{x_9} + S_{x_9})) \times \left(\frac{3}{52}\right) + (X_7 \times \gamma_{x_7} \times S_{x_7} \times (Y_7 \times S_{y_7}) + (X_6 \times \varphi_{x_6} \times (1 - S_{x_6} + S_{x_6}^\theta)) + (Y_6 \times \varphi_{y_6} \times (S_{y_6} + S_{y_6}^\theta))) \times \left(\frac{3}{52}\right)
\]

Change in Y9 =
\[
(Y_6 \times (1 - (\mu_{y_6} + \alpha + \tau_{y_6} + S_{y_6}) \times \left(\frac{3}{52}\right) + (X_7 \times \gamma_{y_7} \times S_{y_7} \times (Y_7 \times S_{x_7}) + (X_6 \times \varphi_{y_6} \times (1 - S_{y_6} + S_{y_6}^\theta)) + (X_6 \times \varphi_{x_6} \times (S_{y_6} + S_{y_6}^\theta))) \times \left(\frac{3}{52}\right)
\]

Change in X10 =
\[
((X_10 \times (1 - (\mu_{x_{10}} + \alpha + S_{x_{10}})) \times \left(\frac{4}{52}\right) + ((X_5 \times \tau_{x_5} \times (1 - S_{x_5})) + (Y_5 \times \tau_{y_5} \times S_{y_5} \times (Y_5 \times S_{x_5} + S_{x_5}^\theta)) + (X_7 \times \tau_{x_7} \times (1 - S_{x_7})) + (Y_7 \times \tau_{y_7} \times S_{y_7} \times (X_9 \times \tau_{x_9} \times (1 - S_{x_9}) + (Y_9 \times \tau_{y_9} \times S_{y_9})) \times \left(\frac{4}{52}\right)
\]

100
Change in Y10 =

\[
\left( Y_{10} \ast \left(1 - (\mu_{Y_{10}} + \alpha + S_{Y_{10}})\right) \ast \left(\frac{3}{52}\right) \right) \\
+ \left( \left( Y_{5} \ast \tau_{Y_{5}} \ast (1 - S_{Y_{5}}) \right) + \left( X_{5} \ast \tau_{X_{5}} \ast S_{X_{5}} \right) + \left( Y_{7} \ast \tau_{Y_{7}} \ast (1 - S_{Y_{7}}) \right) + \left( X_{7} \ast \tau_{X_{7}} \ast S_{X_{7}} \right) \right) \\
+ \left( Y_{9} \ast \tau_{Y_{9}} \ast (1 - S_{Y_{9}}) \right) + \left( X_{9} \ast \tau_{X_{9}} \ast S_{X_{9}} \right) \ast \left(\frac{3}{52}\right)
\]
## Appendix 3: Table of model parameters

### Table 3. Summary of notation for model parameters and information regarding their distribution

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Value</th>
<th>Standard Error</th>
<th>Dist.</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic Parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Growth rate</td>
<td>$\gamma$</td>
<td>0.03</td>
<td>0.0015306</td>
<td>Normal</td>
<td>Assumed</td>
</tr>
<tr>
<td>Maturation rate</td>
<td>$\mu$</td>
<td>0.03</td>
<td>0.0003024</td>
<td>Normal</td>
<td>SWIS 2010-data</td>
</tr>
<tr>
<td>Mortality rate</td>
<td>$\mu_x$</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Susceptible</td>
<td></td>
<td>0.0003</td>
<td>0.0000530</td>
<td>Normal</td>
<td>Statistics Norway</td>
</tr>
<tr>
<td>Infected</td>
<td></td>
<td>0.000547</td>
<td></td>
<td>Normal</td>
<td>Maman et al., 2012</td>
</tr>
<tr>
<td>Late stage</td>
<td></td>
<td>0.0030</td>
<td>0.0007053</td>
<td>Normal</td>
<td>Maman et al., 2012</td>
</tr>
<tr>
<td>ART</td>
<td></td>
<td>0.0045</td>
<td>0.000699</td>
<td>Normal</td>
<td>Velteberg et al., 2013</td>
</tr>
<tr>
<td>Annual rate of change from low activity to high</td>
<td></td>
<td>0.15</td>
<td>0.0806</td>
<td>Normal</td>
<td>Assumed</td>
</tr>
<tr>
<td>Annual rate of change from high activity to low</td>
<td></td>
<td>0.10</td>
<td>0.0204</td>
<td>Normal</td>
<td>Assumed</td>
</tr>
<tr>
<td><strong>Transmission Parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Annual nr. sexual partnership contacts (high)</td>
<td>$r_1$</td>
<td>6.21</td>
<td>0.9750</td>
<td>Gamma</td>
<td>SWIS 2010-data</td>
</tr>
<tr>
<td>Annual nr. sexual partnership contacts (low)</td>
<td>$r_0$</td>
<td>0.69</td>
<td>0.3800</td>
<td>Beta</td>
<td>SWIS 2010-data</td>
</tr>
<tr>
<td>Percent decrease in partnership contacts (due to PrEP)</td>
<td></td>
<td>-0.15</td>
<td></td>
<td>Beta</td>
<td>Assumed</td>
</tr>
<tr>
<td>Percent decrease in partnership contacts (due to ART initiation)</td>
<td></td>
<td>-0.30</td>
<td></td>
<td>Normal</td>
<td>Assumed</td>
</tr>
<tr>
<td>Percent decrease in partnership contacts (due to diagnosis)</td>
<td></td>
<td>-0.10</td>
<td></td>
<td>Normal</td>
<td>Assumed</td>
</tr>
<tr>
<td>Percent increase in condom usage rate due to (low)</td>
<td>$g$</td>
<td>0.80</td>
<td>0.3030</td>
<td>Beta</td>
<td>Assumed</td>
</tr>
<tr>
<td>Baseline persistent condom usage rate (high)</td>
<td>$\alpha_{01}$</td>
<td>0.45</td>
<td>0.0131</td>
<td>Normal</td>
<td>SWIS 2010-data</td>
</tr>
<tr>
<td>Baseline persistent condom usage rate (low)</td>
<td>$\alpha_{00}$</td>
<td>0.499</td>
<td>0.0197</td>
<td>Normal</td>
<td>SWIS 2010-data</td>
</tr>
<tr>
<td>Transmission risk</td>
<td>$\psi_1$</td>
<td></td>
<td></td>
<td>Beta</td>
<td>Pintr(lon &amp; Ambrans, 1997</td>
</tr>
<tr>
<td><strong>Diagnosis Parameters</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Time to diagnosis (years)</td>
<td>$\psi_1$</td>
<td>2.600</td>
<td>0.3000</td>
<td>Gamma</td>
<td>van Sighem, 2015</td>
</tr>
<tr>
<td>Annual baseline diagnosis rate (inverse of avg. time to diagnosis)</td>
<td>$\psi_1$</td>
<td>0.3846</td>
<td></td>
<td>Beta</td>
<td>von Sighem, 2015</td>
</tr>
<tr>
<td>Percent change in condom usage rate due to diagnosis</td>
<td></td>
<td>-0.15</td>
<td></td>
<td>Normal</td>
<td>Assumed</td>
</tr>
<tr>
<td><strong>Treatment Parameters</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial uptake of PrEP</td>
<td>$w$</td>
<td>0.25</td>
<td></td>
<td>Fixed</td>
<td></td>
</tr>
<tr>
<td>Annual PrEP cessation rate not related to change in activity group</td>
<td>$w$</td>
<td>0.10</td>
<td>0.00408</td>
<td>Normal</td>
<td>Assumed</td>
</tr>
<tr>
<td>Annual rate of initiating PrEP after initial uptake</td>
<td>$\mu$</td>
<td>0.10</td>
<td>0.00408</td>
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<td>Assumed</td>
</tr>
<tr>
<td>Annual ART initiation rate</td>
<td>$\psi_2$</td>
<td></td>
<td></td>
<td>Beta</td>
<td>Gazzard et al., 2008</td>
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<td><strong>Disease Progression Parameters</strong></td>
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<tr>
<td>Annual rate of progression to next stage</td>
<td>$\psi_1$</td>
<td>4.1179</td>
<td>0.8333</td>
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<td>Hollingsworth et al., 2008</td>
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<td><strong>Health-Related Quality of Life</strong></td>
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<tr>
<td>Health related quality of life</td>
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<td>Health of MSM in primary infection stage</td>
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<td>0.940</td>
<td>0.058</td>
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<td>Health of MSM in symptomatic HIV infection stage</td>
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<td>0.787</td>
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<td>Health of MSM in late HIV infection stage</td>
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<td>Health of MSM treated with ART</td>
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<td>0.947</td>
<td>0.097</td>
<td>Beta</td>
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<td>Health of HIV susceptible MSM</td>
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<td>0.025</td>
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<td>Health of susceptible MSM taking PrEP</td>
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<td>0.988</td>
<td>0.026</td>
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<td>Drug and Direct Medical Costs</td>
<td>Mean Estimate</td>
<td>Std. Error</td>
<td>Distribution</td>
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<td>direct medical cost of susceptible not on Prep</td>
<td>692</td>
<td>176.5</td>
<td>Gamma</td>
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<td>direct medical cost of ART naïv infected with CD4 level below 200</td>
<td>4710</td>
<td>1,201.5</td>
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<td>686.0</td>
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<td>739</td>
<td>188.5</td>
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<td>one-off cost of HIV infection</td>
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<td>one-off cost of initiating Prep</td>
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<td>cost of adverse effects related to Prep treatment</td>
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<td>one-off cost for transition to death</td>
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<td>12755.1</td>
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<td>cycle cost of Prep</td>
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<td>cycle cost of ART first line treatment</td>
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