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PrEPosterous?

The ethics of state-funded pre-exposure prophylaxis for men who have sex with men at high risk of human immunodeficiency virus.

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Abstract

The debate over state-funded provision of PrEP for HIV prevention in the UK has intensified in recent years due to the establishment of the PrEP Impact Trial and a legal challenge to the NHS' decision not to commission the drug. This thesis explores the ethical and economic issues associated with the provision of PrEP.

I begin with an appraisal of an existing economic analysis of PrEP, highlighting its shortcomings and detailing the sensitivity analyses required for a more useful future analysis.

Three key ethical issues are then explored: adherence, risk compensation, and effective targeting. They are considered in the context of principlism and the importance of autonomy relative to other values. A broadly utilitarian approach is also taken in balancing benefits and harms, accounting for the impact these issues might have on the wider community and population.

Policy implications form the conclusion, providing a suggested way forward. First and foremost, I demonstrate a clear need for further research and economic analysis, noting the arguably hurried nature of PrEP provision. I also argue for daily PrEP to become the default method of dosing, with event-based PrEP kept as a reserve to be sparingly used at the discretion of doctors when clearly appropriate. With PrEP as the appropriate default now, a defence of long-acting injectable PrEP as the default is provided in anticipation of its introduction. Finally, I call for additional efforts to minimise the prevalence of risk compensation and prevention optimism; potential methods are highlighted, such as counselling and SMS reminders.

The overarching conclusion of this thesis is that the introduction of PrEP has been rushed, and there are several unanswered questions. In order to provide PrEP in the most useful and ethical way with minimal unwanted side effects these questions must be answered.

Dedication and Acknowledgements

This thesis is dedicated to my grandmother, whose support and continued interest in my studies has always been appreciated.

I would like to thank my supervisors, Dr Jonathan Ives and Dr Jeff Round, for their useful comments and guidance over the past year, and for continuing to push me.

Finally, thank you to India Cole for her proofreading prowess.

Author's Declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's *Regulations and Code of Practice for Research Degree Programmes* and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

Signed:

Date: Friday 30th August 2019

List of Abbreviations

ART	antiretroviral treatment
BCP	birth control pill
CAS	condomless anal sex
GUM	genitourinary medicine
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
HIV-	HIV-negative
HIV+	HIV-positive
HRI	high-risk individuals (see classifications in *Chapter V*)
LAI-PrEP	long-acting injectable PrEP
LRI	low-risk individuals (see classifications in *Chapter V*)
MRI	medium-risk individuals (see classifications in *Chapter V*)
MSM	men who have sex with men
MSMW	men who have sex with men and women
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NNT	number needed to treat
PEP/PEPSE	post-exposure prophylaxis (following sexual exposure)
PHE	Public Health England
PIT	PrEP Impact Trial
PrEP	pre-exposure prophylaxis
RTU	recommendation of temporary use
STI	sexually transmitted infection
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

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Chapter I: Introduction

Pre-exposure prophylaxis (PrEP) for those at high risk of human immunodeficiency virus 1 (HIV-1)[1] infection through sexual contact is a means of drastically reducing that risk and may contribute to a decrease in infection rates. However, the suggestion of introducing free access to the drug for high-risk populations in the United Kingdom (UK) through the National Health Service (NHS) has proved contentious. The drug is highly efficacious (Molina et al., 2015; Grant et al., 2010; McCormack et al., 2016) though we know less of its effectiveness. Even if PrEP were to be effective in reducing the number of new HIV infections, state provision raises interesting ethical questions: the relationship between individual autonomy and the protection of public health; justice in resource allocation; and nonmaleficence. Whether to make PrEP available through the NHS is more than a question of cost-effectiveness; myriad social and ethical issues must be considered.

I explore these issues and consider if and how the NHS can ethically commission PrEP for men who have sex with men (MSM) at high risk of HIV infection through sexual contact. I am concerned only with this population group. Other groups are at high risk of infection, such as healthcare professionals and intravenous drug users, though provision of PrEP for these groups would involve different ethical issues. Furthermore, past and current PrEP trials and schemes of provision, in addition to the current debate, have been and are concerned almost exclusively with the spread of HIV through sexual contact among MSM.

Before outlining the relevant ethical issues, I first provide a history of HIV and prevention methods. This background is important to understanding the implications of any changes to HIV prevention practices.

[1] HIV-1 will be referred to as HIV.

HIV and prevention history

HIV can be traced back to 1920s Kinshasa, the capital of what is now the Democratic Republic of Congo (Faria et al., 2014). The current epidemic, however, is recognized as having started in the 1980s in the United States of America (USA). The outbreak was first observed among homosexual men, resulting in the disease being referred to in ways involving the word 'gay' (Brennan and Durack, 1981), though cases were soon documented among other populations, such as haemophiliacs (Centers for Disease Control and Prevention, 1982).

Whilst few populations were affected initially, we now know HIV is a risk to all. No one is immune to the virus, but those acknowledged to be at the highest risk of infection through sexual contact are MSM. In 2017, MSM accounted for 53% of new HIV infections in the UK (Public Health England, 2018). Considering only 2% of the UK population identify[2] as lesbian, gay, or bisexual (Office for National Statistics, 2019) this is a significant increased risk. The balance of new infections among heterosexuals compared to MSM is shifting in the UK – both are on downward trajectories, though MSM are on a steeper one – but MSM still account for the majority of new infections (Public Health England, 2018).

Since the 1980s outbreak, condoms have been promoted as the recommended preventative measure against sexual transmission of the virus. This is because condom efficacy is c. 98% (National Health Service, 2017b), and condoms protect against not only HIV but also most other sexually transmitted infections (STIs),[3] in addition to acting as a contraceptive where relevant.

[2] The population will be larger as some may choose to identify as heterosexual but are still MSM.
[3] HIV is often considered an STI. However, any mention of STIs hereafter excludes HIV.

Furthermore, the c. 2% of times when condoms fail (i.e. break) it is possible to check, better enabling one to minimise the risk of infection following potential or likely exposure to the virus. However, despite continued promotion of condom use, the number of new HIV infections in the UK each year remains high (Public Health England, 2018).

Renewed hope in the battle against HIV came in 2004 with the approval of the drug Truvada in the USA (United States Food and Drug Administration, 2004). Initially developed as antiretroviral treatment (ART) for HIV-positive (HIV+) individuals, Truvada contains two antiretroviral medications (emtricitabine and tenofovir disoproxil fumarate, sometimes written emtricitabine/tenofovir) in a fixed-dose combination (Gilead Sciences, 2018). The drug acts to reduce the activity of the enzyme reverse transcriptase which HIV-infected cells use to make new viruses. In doing so it stops HIV-infected cells from making new viruses, or at least slows the process (Hosein, 2016).

Truvada has since been used as post-exposure prophylaxis following sexual exposure to HIV (PEP *or* PEPSE). PEP is the emergency use of antiretrovirals shortly after confirmed or suspected exposure to HIV to prevent the virus taking hold. It is a 28-day course of drugs to be started as soon after exposure as possible – ideally within hours. It is possible to start PEP up to 72 hours after exposure, though within 24 hours is considered best (Cresswell et al., 2016).

It is difficult to assess how effective PrEP is in preventing HIV infection, but it is even more difficult with PEP. It varies significantly depending on how soon after exposure a user commences treatment, and whether they complete the full course as instructed. The World Health

Organization (WHO) states that if started soon after exposure and with full adherence, PEP reduces the risk of HIV infection by over 80% (World Health Organisation, 2014).

PEP is available through the NHS across the UK as an emergency treatment intended for instances such as a split condom, or when a condom was not used for some reason by individuals who would ordinarily have used one[4]. PEP is less efficacious than both condoms and PrEP (combined or individually) in preventing an infection and should not be considered a key part of one's long-term sexual health practices (Cresswell et al., 2016).

What is PrEP?

Truvada is also now used as PrEP. This use has proved controversial, despite the WHO recommending Truvada for HIV prevention among certain high-risk population groups (World Health Organisation, 2016).

Pre-exposure prophylaxis refers to the use of drugs to prevent an infection in those who have not been exposed to it. Whilst this literal definition is general, the term "PrEP" is often used when referring specifically to the use of antiretroviral drugs as a preventative measure against HIV. Truvada is the brand most commonly used for PrEP – indeed "PrEP" and "Truvada" are often used interchangeably – though generics are now available.

[4] These are examples of emergencies that would justify PEP. They are not the only examples. PEP may also be necessary following a non-sexual incident, such as being a victim of a needle attack.

I focus on PrEP as prevention against HIV-1 because this strain of the virus is most prevalent, accounting for the vast majority of HIV infections globally (Nyamweya et al., 2013). HIV-2 is less easily transmitted and is rarely found outside of West Africa, so is less relevant to a discussion of HIV prevention in the UK. Any use of the term "PrEP" from now refers to this specific meaning.

Unlike a vaccination, PrEP requires continued use. Recommended practice is a single daily dose, taken orally. Event-based use is sometimes practiced (see *Chapter IV*), but a single daily dose is preferable due to greater ease of adherence with a routine medication. Research into a monthly or quarterly injectable form of the drug is showing promising results (Evans, 2014; Kaltwasser, 2018). It is possible that PrEP users will switch to long-acting injectable PrEP (LAI-PrEP) in time, though it is currently still being trialled (see *Chapter IV*).

It is important those starting PrEP test negative for HIV. This is to minimize any risk that the virus will develop resistance to the medications found in Truvada, as HIV+ individuals are treated with different drug combinations and dosing. For this reason, trials require potential participants to undergo HIV testing before enrolling.

PrEP efficacy is high. Efficacy refers to the maximum capacity of a drug to fulfil its purpose(s), in contrast to effectiveness which is the capacity of the drug to fulfil its purpose(s) in real life conditions; effectiveness accounts for other factors, such as adherence. Studies place PrEP's efficacy as high as a 99% HIV risk reduction (Anderson et al., 2012). The risk reduction, however, diminishes when a user fails to adhere to daily dosing. Therefore, risk reduction as high as 99% rests on strict adherence. High efficacy does not necessarily entail high effectiveness, therefore concurrent condom use is recommended for additional protection, and to counter the risk of

occasionally missed doses of PrEP; indeed, PrEP is presented as an additional precaution and not as a condom substitute (PrEP Impact Trial, 2017a).

Whilst we do know that PrEP is efficacious, things are less certain when it comes to effectiveness. Whilst acknowledging potential wider problems with the provision of PrEP, major past trials were efficacy trials rather than effectiveness (Molina et al., 2015; Grant et al., 2010). Literature concerning the ethical and social implications when effectiveness is considered – at both the individual- and population-level – is mostly limited to the media and campaign materials. This material, though useful to study, is political rather than academic in nature. It is characterized by broad statements which potentially hold some truth, though are frequently unsupported. One exception is the National Institute for Health and Care Excellence's (NICE) 2016 evidence summary. Through a review of four randomized trials of Truvada the summary purports to explore not only PrEP's efficacy, but also 'issues relating to uptake, adherence, sexual behaviour, drug resistance, safety, prioritization for prophylaxis and cost effectiveness[…]especially at a population level' (National Institute for Health and Care Excellence, 2016). However, the summary fails to fully acknowledge the potential impact of these other issues on the number needed to treat (NNT)[5] and, by extension, the cost-effectiveness. The reason for this is that the trials it reviewed are those which focus on efficacy. Whilst efficacy is important, decisions concerning PrEP provision must consider more.

[5] The number needed to treat is a measure used to illustrate the effectiveness, and by extension cost-effectiveness, of a healthcare intervention. In the case of PrEP, it refers to the number of individuals who would need to be using PrEP in order to prevent one HIV diagnosis.

The availability of PrEP

Whilst PrEP trials/programmes can vary, they tend to maintain similar eligibility criteria. Usually, potential users must be aged 16 or over, test negative for HIV, and be considered within one of the predetermined high-risk groups following a clinical risk assessment. Groups classed as high-risk include MSM who report having had condomless sex in the previous 90 days, and HIV-negative (HIV-) partners in serodiscordant couples[6] whose partners are not known to be virally suppressed. There is also discretion in clinical assessment to permit access to the drug for those who do not fit the eligibility criteria but who are considered to be similarly high-risk. A more detailed explanation of PrEP eligibility is included in *Chapter VI*.

PrEP is available through the healthcare system in only a small number of countries[7], though this number is growing. The drug is arguably most easily accessible in Norway. In October 2016, the Norwegian National Health Service announced it would provide PrEP to at-risk citizens free of charge (Weller, 2016). PrEP was already available for free in France at this time, but under a system of emergency recommendation of temporary use (RTU) (Collins, 2015). Truvada is also available in the USA, though access varies depending on an individual's insurance coverage.

Within the UK, which is the focus of this thesis, Scotland was the first and remains the only country to provide PrEP outside of a trial. The drug was made available on the NHS in Scotland in July 2017

[6] Serodiscordant couples are those in which one partner is known to be infected with HIV and the other is not.

[7] That does not mean to say that PrEP is not being used in other countries as both Truvada and generics can be easily purchased online, in addition to alternative means of obtaining the drug such as clinic hopping (see *Chapter VI*).

(National Health Service Lothian, 2018). Access to PrEP in Scotland is based on the common PrEP criteria earlier mentioned.

Wales also made PrEP available in July 2017, though through the *PrEPared* trial (National Health Executive, 2018). Whilst availability in Wales is as part of a trial, there is no cap on the number of participants. Therefore, all eligible individuals can access PrEP for the 3-year trial period. Truvada was used initially, though the switch to generics was made in summer 2018 (Public Health Wales, 2018).

Similarly to Wales, Northern Ireland is trailing PrEP provision with no cap on the number of participants (I Want PrEP Now a). It will run for two years, providing access to the drug for all who are eligible following similar criteria to those described earlier. Whilst all genitourinary medicine (GUM) clinics will offer initial consultation and assessment appointments, those eligible will only be able to access PrEP following a referral to a centralised service in Belfast[8].

In England, things have been more complicated. Campaigners have long sought freely available PrEP. There have been several campaigns, including websites established to inform about PrEP and provide purchasing guidance for those willing to pay for the drug themselves (Prepster; I Want PrEP Now a). More recently, campaigners protested at the London premiere of 'Bohemian Rhapsody', the Freddie Mercury biopic, suggesting that PrEP could have prevented Mercury's death (Welsh, 2018). Nonetheless, the NHS in England has not made PrEP freely available, and access had been limited to those willing to purchase the drug themselves until a recently commenced trial.

[8] This, of course, raises questions of equal access. Whilst important, this issue will not be dealt with in this thesis.

The *PrEP Impact Trial* (PIT) was established by NHS England to inform its decision as to whether to commission PrEP (PrEP Impact Trial, 2017b). It is far larger than the trials in Wales and Northern Ireland, with the initial budget allowing for 10,000 participants (later increased to 13,000, then doubled to 26,000) for a 3-year period and recruitment commenced in October 2017. The PIT also hopes to answer more questions about the impact PrEP might have in practice:

> '1. How many people attending sexual health clinics need PrEP?
>
> 2. How many of these start PrEP?
>
> 3. How long do they need PrEP for?' (PrEP Impact Trial, 2017b)

The PIT was established as a result of a 2016 legal challenge against the NHS in England concerning PrEP provision (*R (National AIDS Trust) v NHS Commissioning Board (NHS England) 2016*). The challenge sought to confirm where responsibility for the cost of PrEP would fall if it were to be available. NHS England claimed that as PrEP is not treatment it does not fall under its remit, and that preventive strategies are the responsibility of local authorities. The High Court dismissed this argument and ruled that the NHS can provide PrEP. It is important to note, however, that this ruling stated only that the NHS *can* provide PrEP, not that it *must*; it remains the decision of NHS England as to whether it is deemed a justified expense.

Most recently, Ireland's Ministers for Health announced a commitment to implementing a PrEP programme by the end of 2019 (Irish Department of Health, 2019). This was based on advice from

the country's Health Information and Quality Authority. With this being such a recent development there is not yet an indication of what shape the programme will take.

Ethical issues

Debate over PrEP provision for those at high risk of HIV transmission through sexual contact has been heated. Both sides use loaded and emotive language to attack the other. PrEP supporters argue not providing the drug is harming potential users, failing to remove the risk of HIV when an "easy" option is available (Kruger, 2015). The opposition suggest spending tax revenue on a "promiscuity pill" is unethical when funds could be directed to medical care they deem more deserving (Borland et al., 2016).

These simplified arguments exist to populate headlines and garner support by appealing to intuitive values. However, they derive from serious concerns. I engage with several of these serious concerns through evaluation of the developed concerns they were founded upon.

Through a review of the literature, both academic and activist, I have identified several key ethical issues surrounding PrEP provision. Each is dealt with individually to assist in a final assessment of the ethical permissibility of state-provided PrEP for MSM in the UK.

Before engaging with these ethical issues, *Chapter II* introduces the economics of PrEP provision by questioning whether the state ought to provide the drug when infection rates for HIV are low and dropping (Public Health England, 2018). Cost-effectiveness is a key criterion in clinical

commissioning, so discussion of PrEP provision must speak to the financial impact. This is poignant in the case of PrEP as its provision is objected to on the grounds that the money would be better spent elsewhere. Existing cost-effectiveness analyses generally conclude that PrEP is cost-effective, however there is reason to question their results. I analyse the most relevant of these studies and demonstrate its shortcomings. This illustrates the extent and nature of sensitivity analyses necessary, demonstrating that financial arguments concerning PrEP provision are not as straightforward as is often suggested. Many associated costs I consider relate to later chapters of this thesis, so *Chapter II* further justifies the importance of the ethical issues I explore.

I then outline relevant ethical theory in *Chapter III*. This focuses primarily on principlism and the interplay between autonomy and the other three principles of nonmaleficence, beneficence, and justice. It also draws on ideas of bodily integrity and proportionality as they relate to suggested interventions. When discussing bodily integrity, this chapter also introduces the coercion versus withholding distinction which I develop, highlighting its utility in debates such as PrEP provision. I also address the question of sexual liberation and the role I see it playing in this debate. Theoretical stances outlined in this chapter are drawn upon throughout this thesis, making *Chapter III* a useful point of reference.

Chapter IV concerns nonadherence. PrEP effectiveness hinges on the user keeping to the prescribed daily dose. If a user may struggle with adherence, it may be unethical to provide the drug as it may put that user at risk of HIV infection. The risks of nonadherence are stressed to users prior to commencement[9], but it may be that we cannot expect them to be sufficiently recognized. Users may also suffer nonadherence due to forgetfulness or lack of routine. To assess

[9] Assuming PrEP is obtained through official channels.

the likelihood of widespread nonadherence I first look to PrEP trials/studies which have considered the risk. I also examine adherence to both PEP and the birth control pill (BCP) to draw parallels with PrEP. Finally, I look to the potential future of PrEP administration and consider what LAI-PrEP might mean for adherence.

Arguably the most problematic issue with PrEP provision is risk compensation, which is the subject of *Chapter V*. It is with this issue that one looks beyond the primary purpose of PrEP (i.e. HIV prevention) and considers the negative impact provision may have more broadly on the individual user, the NHS, and the wider population. Those opposed to PrEP provision argue that the drug enables, perhaps even encourages, riskier sexual behaviour (such as a decrease in condom use). Users may be at low risk of HIV infection when on PrEP, but they are not protected against other STIs unless additional precautions are taken. Therefore, if risk compensation does arise, PrEP results in an increased risk of STIs for those users. This is ethically problematic not only because that individual is at an increased risk of STIs, but because the wider population is affected by an increased spread of STIs. I assess PrEP studies in which risk compensation was measured, in particular the PROUD and iPrEx (follow up) studies which both explicitly state they assess the effect (McCormack et al., 2016; Grant et al., 2014). I also consider the potential for the seldom acknowledged issue of community risk compensation. This is when those not on PrEP engage in riskier sexual practices as they believe enough individuals are taking PrEP to reduce the risk of transmission throughout the community. I then discuss whether it is ethical to put an individual at greater risk of several infections just to reduce their risk of one, discussing the balance between personal autonomy and both beneficence and nonmaleficence.

The final issue, which is examined in *Chapter VI*, is effective targeting. If one were to deem PrEP ethically justified for certain individuals, the question is raised of how to target provision. To avoid

problems associated with PrEP (namely nonadherence and risk compensation) manifesting in populations outside of those already at the highest risk of HIV infection, it would be important to prevent these other populations accessing the drug. I evaluate the eligibility criteria of the PIT in terms of ease of access for those outside the target population. This includes consideration of the appropriateness of denying access to those who want PrEP, and whether population-level access concerns can justify a blanket denial of PrEP access.

Chapter VII concludes by revisiting economic considerations, informed by ethical discussions. I demonstrate that the NNT for PrEP is, in practice, likely to be higher than anticipated by the trials reviewed by NICE (National Institute for Health and Care Excellence, 2016). I also argue that the NNT is somewhat irrelevant when it comes to PrEP, because clinical risk assessments for eligibility are based on the self-reporting of potential users; not only those for whom PrEP would be intended would access the drug, thus increasing the cost. This brings the cost-effectiveness of PrEP – a key NHS commissioning criterion – into doubt. Further, through highlighting the potential relative harm to both the individual and the population caused by widely available PrEP (i.e. the availability of PrEP beyond the target population), I argue that the question of state-provision of PrEP does not hinge on cost-effectiveness. This clearly marks the importance of considerations beyond cost-effectiveness in the decision as to whether to introduce state-funded PrEP.

Chapter II: Economics

Drug commissioning decisions require consideration of financial costs and benefits; resource allocation is informed by health economic evaluations (Husereau et al., 2013). This is transparently the case in state-funded systems, such as the UK, though still happens under other systems. To justify spending public funds on a new drug, it is generally held that it must be cost-effective; i.e. 'if it gives a greater health gain than could be achieved by using the resources in other ways' (National Institute for Health and Care Excellence, 2008). That does not mean to say that everything that is cost-effective is appropriate, as other considerations – such as ethical implications – must be balanced against cost-effectiveness (National Institute for Health and Care Excellence, 2008). Into such considerations also comes the question of opportunity costs in an increasingly financially stretched healthcare system; funding PrEP necessarily prevents some other service being funded.

The often pivotal role of cost-effectiveness in commissioning necessitates that these studies are conducted to the highest possible standard, accounting for associated costs[10] and, where possible, anticipating the socio-behavioural impact of a drug and how this may affect cost. However, the importance of cost-effectiveness does not mean that something can only be appropriate if cost-effective. Where cost-effectiveness analysis is considered to have misrepresented the health gain in terms of quality of life, or where substantial benefits result from the intervention which are not captured in the measurement of health gain, a cost-ineffective intervention may be considered an appropriate use of NHS resources (National Institute for Health and Care Excellence, 2008).

[10] By associated costs I mean those beyond the cost of the drug itself and the cost of alternative treatments in the absence of it. In the case of PrEP, for instance, this means looking beyond the cost of PrEP and the cost of HIV treatment should someone become infected. Associated costs do not include indirect costs, such as those borne by patients in attending GUM clinics.

There are multiple studies of the cost-effectiveness of PrEP, with at least two focusing on UK provision (Cambiano et al., 2018; Ong et al., 2017). PrEP is commonly deemed cost-effective, with some studies suggesting savings as high as £964m (Cambiano et al., 2018). However, I contend there are flaws in the modelling of these studies, and thus reasons to doubt their conclusions. This thesis demonstrates that several of the assumptions these studies are based on are unjustified and unlikely to be the reality – such as assuming there is no change in sexual behaviour, or that full adherence among PrEP users is to be expected. I demonstrate that in failing to fully outline and justify their assumptions, these studies have fallen short of the CHEERS statement (Husereau et al., 2013).

In highlighting the flaws in existing analyses, I argue there is still a need for a thorough and accurate analysis of PrEP's cost-effectiveness. A discussion of the importance of cost-effectiveness in PrEP decision-making can only take place following suitable analysis, meaning analysis which accounts for the many nuances and additional costs. Whilst such analysis is not the purpose of this thesis, I highlight the issues and associated costs I believe were not addressed by Cambiano and colleagues, but which ought to be. This contributes to the foundation of a future cost-effectiveness study.

The overall purpose of this chapter is to highlight the problematic ethico-economic considerations driving commissioning decisions surrounding PrEP. These issues are revisited from an economics perspective in *Chapter VII*, following more detailed individual discussion.

Existing analyses

Whilst there have been several analyses of the cost-effectiveness of PrEP, I limit my analysis to the Cambiano study (Cambiano et al., 2018). This study is most relevant to UK PrEP decisions as it looks specifically at the UK context and is one of the most recent studies. It is also the Cambiano study which has been referenced by the NHS when claiming PrEP could save the Service £1bn[11] (National Health Service, 2017a).

The Cambiano study sought to evaluate the economic implications of PrEP provision, concluding that provision of the drug would be cost-saving. It notes the effectiveness of daily PrEP, although the study assesses the cost-effectiveness of event-based PrEP rather than daily in its base case[12]. This is a particularly unexpected aspect of the study given it claims to assess cost-effectiveness based on the PROUD trial (McCormack et al., 2016) which investigated daily PrEP. Event-based PrEP use is likely to be less effective than daily use (see *Chapter IV*), which immediately puts a question mark over this study's findings when PrEP's effectiveness is asserted.

Cambiano and colleagues demonstrate that not only is PrEP cost-effective, but cost-saving over an 80-year time horizon. There were, however, several issues with the base case which were not addressed, or at least inadequately addressed, by sensitivity analyses[13]. The base case made the

[11] This NHS article does note that the assumptions the study is based on may turn out to be false, but merely as a concluding remark. The figure of £1bn was rounded from the actual figure of £964m.
[12] Daily PrEP is considered in sensitivity analysis.
[13] Sensitivity analysis is a means of testing the uncertainty of economic analysis by repeating the analysis after changing an assumption. For instance, two analyses may be run assuming 100% and 75% adherence to a drug.

following problematic assumptions: full adherence, quarterly HIV tests by users, and a mean of 4.5 years spent on PrEP.

Full adherence is very unlikely (see *Chapter IV*). Studies demonstrated this prior to the Cambiano study (Grant et al., 2010, Molina et al., 2015). Nonadherence arises regardless of dosing option, but more so with event-based usage (as was considered in this study) as there is no habit established. However, an assumption of full adherence in the base case is not too problematic as sensitivity analysis was performed assuming 63% effectiveness as a result of lesser adherence. This still produced a cost-saving. Therefore, it is possible nonadherence would not significantly affect the cost-effectiveness of PrEP. That is to say that nonadherence alone may not render PrEP cost-ineffective but, combined with other cost factors, it may contribute to such a conclusion.

It is, however, important to note cost-effectiveness alone does not justify PrEP. Ethical issues associated with nonadherence which are explored later in this thesis (see *Chapter IV*) are also important, so we cannot discard worries over adherence based on it not affecting cost-effectiveness.

Quarterly HIV tests are potentially enforceable if users are only provided with three months' worth of PrEP at a time. This would ensure users would have to return to obtain more PrEP, and a condition of receipt could be sexual health screening. However, this is problematic for those in rural areas who are unable to attend a GUM clinic regularly. This is a potential equality of access issue. Sensitivity analysis partially accounted for the lack of consistent quarterly HIV tests by doubling instances of STIs; less frequent testing enables STIs (and indeed HIV) to spread more quickly. This still produced a cost-saving, though may not be truly reflective as it only accounted

for STI instances in PrEP users. Given risk compensation (see *Chapter V*), widespread PrEP may result in an increase in STIs not only within the community of PrEP users, but the wider MSM community, and potentially even beyond that. Therefore, we may see a greater increase in STIs than accounted for, meaning the saving suggested could be unrealistic. Further, there is potential for PrEP to be dispensed by pharmacies in time. This would remove any ability to enforce quarterly testing, potentially worsening the spread of STIs and, in a worst-case scenario, HIV. An infected individual could spread an STI to many in three months, so without quarterly testing STI rates may increase more so.

The average PrEP user being on the drug for only 4.5 years is particularly confusing due to its lack of justification and accompanying sensitivity analysis. Assuming users will take PrEP for an average of 4.5 years and costing PrEP provision on this assumption is problematic for this study's external validity. Given how recently PrEP has been introduced there are not yet studies indicating how long an individual might spend on the drug, but 4.5 years seems too few. A more detailed exploration of the likely length of time an individual would spend on PrEP is provided shortly when I look at the PIT. For now, it is fair to say this study ought to have conducted sensitivity analyses for users remaining on PrEP for longer periods of time. The failure to do so undermines the claim that PrEP is cost-effective, as it only holds true if users stop taking the drug after an average of 4.5 years.

I argue that the above makes the study unconvincing in its conclusion that PrEP is cost-effective. There are factors that will influence the cost-effectiveness of PrEP which Cambiano and colleagues either did not consider, or did not consider in sufficient depth, and thus they have demonstrated the cost-effectiveness of a PrEP programme that would not be replicable in practice. Whilst it may be internally valid, the external validity should be questioned.

I will now look at the PIT and the considerations it is making with regards to economics. Whilst the explicit purpose of the PIT is not to ascertain the cost-effectiveness of PrEP, many of the questions it does hope to answer have cost implications.

The PrEP Impact Trial

The PIT hopes to answer a range of questions regarding, as the name suggests, the impact PrEP would have if available on a large scale in England. These range from questions of uptake to risk compensation, and many have potential financial implications.

One stated aim is to establish how long PrEP users will stay on the drug (PrEP Impact Trial, 2017c). It is hoped that in ascertaining the average length of time spent on PrEP, the drug cost per user will become clear. This is important information for commissioning decisions, as highlighted in my earlier discussion of existing cost-effectiveness analyses. However, such information is an impossible outcome of this trial. The PIT is only a 3-year trial, so in hoping to ascertain average time spent on PrEP in this period suggests users will not want or need the drug for more than three years. This seems unlikely.

It is reasonable to assume a significant number of PrEP users would continue to take the drug for more than three years. Aside from experiencing negative side effects, the only likely reason for an individual to stop using PrEP is a significant reduction in perceived personal risk of HIV infection. Such a reduction in personal risk may result from a user: entering a closed, monogamous sexual relationship with a partner who is either HIV- or HIV+ but virally suppressed; beginning to use condoms consistently (if he did not before); or abstaining from sex. Whilst the

last two are not impossible, they do not seem likely; beginning to use condoms consistently after not doing so for an extended period of time would likely require significant determination as it will not be a habit such an individual will have, and for someone with a history of risky sexual activity to suddenly stop having sex altogether can feasibly be deemed rare.

The most likely reason for a user to stop PrEP, then, is entering a closed, monogamous sexual relationship with a partner who is either HIV- or HIV+ but virally suppressed. In such a relationship, the risk of infection is extremely low. Indeed, infection would only occur in the case of infidelity or the HIV+ partner failing to fully adhere to highly active antiretroviral treatment (HAART). For most PrEP users to find themselves in a closed, monogamous sexual relationship with a low risk partner within three years is a claim which needs supporting. One study explored sexual risk behaviours of MSM in serodiscordant relationships and found many have sex with individuals other than their primary partner (Brooks et al., 2012). Such individuals would have a continuing need for PrEP and may be long-term users. It is feasible, then, that most PrEP users will continue to use the drug for far longer than three years. This is because the MSM community is known to be less concerned with having closed, monogamous relationships than the heterosexual community (Levine et al., 2018); that is not to say it should be, simply that evidence suggests it is not.

Associated costs

As already mentioned, one issue neglected in cost-effectiveness analyses is associated costs which may arise where PrEP is made available. It is not a case of weighing up the cost of PrEP against the cost of HIV treatment for the same number of patients. There are myriad other costs

to consider, ranging from STI treatments to the clinical time required to counsel a prospective PrEP user. Only in accounting for these associated costs can an accurate cost-effectiveness analysis be completed.

The first to consider is STI treatment. The extent to which STI infections would increase in MSM as a result of increased access to PrEP is hard to determine, as it will be contingent on the extent of risk compensation taking place. Cambiano and colleagues assumed no change in sexual behaviour among PrEP users (Cambiano et al., 2018) and thus their sensitivity analysis with greater instances of STIs is unlikely to be representative. It is more probably the case that we cannot yet be sure if there would be a significant increase in the cost of STI treatment as a result of the widespread availability of PrEP, though it is reasonable to suggest there would be an increase and thus it must be accounted for to some extent for an analysis to be externally valid. NICE notes cost-effective interventions may not be considered appropriate to provide where there is good reason, citing 'significant limitations to the generalisability of the evidence for effectiveness' (National Institute for Health and Care Excellence, 2008) as an example. Nonadherence will also play a role in the increased cost of STI treatment. Both nonadherence and risk compensation are dealt with fully in later chapters (see *Chapter IV* and *Chapter V*).

Given the potential for community-level risk compensation (see *Chapter V*), it is also not simply a matter of an increased cost of STI treatment in PrEP users. Instances of STIs may increase among members of the MSM community who are not themselves on PrEP, or even those outside of the community[14]. This will further inflate the cost of STI treatment to be accounted for. However,

[14] STIs may spread outside of the MSM community via men who have sex with men and women (MSMW) affected by risk compensation (see *Chapter V*).

again, it is difficult to determine if this will be significant. Despite the difficulty in determining this, sensitivity analyses in future studies ought to explore this.

Following the increased cost of STI treatment is the increased cost of HIV treatment – or at least the lesser reduction in such costs. Whilst new instances of HIV will decrease overall, there may be some individuals who will contract the virus who would have been at less risk before PrEP. This would result in the HAART savings being less dramatic than expected. Such a phenomenon might come about when an individual previously at low risk of HIV infection suffers both nonadherence and risk compensation. This is discussed further in *Chapter V*, and it is unlikely to affect many, but it is again something to account for as it may contribute to PrEP moving further from being cost-effective.

As already highlighted, it is feasible that users will remain on PrEP for a period far longer than that assumed in economic analyses. Naturally, the longer an individual remains on PrEP the higher the cost. Whilst this is not necessarily an "associated cost" as it is the primary cost when considering PrEP provision, it may rightly be considered one where the assumption is that users will discontinue PrEP after an average of 4.5 years. Any drug costs after this time may at the very least be deemed "additional costs". It is, then, vitally important that more thought goes into estimating the realistic cost of the drug itself so that it does not become both the primary cost and an additional cost in practice.

The costs discussed in this section must all be borne in mind when considering the results of existing economic analyses of PrEP. There is, however, a question mark over each as to the extent of the impact they will have on the cost effectiveness of the drug. This thesis addresses the issues

of adherence and risk compensation in greater depth in an attempt to shed light on this, as well as the potential problem presented by how prospective users are targeted.

Summary

This chapter discussed limitations of a key existing economic analysis of PrEP. In assuming no risk compensation, good adherence, and an average of 4.5 years spent on PrEP by users, the Cambiano study is only internally valid and, as such, has limited use. This highlights the need for a study that starts from a better-informed foundation.

I have touched on several potential issues with PrEP which would impact upon the cost-effectiveness of the drug. These same issues raise ethical questions, which are the subject of this thesis. The following chapters explore them in greater depth, following the outlining of relevant ethical theory which is applied. Economic considerations are revisited in *Chapter VII*, supported by the outcomes of ethical analysis.

Chapter III: Ethical Theory

Ethical analysis in this thesis looks primarily to principlism, considering when autonomy might be justifiably overridden. All suggestions for the infringement of personal autonomy are assessed for proportionality, weighing harms and benefits beyond just the individual. It makes sense to set out relevant understandings of these concepts before application. I also address the question of sexual liberation in this chapter, for reasons that will become clear.

Principlism

Rather than looking to public health ethics, principlism is employed in this thesis due to the positioning of PrEP in the health space. The issues concerning PrEP that will later be explored are not strictly related to individual patient medicine, nor are they wholly public health matters. Principlism is a suitable choice given its flexibility in balancing conflicting values and thus more easily allowing consideration of harms and benefits to the individual, community, and wider population. Nonetheless I will draw on some ideas from public health ethics – particularly when considering proportionality – to complement the application of principlism. First, though, I will outline the understanding of principlism which guides this thesis.

Principlism is an approach to medical ethics which utilises a framework of four ethical principles: (respect for) autonomy, nonmaleficence, beneficence, and justice (Beauchamp and Childress, 2013). The principles are intended to be universally applicable rather than rooted in a particular cultural context (Beauchamp and Rauprich, 2016). This approach is based on the idea that a single principle cannot be suited to all real-world moral dilemmas and, as such, four are presented to introduce broad applicability.

Autonomy

Autonomy can be understood as 'self-rule that is free from both controlling interference by others and from limitations, such as inadequate understanding, that prevent meaningful choice' (Beauchamp and Childress, 2013). Myriad conceptions of autonomy exist, some more demanding than others. One demanding conception is that of Kant. For Kant, man ought to be bound by laws of his own making. This, prima facie, appears to fit with a colloquial understanding of autonomy. However, inclinations and emotional responses are considered external influences by Kant. Owing to Kant's principle of universalisability, the autonomous individual does not act in a way that appeals to personal, non-intellectual factors; 'the will is a capacity to choose *only that* which reason, independently of inclination, recognizes as practically necessary, i.e. as good' (Kant, 2011). This suggests that murder, for instance, cannot be an autonomous act as it would be based on the murderer's personal inclination which cannot be universalised. In essence, the autonomous person under Kant's conception is not autonomous at all by modern standards of *personal* autonomy, in part because it implies a standard of reason that may be unrealistic for some. As noted by Dawson, it is as a result of misreading Kant that one would conclude that he thought autonomy meant to do what one wants (Dawson, 2010). Further, Varelius notes that Kantian autonomy determines answers to questions such as the permissibility of euthanasia, whereas procedural accounts allow for greater flexibility as individuals might arrive at different conclusions (Varelius, 2006). Due to how demanding Kant's conception of autonomy is – and therefore how unrealistic, in my view, it is – I will instead employ a more procedural conception of autonomy adapted from that of principlism's authors, Beauchamp and Childress. Such a conception allows for autonomous action to be individualised, rather than resting on a requirement to reach the "right" conclusion for an action to be considered autonomous.

Beauchamp and Childress present a conception requiring that three conditions are met: intentionality, understanding, and non-control (Beauchamp and Childress, 2013). Understanding and non-control are straightforward, and I will use them as outlined. Firstly, the individual must have an *adequate* understanding, given how impractical a standard *full* understanding is.[15] Adequate will be taken to mean an understanding of the key benefits and harms, demonstrable by the ability to explain these benefits and harms in one's own words. This does mean that a single missing fact *can* result in insufficient understanding, particularly where it relates to a significant risk. Secondly, decisions and/or actions must be free of external control (with the important note that not all influences are controlling). The first condition – intentionality – I will revise.

My issue with Beauchamp and Childress' idea of intentionality is its binary nature; they hold that an act is either intentional or not. Further, they do not provide an outline of what they consider intentionality to mean, merely stating that '[a]cts are either intentional or nonintentional' (Beauchamp and Childress, 2013). In the absence of a definition from Beauchamp and Childress, I will take intention to mean the agent's act being directed towards their aim(s); an *accidental* act that fulfils the criteria of understanding and freedom from external control is not autonomous. They note that the conditions of understanding and non-control can be met 'to a greater or lesser extent', whereas an act is either intentional or not (Beauchamp and Childress, 2013). I suggest that there are levels of intention and that this condition may also be a matter of degree. To elaborate on this, I look to split-level theories of autonomy despite Beauchamp and Childress dismissing them.

[15] The idea of full understanding is problematised by Manson and O'Neill in the context of informed consent. They suggest that it may be too demanding to expect individuals to grasp complex scientific information (Rethinking Informed Consent in Bioethics, 2007). This is discussed in relation to participating in research, citing misunderstandings of research design such as placebos, but this point about the demands of full understanding is equally relevant to patients consenting to an intervention such as PrEP.

Dworkin presents the idea of first- and second-order preferences, whereby the autonomous individual's second-order preferences allow critical reflection on his/her first-order preferences to either accept or change the latter (Dworkin, 1988). First-order preferences are our more base, instinctive preferences, whereas second-order preferences are more reasoned. The distinction is not necessarily a measure of quality – though in many cases higher order preferences may be deemed of higher quality – but is a note on the level of reason involved. Examples of higher and lower order preferences often relate to one another. For example, I may have the first-order desire to eat an entire tub of ice cream whilst contemporaneously having the second-order desire to not be obese. They do not necessarily sit in opposition, but it is where they do not align that is ethically interesting; we can question their interaction and set a threshold for autonomous action.

Whilst this split-level theory still entails a binary result (i.e. one is autonomous or not), I will apply the idea of first- and second-order preferences to Beauchamp and Childress' intentionality to afford it a spectrum. Thus, from stronger to weaker in terms of force exerted towards one's aim[16], an individual may act:

(a) In accordance with both his/her first- and second-order preferences, where they happen to align
(b) In accordance with his/her second-order preference and against his/her first-order preference, where the first-order preference was dismissed following critical reflection
(c) In accordance with his/her first-order preference and against his/her second-order preference, where the first-order preference was pursued following critical reflection

[16] It is important to note that where first- and second-order preferences they misalign, each weakens the intentionality of the other.

(d) In accordance with his/her first-order preference and against his/her second-order preference, where the first-order preference was pursued following negligible critical reflection

Actions (c) and (d) are somewhat similar in that one has pursued his/her first-order desire against his/her second-order desire, but there is an important distinction in terms of the extent of critical reflection. Both would qualify as autonomous under Dworkin's split-level theory as critical reflection has taken place. However, (d) is *less* autonomous as there is *negligible* critical reflection. Take, for example, a cheating spouse. The spouse has the first-order desire to cheat with someone based on a sexual attraction whilst simultaneously having the second-order desire to be faithful to his/her spouse and maintain a happy home life. A single instance of infidelity *in the moment* would constitute action (d) as there would likely still have been a brief moment of critical reflection and the act may result in a strong feeling of regret, whereas multiple instances would constitute (c) as the spouse has the opportunity to critically reflect to a greater degree over time. Therefore both (c) and (d) are autonomous acts of infidelity, but the level of intentionality is greater in (c) owing to the level of critical reflection involved. As such, (c) is a more complete expression of autonomy; this is, therefore, a more substantive conception of autonomy than that of Beauchamp and Childress, but still retains the procedural element and is not as problematically demanding as Kant's autonomy.

Given the importance of rational decisions in healthcare, only (a), (b), and (c) will be considered sufficient – assuming the criteria of understanding and non-control are met – for an action to be autonomous. As such, this is not an entirely procedural conception of autonomy as if it were, (d) would also be sufficient. Retaining the substantive element in deeming (d) insufficient is due to the medical context; with trivial day-to-day actions (d) would be sufficient as it is still autonomous,

albeit a lesser expression of autonomy. Given the potential risks associated with PrEP which I will come to discuss, providing the drug following negligible critical reflection by the would-be user presents greater risks than benefits (this will be explored in later chapters).

Autonomy, then, will be used in this thesis to refer to a hybrid of the Beauchamp and Childress model and that of Dworkin. Intentionality, understanding, and non-control are conditions that will all have to be met to deem an individual's decision/action autonomous, and all three will be taken as matters of degree. Therefore, combining elements of both Kant's substantive and Beauchamp and Childress' procedural accounts of autonomy, the term "sufficiently autonomous" will be used where a decision/action sufficiently meets all three criteria.

If individuals have a right to autonomy, there must be a corresponding duty to respect (and potentially facilitate) that autonomy. Mill's harm principle holds that the autonomy[17] of an individual ought to be respected by the state unless to prevent harm to others (Mill, 2006). For the general population, respect for autonomy can be characterised thusly – as a negative duty to not interfere except in extreme circumstances. In a healthcare context, a more demanding account of 'respect' is needed, which requires medical actors[18] to actively facilitate the ability of individuals to exercise their autonomy. For a patient to make an autonomous decision in the way I have outlined, it is necessary for medical actors to *enable* understanding. Beyond simply an ethical requirement, this was ruled to be a legal requirement in the case of *Montgomery v Lanarkshire Health Board 2015*. As such, medical actors should be providing necessary information, including alternative options. For example, a drug might be offered in both pill and

[17] Mill wrote specifically about 'individual liberty'.
[18] Medical actors can be taken to include clinicians as well as those responsible for commissioning decisions, both of which are relevant to the PrEP debate.

capsule form so that the patient is able to choose the option that best suits them. To offer only one option creates a binary decision between taking the drug and not which, depending on the nature of the treatment, might prove coercive as a patient cannot reasonably say no. Of course, this does have to be within the parameters of clinical feasibility, so some options will have to be binary.

Principlism is often criticised as an approach for the primacy it places on autonomy. Indeed, Gillon refers to the principle as 'first among equals' (Gillon, 2003). Whilst an oxymoron, such a position appears to have been cemented since Beauchamp and Childress first coined the quartet. Nonetheless, there is opposition to the prioritisation of autonomy. For example, appealing chiefly to autonomy might sometimes result in supporting what is known to be beset with problems. Dawson argues this point, presenting the example of advanced directives which may respect patient autonomy but are also known to be problematic for other reasons (Dawson, 2010). Dawson's point is particularly pertinent in this thesis as will later be demonstrated. Some advocate instead for a more balanced principlism (Callahan, 2003; Lepping et al., 2016). It is, in fact, not uncommon for proponents of autonomy's pole position to inadvertently support a more balanced principlism themselves. One such example is Gillon, who argues respect for autonomy must be qualified by respect for the autonomy of all potentially affected persons (Gillon, 2003). A consideration of the autonomy of all who might be affected falls more into an idea of justice. Dawson, therefore, advocates value pluralism, noting that values other than autonomy are *as* important and that in some situations they ought to take precedence (Dawson, 2010). This thesis will employ a balanced principlist approach, giving fair consideration to the other three principles: nonmaleficence, beneficence, and justice.

Nonmaleficence

The principle of nonmaleficence is rooted in the Hippocratic tradition of *Primum non nocere*. Nonmaleficence is the idea that the work of a doctor is not to harm the patient and is thus a negative obligation. A harm is understood as an adverse effect on the interests of X (Beauchamp and Childress, 2013). However, harmful actions in themselves are not necessarily wrong and can be justified if they are performed in order to bring about greater benefit that serves the patient's interests, such as the amputation of a gangrenous limb. In actuality, then, nonmaleficence is more the avoidance of harm *in the absence of appropriate justification*. Factoring in harm is essential in decisions about the provision of drugs such as PrEP, as side effects – medical *and* otherwise – can be significant enough (as I will demonstrate) to bring into question the importance of respecting an individual's autonomous decision to take the drug.

Given the potential for PrEP to harm those beyond the individual taking the drug (see *Chapter V*) nonmaleficence must also be considered at the population level. It will then become a trade-off between lesser and greater harms to the individual and the population (Schroder-Back et al., 2014). Here the flexibility of principlism, and thus my reason for choosing such an approach, is apparent. It can apply to decisions with very clear implications for both individuals and populations, and PrEP is one such decision.

Beneficence

Beneficence and nonmaleficence are often conflated. Frankena, for example, includes an obligation 'not to inflict evil or harm' (clearly nonmaleficence) as part of his conception of beneficence (Frankena, 1973). Gillon notes an important distinction between the two principles,

in that nonmaleficence is general whereas beneficence is more specific; we ought not to harm *anyone*, whereas our duty to do good only applies in relation to *some* people (Gillon, 1985).

I agree with Beauchamp and Childress – and Gillon – that to combine beneficence and nonmaleficence into one principle is problematic, and so beneficence is taken as a positive obligation to contribute to the welfare of the party concerned (Beauchamp and Childress, 2013). It has no greater importance than nonmaleficence, nor lesser. It simply requires that the medical actor do what improves the welfare of a patient *unless* a suitably strong reason against that course of action arises from one of the other principles.

Justice

Of the four principles, justice is the one I am least concerned with in this thesis, though it does act as a backdrop. As already highlighted, there is a major question of cost-effectiveness with PrEP that I have demonstrated is not yet answered. However, I do not wish to focus on questions of resource allocation. The financial complexities of PrEP provision require thorough economic evaluation prior to an ethical appraisal, so this will not be discussed.

The extent of engagement with the principle of justice in this thesis is the application of the other principles at both the community and population levels. As such, it is a distributive justice approach – as outlined by Beauchamp and Childress (Beauchamp and Childress, 2013) – that I will employ in relation to the right of all citizens to health. Thus, where the actions of one would infringe upon this right in others, reasonable means of preventing that action are justified.[19]

[19] See my earlier discussion of Mill's harm principle.

Justice, then, is appealed to in beneficence and nonmaleficence, as well as the autonomy of those other than the (potential) PrEP user, justifying the infringement of autonomy; it is a matter of avoiding an undue and disproportionate burden to others for the benefit of a few. Therefore, justice will not often be explicitly mentioned, but will be an implicit factor in the community- and population-level application of the other principles.

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As earlier stated, I will be using a balanced principlism, whereby no single principle automatically dominates. Far more has been said about autonomy than any other, but this should not be taken as an indication of greater importance. Rather, it is due to the complexity of the principle and the wealth of conflicting literature on it compared to the others which necessitates lengthier engagement.

In addition to the criticism of principlism's focus on autonomy, the approach is often criticised for failing to provide action guidance. Notably, Clouser and Gert argue that the four principles merely provide 'headings for a discussion' (Clouser and Gert, 1990). Contra this, I suggest one of the benefits of principlism is the flexibility this permits. Blindly following a predefined theory is problematic, as is apparent in several thought experiments relating to, for example, utilitarianism.[20] Instead, principlism provides important points of reference for a consideration of the most appropriate course of action whilst also allowing for the incorporation of other complementary principles, examples of which I will now discuss.

[20] For example, Philippa Foot's trolley problem, or John Harris' survival lottery.

Bodily integrity

In the arguments that follow, where suggestions are made that patient autonomy be deprioritised in favour of either beneficence or nonmaleficence, I make an important distinction between coercion and withholding. The foundations of this distinction are built on ideas of bodily integrity.

The coercion-withholding distinction holds that forcing an intervention or treatment upon an individual is generally harder to justify than withholding it.[21] For instance, forcing a patient to undergo dialysis without consent is significantly harder to justify than refusing to start a patient on dialysis at their request. It is important to note that this distinction is only intended to apply to interventions and treatments which are already sanctioned by a suitable authority.[22] As such, criticism based on examples such as starvation (withholding) being more easily justified than force feeding (coercion) do not undermine this distinction, because starvation is not an approved treatment/intervention and thus does not fall within the boundaries of the distinction.

The basis for this distinction is respect for bodily integrity. Its relevance is nicely summarised by Herring and Wall: 'giving a patient treatment they do not want is interfering with not only their autonomy but also their right to bodily integrity. Whilst refusing treatment to a patient who wishes it is interfering in their autonomy alone' (Herring and Wall, 2017). In following this distinction, I look to Feldman's definition of bodily integrity as 'a right to be free from physical

[21] The thought process behind this distinction was prompted by a discussion of active and passive paternalism in Michael Ardagh's *Paternalism to autonomy and back again* (1998).
[22] Such authorities include the WHO, NICE, and PHE.

interference'(Feldman, 2002). This, notes Feldman, encompasses negative liberties against acts such as physical assault and degrading treatment (those being the most relevant to this situation).

In interfering with a greater number of rights, coercion necessitates a higher level of justification. However, withholding still frustrates autonomy so requires suitable justification. Justification arises when an intervention or treatment causes more harm than benefit.[23] Returning to the dialysis example, consider a patient with kidney failure for whom dialysis has been considered. The medical team conclude the patient will not clinically benefit from dialysis due to the poor prognosis arising from multiple comorbidities, though the patient insists (s)he wants to try it. The harms associated with dialysis are significant: extensive side-effects, necessary lifestyle changes to conform to demanding treatment, as well as increased risk of, for example, anaemia, sepsis, and hernia. Given the comorbidities of the patient in question, there are greater risks. In this case, then, the harms of undergoing dialysis are greater than the benefit as the benefit is limited to satisfying the request of the patient (because the medical team have determined that there is no clinical benefit). Even when psychological harm to the patient caused by refusing to start them on dialysis is considered, withholding the therapy is still less harmful overall. Therefore, withholding dialysis may be justified in this scenario as there is minimal insult to autonomy. Such a scenario would be appropriately categorised under (c) or (d) in terms of the intentionality criterion of autonomy earlier outlined, as the first-order preference for health and the second-order preference to be dialyzed do not align, and critical reflection will have taken place but it may have been negligible.

[23] I acknowledge that this is paternalistic action, though I have not framed it as such. This thesis is, as outlined, framed in terms of principlism. I have therefore avoided the use of the term "paternalism" as there is insufficient space to fully engage with the theoretical content that would become necessary.

Withholding might further be justified by considering the integrity of medical practice. Doctor's ought not to be compelled to provide an intervention they deem inappropriate or futile (Jecker and Schneiderman, 1993), and there is a risk of moral distress if such an expectation were to be placed upon them (Jameton, 1984). Thus a limit to autonomy exists in the patient having 'the right to refuse treatment, but not to demand it' (Herring and Wall, 2017). Herring and Wall provide the example of cosmetic surgery, whereby a patient indeed has the autonomous right to refuse such surgery, though a patient has no guarantee of such surgery being made available if sought through the NHS. To protect the integrity of medical practice and the health of the patient, it is important to permit this degree of limitation in the decision about what options are made available to the patient, thereby permitting the previously discussed binary option between treatment or no treatment in some circumstances based on clinical discretion.

It is important to note that the distinction does not hold that withholding is *easily* justified. Rather, it is *easier* to justify than coercion because of the lesser insult to autonomy in that it does not disregard bodily integrity. In some instances, withholding will be unjustifiable, whilst in others coercion will be justifiable.

Proportionality

In considering interventions, an important factor is proportionality. For an intervention to be proportionate, the relationship between the ends and means must be 'appropriate' (Hermerén, 2012). Much like a harm-benefit calculation, the outcome sought must be sufficiently beneficial to outweigh whatever harm the intervention brings (for instance, an insult to autonomy). Childress and colleagues highlight the importance of proportionality in a public health context in

arguing the essentiality of 'the probable public health benefits outweigh[ing] the infringed general moral considerations' (Childress et al., 2002). In that sense, proportionality can be viewed as both normative and methodological (Schroder-Back et al., 2014).

Proportionality speaks to an innate feeling of justice, ensuring that collateral damage is limited in pursuit of health goals. Interestingly, Childress and colleagues consider '[l]east infringement' an altogether separate moral consideration (Childress et al., 2002). I do not see this distinction as useful and, rather, believe that the idea of minimising infringement is encompassed by the principle of proportionality. As such, I look to Hermerén's characterisation of the principle as quad-conditional (Hermerén, 2012).

Hermerén first outlines three conditions he draws from the European Group on Ethics – (1) the importance of the intended goal, (2) the relevance of the means to achieving that goal, and (3) that means being the most favourable (i.e. no less controversial means is available) – before providing a fourth in '[n]on-excessiveness' (Hermerén, 2012). This fourth, important, condition requires that when a certain means fulfils conditions (1), (2), and (3) it still should not be excessive; an end can be disregarded if the means of achieving it is excessive. To illustrate this Hermerén provides the example of an old man in a wheelchair who is at home alone and observes a boy stealing apples from his tree, before shooting at the boy with his gun (Hermerén, 2012). The goal of preventing theft is important, shooting the boy is likely to be successful in that regard, and there are no feasible alternatives. However, it is reasonable to assert that to shoot a child is an excessive way of preventing the theft of a few apples. The importance of this fourth condition is where the principle of proportionality in its academic sense aligns with proportionality in its colloquial sense; conversational use of 'proportional' concerns notions of reasonableness and non-excess.

Sexual liberation

PrEP, much like the BCP, can sexually liberate users. It is important to address the role I see sexual liberation taking in policy decisions such as PrEP and pre-emptively deal, here, with objections to later conclusions.

The World Health Organization (WHO) notes the importance of 'the possibility of having pleasurable and safe sexual experiences' in its definition of sexual health (World Health Organization, 2015) which PrEP is said to provide (Mabire et al., 2019). However, the WHO definition also notes that '[f]or sexual health to be attained and maintained, the sexual rights of all persons must be respected, protected and fulfilled' (World Health Organization, 2015). In relation to my earlier discussion of justice, this is why I adopt a position of the primacy of physiological health. Sexual liberation being integral to a "healthy" sex life is important, but how broad this conception of liberation ought to be is a moot point, especially – as will be shown in later chapters – when the pursuit of such liberation comes at a cost to the health of others.

Sexual liberation is important to the point that, provided all parties consent, people should be free to have sex with who they want and when they want. However, it should be the responsibility of these individuals to take reasonable precautions to protect themselves from health risks associated with sexual activity, such as HIV and other STIs. Such precautions include sexual health screenings when appropriate[24] and condoms, again when appropriate.[25] These being easily

[24] Regular sexual health screenings are advised for those who are regularly engaging in sexual activity with new partners. Those in closed, long-term relationships have little to no need for them.
[25] Whilst the use of condoms or another barrier method (such as a dental dam) is recommended for vaginal, anal, and oral sex, it is arguably unrealistic to expect that one is used for the purposes of oral sex.

available fulfils the WHO point about safe sexual experiences. Indeed, in keeping with the earlier outlined conception of respect for autonomy, medical actors ought to ensure the provision of these options. However, whilst PrEP can be seen as fulfilling it further, it equally – as will be demonstrated in later discussion – infringes upon the other important aspect of the WHO definition.

CAS with an individual whose sexual health status you are unsure of is, in a medical sense, objectively unhealthy as it presents a risk to one's own health and, taken further, the health of others if you were to become infected and later pass that infection on. This is discussed in greater depth later in this thesis, but for now I will note that the importance of enhanced sexual freedom and enjoyment PrEP might afford users is not, to my view, more important than physiological health and the protection of those beyond the users from infection. A full discussion of the relevance of sexual liberation to such decisions constitutes a debate in its own right, and constraints on space prevent me engaging fully with this debate. As such, this thesis will proceed on this basis and sexual liberation will not be taken as a benefit of PrEP.

Summary

The theoretical positions outlined in this chapter will be applied throughout this thesis. This initial overview will act as a useful point of reference and remove the need for repetitive background theory in subsequent chapters.

This chapter has also demonstrated the relatively low importance ascribed to sexual liberation in this thesis. As criticism is anticipated on this basis, this has been important in establishing the reasons as a pre-emptive response to such criticism.

Chapter IV: Adherence

The key factor differentiating efficacy and effectiveness with PrEP is adherence. Only users who fully adhere to the drug as instructed experience the level of protection from HIV infection they are likely expecting. There are potential ethical issues in providing PrEP if users struggle with adherence.

If PrEP users are expecting effectiveness of 90% or more, but struggle to maintain full adherence, there is a disconnect between expectations and reality in protection from HIV. Whilst users would be informed of the importance of adherence and the potential consequences of missing doses (particularly if coupled with risk compensation), it is perhaps unrealistic to expect sufficient acknowledgement of the risks. It seems likely some users will assume missing the occasional dose will not make a difference, and/or human error will result in some missed doses.

It is necessary to initially consider the differences between available dosing options. I explain the main two – daily and event-based – as well as a third, less common option of so-called *Ts and Ss*. Following this, I focus predominantly on daily usage for reasons which are explained.

To consider the extent to which we can expect full adherence from PrEP users, I look at indications in existing PrEP studies. There are reasons to expect lower adherence in real life, which I expand on in my discussion, but we can still learn from these trials. I also consider adherence to both PEP and the BCP; there are useful parallels which make them more useful to consider than, say, adherence to antibiotics.

After establishing likely adherence to PrEP, I consider ethical implications. Where nonadherence is experienced, there are questions of nonmaleficence in providing PrEP. If protection from HIV is

not at the level expected by the user as a result of nonadherence, there is the potential for harm. This is the case particularly where nonadherence is experienced alongside risk compensation (see *Chapter V*). I first demonstrate that nonadherence at a level where PrEP is overall causing more harm than good can justify denying access to PrEP, before qualifying that with the fact nonadherence to that level is unlikely. I then argue for appropriate action to assist in minimising PrEP nonadherence. This is justified in terms of effectiveness and proportionality in overcoming the increased risk and resulting harm introduced by nonadherence.

Finally, an overview of the future of the administration of PrEP is provided. Where the requirements on the individual are reduced (i.e. no daily pill) the chances of nonadherence will be reduced. This may overcome some of the ethical challenges. I consider current research into LAI-PrEP and how its introduction may affect ethical issues in PrEP provision. This includes a proposal of LAI-PrEP as the default option, looking to beneficence as justifying reduced options.

I begin by detailing the current options for the use of PrEP and outlining how their differences may affect adherence.

Dosing options

There are currently two main options for PrEP administration; daily and event-based (also known as *on demand*). Daily usage is straightforward – users take one dose each day, much like the BCP (Umbrella, 2017). Ideally the pill is taken at the same time each day to maintain drug levels in the body.

Event-based usage is less straightforward. It requires users to anticipate CAS and take a double dose of PrEP 24 hours before, then two further doses, one 24 hours later and another 48 hours later (Umbrella, 2017). This approach is unlikely to be suitable for many. Sex is often unplanned, particularly CAS. It is also possible sex may be anticipated with the intention of using a condom, only for the condom to be forgotten at the last minute, or even to break and for the individuals concerned to continue without a replacement – if this happens then event-based PrEP offers no protection. There is a risk with event-based usage that individuals will find themselves engaging in CAS when not protected, simply because they have not anticipated such an occurrence. Nonetheless, event-based dosing was used in the IPERGAY study (Molina et al., 2015).

A third approach is *Ts and Ss*. This method requires four doses each week, on days starting with either T or S[26] (I Want PrEP Now c). Those opting for this method are advised to complete an initial week of daily dosing, before dropping down to four per week. The theory behind this method is that those not frequently engaging in CAS do not need a high concentration of the drug in their blood, and four pills each week will be enough. This is problematic because the lower the concentration of the drug in your body the lesser the protection from HIV it provides. Further, it is realistic to assume some users would suffer nonadherence as it is an unusual routine to get into[27].

It is understandable why *Ts and Ss* came about, as it is aimed at those purchasing PrEP themselves. The cost of PrEP out-of-pocket can be prohibitively expensive, so *Ts and Ss* aimed to almost half the cost. By spacing out dosing and increasing the frequency at the weekend[28], it

[26] Tuesday, Thursday, Saturday, and Sunday.
[27] There is no data on adherence to *Ts and Ss*.
[28] This rests on the assumption that those who are not in relationships are more likely to have sex at the weekend.

intends to maintain a drug concentration that is hoped to be enough to protect against HIV. It is an "anything is better than nothing" approach, which is potentially troubling as users may not sufficiently recognise that the level of protection they are receiving is reduced compared to daily PrEP. The *Ts and Ss* method is not widely acknowledged, though warrants a mention.

Daily usage is considered the best option because not only does it maintain drug levels, but also makes adherence easier. It is for this reason I mainly consider daily usage throughout this chapter, though I touch on the other dosing routines when discussing ethical implications.

PrEP adherence

Studies of PrEP adherence are limited but results from PrEP trials can be useful in providing early indications of the reality if the drug were made widely available. However, any findings are to be taken cautiously as higher adherence is to be expected in trials than in real world conditions (Osterberg and Blaschke, 2005).

Findings from the iPrEx study provide useful information on the potential impact of side effects on PrEP adherence (Grant et al., 2010). Self-reported pill use in the PrEP group versus the placebo group was lower at week 4 and at week 8 (though the difference was smaller at week 8) but was similar from then on. Given the fact that side effects of PrEP are experienced in the first few weeks before subsiding, it is very possible that this difference in adherence is a result of some of the PrEP group experiencing side effects and missing doses.

According to Gilead[29], 7% of PrEP users experience headaches and 4% suffer abdominal pain (Gilead Sciences). It is not clear whether these side effects would be severe enough to cause nonadherence in a significant number of users, but it is possible. Further, these minor and common side effects arise in the first few weeks of PrEP usage before subsiding in the few weeks following, making it important that new users are aware of this and do not think they will persist; failure to provide such information could result in premature discontinuation.

The IPERGAY study is useful in demonstrating why event-based usage presents adherence difficulties for users (Molina et al., 2015). This study looked at MSM at high risk of HIV infection and their usage of event-based PrEP. Not only did 29% of participants take their assigned drug at a suboptimal dose, but 28% did not take it at all. Therefore, only 43% of participants took the drug as instructed. This level of nonadherence is worrying and, if found in practice long-term, would undermine the purpose of PrEP provision. This nonadherence may have been because the study was looking at event-based PrEP, so there was no routine for participants to get into. The importance of routine for adherence is discussed later in this chapter.

As previously mentioned, adherence findings from PrEP trials are not entirely reliable. This is due to the likely characteristics of participants. Trial participants are more likely to engage in health-seeking behaviour; to choose to enrol in a trial and fulfil the associated obligations suggests greater interest in health and a desire to see advancements in HIV prevention and care, meaning trial participants are more likely to focus on adherence. There is, though, a chance this would be countered by the fact that participants' knowledge that they could be receiving a placebo may cause nonadherence.

[29] Manufacturer of Truvada.

Trial participants are also likely to be more confident about their sexuality and lifestyle; it seems unlikely an individual uncomfortable with their sexuality or ashamed of their lifestyle would enrol in a trial which they are eligible for based on their sexuality and lifestyle. PrEP use comes with a certain amount of social stigma (Calabrese and Underhill, 2015), which may cause MSM who are less confident and therefore less able to ignore it to question their use of the drug, and thus have issues with adherence.

Finally, there is the fact self-reporting is the most frequently used measure. This is an inherently unreliable means of ascertaining adherence, though is still common in health monitoring. Problems with self-reporting are explored in *Chapter VI*.

These studies suggest some issues with adherence may be experienced, particularly with event-based usage of PrEP. However, results are mixed. Further findings are needed, which may come as a result of the PIT. Meanwhile, we can look to evidence of adherence to drugs with similar obstacles for users.

Lessons from post-exposure prophylaxis

PEP adherence may provide useful insights into expected adherence to PrEP because both are aimed at the same population group(s) and utilise the same drugs.

A systematic review and meta-analysis in 2014 assessed adherence to PEP, including 97 studies (Ford et al., 2014). Overall, it was discovered that adherence to the full 28-day course of PEP is

poor. The broad nature of this review means the average completion rate of 56.6% includes various populations, however when broken down we find that still only 67.2% of MSM completed the full course. Whilst this is higher than the average, it is still poor given the severity of the scenario PEP is used in. A number of these discontinuations will be attributed to the discovery that there was no exposure to HIV, but only a small number[30]. If similar adherence was found among PrEP users, it would undermine the purpose of making the drug available as users would not be significantly protected from infection as intended.

Another study, where 83% of patients were MSM, found only 4% discontinued PEP (Thomas et al., 2015). However, 16% were lost to follow-up. It is reasonable to assume that of patients who failed to attend follow-up, a significant number may have been nonadherent; if you are fearful of HIV and have identified a risk of infection, then complete a course of PEP, you would likely attend a follow-up to seek assurance that you have not become infected. Further, with this study measuring adherence by self-reporting it is likely that, accounting for social desirability bias, the rate of discontinuation was higher than reported. Regardless of the extent of discontinuation, this study is useful in also telling us 70% of those who failed to complete the full course of PEP cited side effects as the reason (Thomas et al., 2015). This is important as there are side effects associated with PrEP use, as already highlighted, which would be the same as those experienced by users of PEP.

Evidence varies, but findings concerning PEP do suggest some level of nonadherence is to be expected of PrEP, as well as some discontinuation. Even if discontinuation were as low as 4% this would still be a noteworthy issue – at the very least, it would be important to explore the reason(s)

[30] A guaranteed negative HIV test is not possible within 28 days of exposure. Finding out there was no exposure to HIV would require assurance from the sexual partner(s).

for discontinuation. This would present a potential ethical objection to the provision of PrEP, suggesting the risk of nonadherence would need addressing if PrEP were to be made widely available.

Lessons from the birth control pill

Parallels are consistently drawn between the BCP and PrEP (Myers and Sepkowitz, 2013). The two most common issues raised with both are risk compensation (see *Chapter V*) and adherence. In terms of adherence, the BCP is similar to PrEP in that its effectiveness is directly related to consistent and correct use (Moreau et al., 2006). Concerns were raised when the BCP was invented that women would struggle to adhere to the prescribed daily pill, particularly those from poorer/uneducated backgrounds (Myers and Sepkowitz, 2013). It makes sense, therefore, to assess BCP adherence and consider whether lessons might be learned.

There is much variation in reported adherence between studies. Findings of women missing at least one pill each cycle range from 20% (Moreau et al., 2006) to 52% (Molloy et al., 2012), with women missing two or more ranging from 7% (Moreau et al., 2006) to 22% (Rosenberg et al., 1998). These studies are from different countries, and indeed different decades, which explains some difference in findings. What is clear, though, is that nonadherence is prevalent. Even by the lowest figures, 20% of women missing one pill each cycle and 7% missing two or more is not insignificant. It is nonadherence that results in the failure rate of the BCP during typical use being notably lower than in perfect conditions; 8% and 1% respectively (Trussell, 2004).

An emerging theme in BCP adherence is routine. Studies find women without a fixed time each day when they take the pill are far more likely to have some level of nonadherence (Rosenberg et al., 1998; Molloy et al., 2012; Moreau et al., 2006). One UK study found 90% of those who never missed a pill had a routine, whereas only 44% of those who missed two or more each cycle did (Molloy et al., 2012). This reflects earlier findings in the USA that lack of a routine suggests a woman is more likely to miss two or more pills each cycle (Rosenberg et al., 1998). If this were the case with PrEP, efforts would be needed to get users into a routine to aid adherence.

Unpleasant side effects have also been found to cause nonadherence to the BCP (Moreau et al., 2006). A similar effect has been observed in HIV+ individuals who are on HAART (Ammassari et al., 2001), as well as those using PEP as discussed earlier. This is, as already highlighted, a potential concern with PrEP as the drug has common side effects.

Considering findings concerning adherence to the BCP, it is again important to keep in mind the risks associated with self-reporting. One study looking at BCP adherence found a significant gap between women's reporting of their adherence and the reality (Potter et al., 1996). It is possible adherence to the BCP is worse than is suggested by the studies referenced.

It is evident some women struggle to maintain full adherence to the BCP for a variety of reasons. Common reasons are lack of routine and side effects, which are issues that may foreseeably arise with PrEP. We can, then, approach PrEP policy having learned from the experience of the BCP by attempting to minimise the impact of these factors on adherence. This would help minimise nonadherence and associated issues.

Ethics surrounding nonadherence

It is, based on early studies of PrEP adherence, and the reality of PEP and the BCP, realistic to expect nonadherence to PrEP which may lead to increased risk of HIV infection in some users and/or affect the reduction of the risk of infection in the wider community/population. This raises ethical concerns to address prior to PrEP becoming widely available. The relationship between autonomy and both nonmaleficence and beneficence is key if making PrEP unavailable due to adherence issues is considered, or if any intervention(s) which may compromise the user's choice are proposed.

The first issue is the impact of nonadherence on PrEP's effectiveness. If a user is not fully adherent to PrEP, he will not experience the maximum protection it can provide and which he may expect. Healthcare staff would inform users of the dangers of nonadherence, but the extent to which this information would be sufficiently understood and followed is in doubt. This results in a potential disconnect between user expectations and the reality of PrEP's effectiveness. Those seeking PrEP may already believe it cannot fail due to the positivity attached to word-of-mouth and online promotion within the MSM community (I Want PrEP Now b), which is itself an issue, but as nonadherence causes effectiveness to drop the disparity between the patient's beliefs about the effectiveness of the therapy and the reality will grow assuming expectations are unchanged. This may be worsened if risk compensation also arises in a nonadherent user; with the effectiveness of PrEP dropping due to his nonadherence, and the risk of HIV infection increasing due to risk compensation, the gap between expectation and reality grows yet further. If this were to result in the effectiveness of the drug being compromised to the point that the intervention does more harm than good, not making PrEP available may be justified based on nonmaleficence.

This would be a proportionate denial of the prospective PrEP user's autonomy based on 'a defect in their decisionmaking [*sic*] that leads them to engage in self-harming activity' (Buchanan, 2008). 'Defect' may seem an overly harsh term, but if a PrEP user were to be nonadherent, this would not likely be a sufficiently voluntary decision. Human error is the main reason for this nonadherence. Whilst the user might recognise that he is occasionally missing doses and think nothing of it, he may not, at the time he is due to take his daily pill, be making an active decision not to as the thought may not cross his mind. As for users who may miss doses because of side effects, this too cannot be considered a sufficiently voluntary decision; the unpleasantness of the side effects may partially impair judgement as the individual may not be thinking through their decision in terms of weighing up the side effects and the potential health impact of missing doses, and they may not sufficiently understand the risks of nonadherence. As this nonadherence would be a non-voluntary decision, to deny access to PrEP would not be imposing a view of the good which is against that of the individual. In fact, it would be entirely consistent with the good they have chosen for themselves – the avoidance of HIV infection (second-order preference) – which this would seek to support; in terms of intentionality, such an individual would be acting in accordance with classification (d) as negligible critical reflection is taking place (see *Chapter III*).

Even if this nonadherence were considered sufficiently autonomous, it is important to remember autonomy is not the sole focus of ethical healthcare provision. There is no necessary reason to prioritise autonomy over other ethical values (Lepping et al., 2016). In this case, nonmaleficence permits the denial of PrEP access and the potential harms to the would-be user are great enough that respect for his insufficient autonomy can be denied. In balancing ethical priorities, denying potential users PrEP to prevent potential harm is not a significant enough insult to autonomy as to undermine the justification. Further, it is a matter of not introducing a new intervention rather than denying access to an existing one; to deny an individual access to an intervention that is

widely available would require greater justification (see *Chapter III*). If nonadherence results in a significant drop in the effectiveness of PrEP, then, it would be justified to deny access to the drug.

However, missing the occasional dose, provided it is not consistent, will not drastically reduce the effectiveness of PrEP. For the effectiveness to drop to the point where the user's risk of HIV infection becomes clinically concerning, adherence would have to be very poor – i.e. consistently missing multiple doses each week. This is unlikely to be the case for many users. Therefore, occasional missed doses when a user is on a programme of daily PrEP is to be discouraged but is not clinically problematic so does not alone justify the denial of access to PrEP on the basis of nonmaleficence.

That does not, however, mean efforts should not be made to prevent/minimise nonadherence, as there is potential for nonadherence to lead to discontinuation over time. Eventual discontinuation presents a more poignant concern.

If a user becomes nonadherent to any extent, it is possible he will struggle with adherence more over time, potentially discontinuing the drug entirely or becoming nonadherent to an extent that he is afforded is minimal protection. Whilst this is not itself problematic, if coupled with risk compensation (see *Chapter V*) there is potential for that user to be at a greater risk of HIV infection after discontinuing PrEP than he was before he began taking the drug.

Risk compensation is considered in *Chapter V*, but for the purposes of this discussion it is the phenomenon whereby a PrEP user begins to engage in riskier sex as a result of his perceived protection from HIV when taking PrEP. This would primarily mean an increase in CAS, perhaps to

the extent of entirely abandoning condom use. Once this response to PrEP has taken place, whether intentional or not, it is not reasonable to expect it to be reversed. Once an individual is out of the habit of using condoms, it may be difficult for him to revert and stop engaging in risky sexual practices after discontinuing PrEP; this is nothing to do with perception of or concern about risk, but simply difficulty in changing habits. Such users will no longer be receiving the protection of PrEP whilst engaging in riskier sexual practices, putting them at greater risk of HIV infection than before they commenced with PrEP, in addition to an increased risk of STIs.

For similar reasons to those discussed in relation to occasional nonadherence earlier in this chapter, some form of intervention is justified in this situation. The increased risk caused by eventual discontinuation is likely to result in harm to some users, thus justifying action to remove this risk even if compromising autonomy. In determining the appropriateness of a potential intervention, proportionality is vital (Childress et al., 2002). To deny access to PrEP is not a proportionate response here, or at least not as a first response. This is because it should be possible to flag users who are heading in the direction of discontinuation and provide necessary support as prevention. If effective methods can be introduced to prevent nonadherent users reaching the point of discontinuation, there is no reason why PrEP cannot be made available – at least in terms of adherence concerns – because the harm that could arise is prevented.

All users will have the importance of adherence explained to them before receiving PrEP, but this is insufficient. As highlighted, nonadherence is not always entirely intentional, but, rather, something that can happen as life gets in the way. It is vital safeguards are in place to flag nonadherence early and address the issue before discontinuation occurs, as the potential harm of discontinuation is generally preventable so allowing it is a failure to respect the principle of nonmaleficence without just cause. Firstly, early consultations must consider the routine of the

user, establishing a fixed daily time to take the drug. Whilst this routine cannot be enforced, telling a potential user he must take the pill at a fixed time rather than presenting it as best practice is a good starting point. This may be perceived as acting against the user's autonomy to the extent that it is trying to impose a routine, but this is justified both because it is a very minor infringement and because lack of routine is a significant cause of nonadherence; ergo, it is an instance of beneficence which is also proportionate. Establishing routine is in the user's interests even if inconvenient, and the potential harm he could be exposed to without routine is greater than this trivial infringement of autonomy. Autonomy would be respected to the extent that the user would be party to establishing a suitable time each day, but the imposition of routine is both in the interests of the individual user and the wider population and is therefore justified in terms of both nonmaleficence and beneficence.

Initial consultations could consider research on personality traits that have been shown to be both negative and positive predictors of adherence behaviour, which would allow healthcare staff to identify users who may benefit from additional support in establishing good adherence (Axelsson, 2013; Axelsson et al., 2011; Munro et al., 2007). A randomised controlled trial of an SMS service to support PrEP adherence in Chicago has shown promising results (Liu et al., 2018), presenting an option for all users rather than just those most likely to struggle. Those receiving PrEP should also be monitored for adherence so healthcare staff can intervene as soon as possible to prevent discontinuation. SMS reminders and user monitoring are minimally invasive additions to PrEP provision, representing nudges at most. They are justified both in the interests of individual PrEP users and the wider population, as they have the potential to remove harm without significantly denying users their autonomy; if they insulted autonomy to a greater degree they may not be justified, but this is not the case.

With processes for establishing and monitoring adherence, as well as addressing problems early, ethical issues arising from nonadherence can be minimised to the point that they are no longer obstacles to the provision of PrEP. Therefore, nonadherence does not present significant enough ethical barriers to deny access to PrEP provided additional means of supporting users which restrict autonomy only to a proportionately small degree are introduced.

My focus thus far has been on daily usage as it is the best method, though it is worth briefly noting ethical issues surrounding other usage options. With both event-based usage and *Ts and Ss*, the issues are similar to those with daily, though more acute; if a user opts for one of these dosing options over a daily pill, the potential for nonadherence is far greater. Event-based usage does not allow a user to benefit from routine at all, and the sporadic nature of the *Ts and Ss* routine is such that users are far more likely to be nonadherent to this option than daily dosing.

For these other dosing options, the same remedies would be suitable and with the same justifications. There is, however, one further issue that stems from these two approaches. That is in the user's consultation with healthcare staff ahead of starting PrEP. It would be ethically questionable for healthcare staff to present any option other than daily dosing in the first instance.

Offering only daily dosing is a greater infringement of autonomy than previous suggestions, as it denies the user a choice. However, specifying instructions for the taking of prescribed drugs is standard practice. We are not given an option as to how frequently we take doses of a course of antibiotics, and there are similar clinical reasons to impose daily PrEP.

There is a risk the lack of choice will discourage some potential users who would benefit from PrEP. Some may feel event-based usage is more suitable if they only occasionally engage in risky sexual practices, and denying them this option may discourage them from accessing PrEP altogether. However, this infringement of autonomy is justified on the bases of both nonmaleficence and beneficence due to the increased likelihood of nonadherence with event-based usage and *Ts and Ss*. Allowing a user to choose one of these other dosing options is to open him up to potential harm when he may not sufficiently acknowledge it. It is in the user's interests to take PrEP daily to maximise adherence, and removing the choice is a proportionate denial of autonomy as it still allows access.

It may be that in some, albeit very rare, cases event-based usage is the best option for a potential user. For example, if an individual is generally low risk, though occasionally visits a bathhouse[31] and engages in risky sexual practices. There would be no need for this individual to take PrEP daily, and appropriate dosing before and after these trips to bathhouses would afford him strong protection against HIV infection. In such circumstances, it would be appropriate to allow healthcare staff to permit access to PrEP for event-based usage accompanied by appropriate guidance. For such potential users, it is better to allow access to event-based PrEP than for them to receive no PrEP at all. The requirement of necessity (Childress et al., 2002) is removed (meaning the necessity for daily PrEP as the only option), and beneficence is best met by making an exception. However, this is not a common occurrence, and daily PrEP ought to be imposed as the standard. Interestingly, the current PIT does permit potential users to choose a routine. This, I hold, is unethical and should not continue at the close of the trial.

[31] Venues where men can meet other men for casual, sometimes anonymous, sexual encounters. They are also referred to as 'gay saunas'.

Future of PrEP administration

Ethical issues I have just discussed pertain to PrEP taken either daily, on the days required by the *Ts and Ss* approach, or as an event-based precaution. All three options require the user to regularly remember to take the drug, and thus may result in nonadherence as highlighted. If other options for administering the drug were available, such as those currently being developed, some of these issues may become irrelevant, or at least less relevant.

Of particular interest is LAI-PrEP, and clinical trials are currently taking place (Kaltwasser, 2018). The injectable, it has been suggested, would be taken every other month, in the hope that six doses each year will be easier for users to adhere to than daily/occasional pills.

There are many benefits of the introduction of LAI-PrEP. Not only would it simplify adherence, but by administering the injection in a clinic healthcare teams would be able to maintain a record of a user's adherence[32]. Regular clinic appointments to obtain daily PrEP do enable healthcare teams to test users for STIs, but there is no feasible method beyond self-reporting to ascertain adherence[33].

One potential issue is whether a user would fail to attend regular appointments for his next dose. This is possible, though unlikely to be common as no issues have been observed in users attending

[32] This assumes that LAI-PrEP would have to be administered by a healthcare professional rather than the user. It is possible that it may be self-administered eventually, but this would not likely be the case in the near future.

[33] Tests to check the level of the drug in the user's blood are an option, but they would only show whether that user has been taking the drug recently. This, therefore, cannot be considered a reliable measure of adherence for any of the three existing approaches discussed.

quarterly clinic appointments to collect daily PrEP. Even though LAI-PrEP would require slightly more frequent visits – every other month rather than quarterly – this is not a significant enough increase to lead one to expect many users to struggle.

LAI-PrEP would almost entirely remove the issue of nonadherence. The only related issue remaining is discontinuation. However, discontinuation would be far less likely to arise when a user is receiving LAI-PrEP than if taking PrEP in pill form as there would not be the potential for a gradual reduction in adherence leading to discontinuation. For someone receiving LAI-PrEP to discontinue would require either an active decision to do so, or serious difficulties in attending an appointment every other month[34].

The potential for LAI-PrEP raises the question, given my earlier assertion that daily PrEP ought to be imposed as the standard due to it having the lowest chance of resulting in nonadherence, of whether LAI-PrEP ought to be the standard if introduced. Nonadherence to LAI-PrEP is, as explained, not possible in the standard understanding of nonadherence. As such, I hold that if LAI-PrEP were introduced in clinical practice, it ought to become the default dosing option for the same reasons daily dosing ought to be the default now. Whilst the lack of choice would still insult the user's autonomy, it would do so less overall. This is because there would be no need for a fixed time to take PrEP to be agreed with users, no need for daily SMS reminders[35], and no need for more invasive means of monitoring adherence. Therefore, the introduction of LAI-PrEP will both improve adherence and allow greater respect for the autonomy of PrEP users overall.

[34] As LAI-PrEP would cover an individual for two months, it is not possible for users to discontinue between clinic visits as with oral PrEP.
[35] These reminders would be far less frequent if only alerting users to the fact they need another injection.

It is worth mentioning an alternative long-acting PrEP currently being developed in the form of a subdermal implant (Intarcia, 2016). Research into a PrEP implant is not as far along as LAI-PrEP but the technology may become available in the future. If available, the implantable PrEP would, it is hoped, last up to 12 months. A study has suggested that MSM may prefer a non-visible implant to LAI-PrEP in part because of protection duration; needing to attend a clinic less frequently is appealing (Greene et al., 2017). However, visiting a GUM clinic less frequently means less frequent STI testing. Improved ease of adherence in the case of a PrEP implant, then, could worsen the impact of risk compensation as STIs would be discovered and treated later than they would be with quarterly clinic visits. It is less clear that implantable PrEP ought to be the default means of dosing if available; LAI-PrEP may be better as it removes the adherence demands of daily PrEP from the user but still necessitates regular clinic visits to monitor health. Nonetheless, subdermal PrEP implants are far from ready, so the question as to whether it ought to be the default mode of administration can wait.

Summary

Data concerning adherence to PrEP, PEP, and the BCP all point to PrEP nonadherence being a realistic prospect. It is not clear how prevalent it will be, but it will likely happen to some users. There is an issue of harm being caused in providing the drug if nonadherence reaches the point of discontinuation, particularly if coupled with risk compensation.

The risk of nonadherence reaching the point of discontinuation in users is not alone great enough to make widespread availability of the drug necessarily unethical. However, the potential for nonadherence does need to be taken seriously and efforts must be made to minimise it. Only

then can the risk of undue harm to users be all but removed. Various methods may be feasible, such as mHealth approaches in the form of SMS alerts and/or greater efforts to monitor users and identify those struggling with adherence early.

These issues and resolutions relate primarily to PrEP taken as a daily pill. This is the best method in terms of promoting adherence which ought to be the default, with other routines considered only in exceptional circumstances.

Things may change with the introduction of LAI-PrEP, though this is not likely to be a reality for several years. Until then, the best way to promote adherence and avoid potential harm to users is to consider daily dosing the default, and to support users in establishing routine. If and when LAI-PrEP is introduced, provided no further ethical issues arise which could compromise it, it should become the default method of administering the drug as this will remove the possibility of nonadherence and minimise discontinuation, thus reducing potential harm to users.

Chapter V: Risk compensation

In this chapter I consider how risk compensation[36] – PrEP users feeling protected from HIV and engaging in riskier sexual practices – may affect how ethically defensible provision is. Whilst PrEP is prescribed as an additional precaution to be used concurrently with condoms, users may not sufficiently understand and/or follow this instruction. One study has even shown risk compensation to be an expected phenomenon in serodiscordant MSM couples (Brooks et al., 2012). This has raised concerns that PrEP is enabling, perhaps even encouraging, risky sexual behaviour, with Duran raising the question, 'For men who engage in unsafe sex with other men, is this [PrEP] just an excuse to continue to be irresponsible?' (Duran, 2016).

Following an initial explanation of the theory of risk compensation, I ask whether it is likely individual-level risk compensation in PrEP users would result from widespread provision of the drug. This requires separate consideration of three sub-groups of potential PrEP users, the classification of which is outlined. I look to previous trials of PrEP and any evidence of risk compensation they provide, as well as qualitative studies which explore the phenomenon. I then consider community-level[37] risk compensation, which has a lesser evidence base but is just as important. To estimate the likelihood of risk compensation at the community-level, I look at the impact of the introduction of HAART on sexual behaviour in MSM.

After assessing the likelihood of both individual- and community-level risk compensation, I discuss whether the existence of these phenomena is an obstacle to the ethical provision of PrEP. Acknowledging the value and role of justice, I consider the indirect impact risk compensation might have on the wider population, as well as questioning whether the effect it may have on the

[36] Also known as 'risk homeostasis' or 'behavioural disinhibition'.
[37] Community referring to the MSM community.

individual – be that a PrEP user or an individual who is affected by community-level risk compensation – can be reconciled with the principles of beneficence and nonmaleficence.

When discussing the benefits and harms of PrEP, I consider only health-related effects. Sexual liberation is often raised as a benefit of PrEP which may be considered as countering the harms of risk compensation. I do not, however, take this into consideration for the reasons outlined in *Chapter III*. Where PrEP is available it is provided as an additional precaution, to be used alongside condoms. It is not intended as a replacement for condoms or to encourage CAS so I focus only on health-related issues and consider reduced condom use a negative consequence. If one were to consider sexual liberation as an important benefit, my conclusions may not hold.

I will begin by providing a more detailed explanation of what risk compensation is and what it means in the context of PrEP.

What is risk compensation?

Risk compensation describes the phenomenon whereby real or perceived protection from a risk provided by an intervention results in riskier behaviour (Cassell et al., 2006). The theory of risk compensation rests on the idea that individuals have target levels of risk which they aim not to exceed. Consequently, when an intervention reduces the risk of X, there is room for an individual to increase the risk in other ways without exceeding their target level of risk (Wilde, 1982). Take, for example, road safety. Seatbelts were introduced to reduce the risk of harm in road traffic collisions. Consequently, drivers wearing seatbelts may feel more protected and take less care to

avoid collisions, resulting in riskier driving practices (Richens et al., 2000). Another parallel is found in the case of sunscreen use and an increase in sun exposure (Autier et al., 1998).

With PrEP, risk compensation means users recognising the protection from HIV the drug provides and engaging in riskier sexual behaviours. In addition to decreased condom usage, there may be an increase in the number of partners, shorter periods of time between partners, less concern with partner characteristics, and a decrease in serosorting,[38] all because users feel at less risk of HIV infection (Nguyen et al., 2018). This is supported by a perception that STIs are easily cured (National LGBTQ Task Force Action Fund), suggesting the main reason for using condoms would be HIV prevention. These riskier behaviours put users at an increased risk of STIs and potentially HIV if users were nonadherent (see *Chapter IV*).

This change in sexual behaviour may be intentional, whereby an individual acknowledges the effect of PrEP and decides riskier sexual practices are not as worrying as previously, or passive, such as an individual who initially consistently uses condoms in addition to PrEP but gradually does so less, perhaps for the sake of convenience, justified by a background belief that he is protected. Risk compensation theory would be directly applicable to the potential increased risk of HIV from PrEP users engaging in riskier sexual practices. There are, however, other effects to consider, such as the increased risk of STIs individuals put themselves at. Whilst other risk behaviours which may arise in PrEP users are concerning, the primary focus of this chapter is the increase in CAS.[39]

[38] The practice of deciding against sexual activity with HIV+ individuals.

[39] An increase in CAS is the most commonly raised issue concerning risk compensation with PrEP and is that which can be most clearly linked to an increase in STIs. Other high-risk behaviours would only significantly contribute to an increase in STIs if accompanied by CAS.

Sexual risk compensation among MSM may also arise due to greater HAART availability, or the knowledge that HIV+ individuals with an undetectable viral load cannot pass on the virus[40] (Rodger et al., 2019). These contributing factors are touched on, though PrEP remains the primary focus. It is unlikely these other contributors are acting alongside perceived protection from PrEP as HAART has been available for many years, and it is likely to be difficult for many men to knowingly have CAS with an HIV+ individual even if they know they cannot pass on the virus, as the stigma associated with HIV is still strong.

Risk compensation is potentially the most problematic issue surrounding PrEP provision. This is primarily due to the extent of disagreement over the reality of the phenomenon. Whilst some studies have found risk compensation (Newcomb et al., 2018), others argue PrEP is more likely to result in safer sexual practices (Grant et al., 2010). The latter is based on the requirement of most systems of provision requiring frequent (usually quarterly) visits to a GUM clinic, and the suggestion that regular reassurance of the need for condom use in addition to PrEP will eventually have a positive impact in influencing sexual risk behaviour. What intuitively feels more realistic is that risk compensation associated with PrEP will be somewhere in between; some users will begin to take more risks with their sexual health, some will begin to practise safer sex, and others will continue acting just as they did before they commenced PrEP.

Continuing as before does not necessarily mean the concurrent use of PrEP and condoms. The main target population in the PIT is those who frequently engage in CAS (PrEP Impact Trial, 2017b). For these individuals, risk compensation is less relevant. They may begin to be less cautious of who they engage in sexual activity with, meaning not asking potential sexual partners

[40] Knowledge of this has resulted in the so-called U=U (Undetectable = Untransmittable) movement.

about their sexual health, but if these individuals did not use condoms before commencing PrEP then it is not possible for there to be a reduction in their condom usage.

I will now move to consider the likelihood that PrEP would result in risk compensation and, if it would, the extent to which it would.

Does/would PrEP cause risk compensation?

Risk compensation does not affect everyone in the same way. Some will be unaffected. Members of the MSM community are not equally committed to practising safe sex, so there is a range of attitudes to condom use. It is prudent to distinguish between sub-groups of MSM to discuss risk compensation. I discuss three groups: (1) those who already engage in CAS either always or frequently; (2) those who mostly use condoms, but occasionally engage in CAS; and (3) those who consistently use condoms.[41] These groups are considered, and thus referred to as, high-risk individuals (HRIs), medium-risk individuals (MRIs), and low-risk individuals (LRIs) respectively. Classifying them as such is not based on any strictly medical grounds, but an intuitively fair assessment of the risk of HIV infection in those who fit these groupings how they may be differently affected by risk compensation.[42]

[41] It is worth noting that those who fit one of these categories but are in a monogamous relationship with a partner who is HIV- are not being discussed. Such individuals are at a very low risk of HIV infection, in that a risk of infection through sexual activity would exist only as a result of infidelity. Those in open relationships (broadly defined), however, are still at risk and are, therefore, included in discussion.

[42] This assumes there are no non-sexual HIV risk factors in their lives. If a man were also an intravenous drug user there would be additional risk, but it is fair to assume that the majority of MSM are not intravenous drug users.

HRIs are the primary target audience for PrEP. Those consistently engaging in CAS are at a very high risk of HIV infection, with this risk increasing with the frequency both of instances of CAS and of new sexual partners (Wilton, 2012). The potential for risk compensation among this group is limited; as they already engage in regular CAS there is little, if any, room for a higher percentage of their sexual encounters to involve CAS. Indeed, one individual who would fall under this classification stated: 'the notion of wearing a condom is almost as oppressing as abstinence' (Alvarenga, 2017). It is, however, possible for them to engage in more CAS in terms of frequency. It is also possible for them to grow less concerned with serosorting. If the HIV+ individuals HRIs have CAS with are virally suppressed this is not problematic as HIV cannot be passed on in such a scenario, but those who are newly diagnosed and not virally suppressed do present a risk to HRIs even if adherence to PrEP is perfect.[43]

Risk compensation findings from PrEP trials are mostly applicable to HRIs as this group is the target population. These trials almost unanimously deny the occurrence of risk compensation in PrEP users[44] (Grant et al., 2014; Molina et al., 2015; McCormack et al., 2016; Grant et al., 2010). The IPERGAY (Molina et al., 2015) and the iPrEx (Grant et al., 2010) studies both observed no change to sexual practices among participants, with iPrEx going further in finding both an increase in condom use and decrease in the number of sexual partners. However, both were placebo-controlled trials. It is unrealistic to expect useful data on risk compensation in a placebo-controlled trial as participants do not know whether they are receiving the drug; without knowledge that one is on PrEP for certain, the psychological process behind risk compensation cannot take place. Safer sexual practices in this trial may have resulted from greater awareness of HIV risk; participation in the trial would expose individuals to more information about the virus

[43] With perfect adherence there would be minimal risk, but still some as PrEP is not 100% efficacious.
[44] Participants in these trials would be classified mostly as HRI, with some MRI.

and its transmission. For this reason, we can dismiss these findings as conclusive on the point of risk compensation.

The PROUD (McCormack et al., 2016) study, however, and an extension to iPrEx (Grant et al., 2014), were both open-label trials. Participants in both the immediate and deferred groups of the PROUD study had balanced baseline characteristics, and findings suggested there was no change in sexual behaviour. PROUD claims to 'refute concerns that the effectiveness of PrEP would be compromised in a real-world setting' (McCormack et al., 2016) by noting no significant difference in STIs between groups. However, this study was just 84 weeks long. Risk compensation is not an immediate response. The added sense of protection is something that develops over time, leading to a gradual decline in condom use. A long-term study would be required to properly examine the likelihood of risk compensation resulting from PrEP provision. The iPrEx extension is similarly problematic, having lasted just 72 weeks (Grant et al., 2014).

It is important to qualify findings concerning risk compensation in early PrEP trials with the fact participants are highly motivated individuals in the MSM community whose experiences may be different to those of potential future PrEP users. As noted by Grace and colleagues, these individuals are 'more likely to experience and/or report an optimistic or positive outlook on PrEP' (Grace et al., 2018). Further, when risk compensation is measured primarily through self-reporting,[45] social desirability bias may distort findings (Treibich and Lepine, 2018); those engaging in riskier sexual activity as a result of PrEP may lie about condom use as they do not want to admit to something perceived as socially undesirable (see *Chapter VI*).

[45] Incidences of STIs are also considered to assess risk compensation, but such a measure is unreliable during a short trial.

More recently, several studies have looked at risk compensation among PrEP users (Nguyen et al., 2018; Beymer et al., 2018). They are likely to be more reliable than PrEP trials as not only do they assess risk compensation through STI instances rather than self-reporting, but also the participants were not part of a clinical trial.

These studies do show, based on a comparison of STI instances in the 12 months before and after PrEP initiation, that risk compensation does happen. Nguyen and colleagues found STI instances increased from 52 to 91 (n=109), in addition to two cases of HIV seroconversion (Nguyen et al., 2018). Increases were evenly spread across STIs, with the only decrease found in urethral gonorrhoea. Beymer and colleagues, however, found very different results between STIs based on a larger cohort (n=275) (Beymer et al., 2018). Prevalence of many STIs remained the same, though rectal chlamydia instances increased by 29% and syphilis by 164%. The increase in syphilis may be explained by the possibility of transmission despite condom use, or the overall upward trend in syphilis at that clinic. Rectal chlamydia, however, did not see an overall increase in instances at that clinic, so the increase among PrEP users may more feasibly be attributed to risk compensation. It makes sense that the increase would be in a rectal rather than oral STI as the (dis)use of protection for oral sex is unlikely to be affected by PrEP. With both studies examining risk compensation only over a 12-month period it is possible risk compensation would not yet be notably observable. There remains, then, a need for a study which measures long-term trends.

The participants in most previous PrEP trials and studies have been HRIs. Therefore, if one were to accept the findings of these trials on risk compensation there is no information on risk compensation in MRIs or LRIs. Whilst HRIs are the target audience for PrEP, it is naïve to think they will be the only ones accessing the drug (see *Chapter VI*). It is important to explore the possibility of risk compensation among others.

MRIs are those who mostly use condoms, but occasionally engage in CAS. This group is perhaps most susceptible to risk compensation in theory, as the fact they already engage in CAS from time to time suggests it is something they enjoy but try to avoid out of fear of the potential consequences, perhaps when the sexual history and/or HIV status of their sexual partner(s) is unknown to them. When you add to this scenario the protection PrEP affords, it is reasonable to assume some MRIs would respond with a greater tendency to engage in CAS. Fear of HIV might gradually erode due to their knowledge of the efficacy of PrEP (with them likely equating efficacy with effectiveness) and they may more frequently engage in CAS, with some possibly reaching the point of becoming classed as HRIs.

In Canada in 2016, risk compensation emerged as a theme in a study of the impact of PrEP on the social and sexual lives of MSM (Grace et al., 2018). Several interviewees described PrEP as liberating them from the need to use condoms, with some drawing an analogy with the BCP liberating women sexually. One, talking of his experience as a PrEP user, said: 'Now that I can have bareback sex [CAS] again, it's just fantastic. Sex has been liberating again thanks to PrEP' (Grace et al., 2018). This particular interviewee spoke of frequent visits to bathhouses and an active sex life. Combined with him saying he can now have bareback sex *again*, this suggests he is rightly classed as MRI. This study also noted a key overarching assumption in the social and sexual networks of the men interviewed was that PrEP and CAS are frequently equated.

We certainly cannot take the experience of one man and the general views of the sample interviewed in this single study as representative of the entire MRI population, but the fact these examples exist is evidence that risk compensation will take place among MRIs to some extent. Further, a recent systematic review and meta-analysis of the relationship between PrEP and risk compensation found evidence of MSM transitioning from inconsistent condom use to never using

condoms (Traeger et al., 2018), and these individuals would fall under the classification of MRI. This study also found the association between PrEP use and STI diagnoses to be stronger in later studies, suggesting increased faith in the drug has also contributed to an increase in risk compensation over time (Traeger et al., 2018). It is hard to say how widespread it would be, but it is very likely to happen to some degree if PrEP were made widely available, and that needs to be accounted for in any decision to roll out the drug.

I will now consider risk compensation among LRIs. The fact LRIs consistently use condoms may be for any reason but is most likely a desire to avoid STIs and, most importantly, HIV. LRIs have absorbed the long-term message that condoms are the best way to practise safe sex and are taking it seriously. It is unlikely they would knowingly have even protected sexual intercourse with an HIV+ individual out of fear of infection. You may think risk compensation is very unlikely among this group. Indeed, under PIT guidelines, if they were being honest in a clinical risk assessment, LRIs would never have access to PrEP through official channels.[46] However, there is a possibility that LRIs would lie to access PrEP or purchase it online; if these individuals are so fearful of becoming infected with HIV, it does not seem unreasonable to assume some would lie about their sexual behaviour to access PrEP if the drug were available. One could also argue that even if PrEP were not made freely available it is accessible online. This is true, but instances of LRIs purchasing the drug online would likely be rare without the national promotion and awareness that would come with the introduction of PrEP. But the question is: would LRIs accessing PrEP result in risk compensation?

[46] Official channels are the PIT or, if PrEP is made available afterwards, GUM clinics.

One PrEP user who perfectly fits the description of an LRI is Joel Alcaraz, who has written about his experience online (Alcaraz, 2015). Alcaraz described his thoughts concerning sexual contact with HIV+ partners: 'My fear was so deep I could barely kiss them without thinking about the terrorist virus within their bodies' (Alcaraz, 2015). Given how severe Alcaraz's fear of HIV was, even PrEP, it would be reasonable to assume, would have been insufficient to prompt risk compensation; someone like Alcaraz would likely want PrEP as an added precaution only, with no view to replacing condoms. However, Alcaraz wrote of how since starting to take PrEP he has become more open to CAS. Further, he has since been diagnosed with STIs, which he claims never happened prior to him starting on PrEP.

A similar story, both more recent and from the UK, is that of Adam MacLean (Ryan, 2018). Having previously used condoms 100% of the time for over a decade, MacLean initiated PrEP following CAS during a drunken encounter. He confesses both his condom use and fear of HIV began to decline when on PrEP. Whilst we do not know if MacLean began to contract STIs as a result, what is certain is his risk compensation would have put him at a greater risk of doing so. Rather than completing a course of PEP after the incidence of CAS and continuing to use condoms, MacLean made a decision which later put him at greater risk of STIs.

The stories of both Alcaraz and MacLean highlight the potential for risk compensation among LRIs. This is something seldom acknowledged due to the fact LRIs are not the target population. However, LRIs may access PrEP.

Risk compensation among individuals taking PrEP is something to be expected if the drug were to be made available. The extent to which the phenomenon would be significant enough to

outweigh the benefits of PrEP, however, is up for debate, particularly among the different risk-based sub-groups. Whilst it is likely that widespread availability of PrEP would result in riskier sexual practices among some users, this does not necessarily mean PrEP should not be made available, as it is possible the benefits outweigh the harms. Equally, additional efforts could be made to prevent risk compensation. I consider the extent to which risk compensation should affect decisions surrounding the availability of PrEP later in this chapter. First, though, I assess the likelihood of risk compensation taking place at a community-level.

Community-level risk compensation

Risk compensation is, first and foremost, concerned with changes to the risk activity of the individual the intervention is aimed at (i.e. PrEP users). However, an interesting study in Australia raises the issue of community-level risk compensation, or 'prevention optimism'[47] (Holt et al., 2018). Prevention optimism in the context of PrEP describes the situation whereby widespread availability of PrEP results in increased risky sexual behaviour by those not on the drug themselves due to a belief that enough others will be on PrEP to afford them protection – almost like herd immunity. It is important we consider the effect PrEP may have on 'community norms and practices' (Holt and Murphy, 2017) as well as PrEP users themselves.

Following the introduction of PrEP, condom use by MSM in San Francisco, USA, decreased (Chen et al., 2016). This included individuals not themselves using PrEP, which researchers suggested was a result of the assumption that other men would be. This demonstrates a potential for

[47] The term 'risk compensation' will be used solely to refer to individual-level risk compensation from now on. Community-level risk compensation will be referred to as 'prevention optimism'.

prevention optimism following the introduction of PrEP; not only PrEP users engaged in more CAS, but the wider community too.

Prevention optimism has also resulted from the availability of HAART for the treatment of HIV+ individuals. Knowledge that HAART enables HIV+ individuals to live normal lives, in contrast to the devastating prognosis that once followed a diagnosis, appears to reduce fear of the virus.

One study in Amsterdam found MSM were generally realistic about the continued need for condoms following the introduction of HAART and acknowledged that the treatment does not affect one's chances of infection (Stolte et al., 2004). However, those who perceived a lesser threat of HIV/AIDS given the availability of HAART were more likely to engage in more CAS. These results are reinforced by a meta-analysis carried out to assess the relationship between HAART and sexual risk behaviour (Crepaz et al., 2004). Previous studies have disagreed with this conclusion (Elford et al., 2002; Huebner and Gerend, 2001). However, both were cross-sectional studies. The Amsterdam study (Stolte et al., 2004) was longitudinal, so is more reliable in assessing behavioural changes like prevention optimism.

There appears to be a risk of prevention optimism with PrEP. However, a valid point is made by Stolte and colleagues (Stolte et al., 2004) that their findings should not be generalised as applicable to the whole MSM population. Whilst their study was concerned with the impact of HAART availability, this message is just as relevant to the case of PrEP. Prevention optimism would not necessarily be a widespread phenomenon if PrEP were made available, and certain sub-groups of the population may not respond in such a way at all. In considering the ethics of PrEP as an intervention, it is important to acknowledge this likelihood of prevention optimism whilst

remaining realistic about how widespread it would be as it would be difficult to accurately ascertain this data.

Now that I have presented a case for the likelihood of risk compensation at both the individual- and community-levels, I explore the extent to which this affects the ethics of PrEP provision.

Ethics and risk compensation

The risk compensation debate surrounding PrEP concerns the question of whether a reduced risk of HIV is a good enough reason to put an individual at a potential increased risk of STIs. The intention of PrEP – reducing users' chances of HIV infection and, as a result, reducing the spread of the virus – is good. However, equally, an increased risk of STIs is problematic. If the benefit of reducing the risk of HIV outweighs the harm of increased susceptibility to STIs, PrEP may be deemed ethically sound. Here lies the ethical conflict, chiefly as a matter of autonomy versus nonmaleficence, though questions of beneficence arise in considering HRIS as well as justice from a population-level perspective. The move to deny access to PrEP may, I suggest, be justified on such grounds.

PrEP for HRIs is the least ethically problematic. We know risk compensation does not affect these individuals as they already consistently engage in CAS. PrEP appears to afford HRIs the benefit of a reduced risk of HIV without the harm of an increased risk of STIs. Therefore, at an individual-level, the provision of PrEP to HRIs is ethically permissible and may even be considered a beneficence-based imperative. Objections to PrEP for HRIs based on risk compensation are only possible from a community- or population-level perspective, which I discuss later in this chapter.

Individual-level risk compensation may, however, be a valid ethical objection to the provision of PrEP to MRIs and/or LRIs.

If PrEP were available to MRIs, STI diagnoses in this group would likely rise. This group is likely to be affected most by risk compensation as they are already open to CAS, and their commitment to condom use may gradually erode.

MRIs would certainly derive some benefit from PrEP in terms of a reduction in HIV diagnoses. Before PrEP, this group is usually protected by condoms from both HIV and STIs, though not always. For those instances where condoms are not used, the risk of HIV infection would be almost entirely removed if they were taking PrEP (assuming good adherence). Likelihood of HIV infection for MRIs is, then, going from moderate to negligible. This drop is not significant, though given the incurable nature of HIV an intervention which even slightly reduces the chances of infection for MRIs is, at first glance, beneficent; indeed, it is for this reason that I have noted the justification of PrEP provision for HRIs above. However, members of this group could be significantly affected by risk compensation.

An increase in STIs among MRIs would constitute harm. Even if STIs are not perceived as serious and it is only HIV they hope to avoid, an intervention resulting in greater susceptibility to STIs fails to fulfil the principle of nonmaleficence where a suitably greater benefit does not exist. Acting to prevent PrEP access is justified on the basis of nonmalefience, and does not inappropriately infringe on the individual's autonomy as not perceiving STIs as serious can be taken as a defect in decision-making; the rise of antibiotic resistance in STIs is not common knowledge, so it is reasonable to assume most individuals presenting at GUM clinics are not sufficiently aware of the

risks associated with STIs. The fact anyone given PrEP is told to also use condoms is not a strong enough counterargument as even if an MRI says he sufficiently understands the need for condoms in addition to PrEP at a GUM clinic, this does not mean that he will take this message on board in practice; such an individual may only fit classification (d) in terms of intentionality, thus deeming him insufficiently autonomous. This is partially because risk compensation is not necessarily an active decision by the individual. The feeling of protection from HIV grows almost subconsciously, resulting in individuals having more CAS despite originally intending to take PrEP as an additional precaution rather than a replacement. It may also be that an individual simply lies in saying he accepts the need for concurrent condom use when in fact he has no intention of doing so, though this is unlikely to be the case with a significant proportion of MRIs.

As MRIs are afforded only a small additional amount of protection from HIV when taking PrEP, there would need to be almost no adverse effects for this intervention to be ethically sound. The benefit of PrEP for MRIs is small enough that the increased risk of STIs outweighs it. The balance of good to bad outcomes at the individual-level when PrEP is provided for MRIs is such that it cannot be considered an ethically permissible intervention overall as it violates the principle of nonmaleficence. Of course, it would be excessive to declare all MRIs who take PrEP would succumb to risk compensation. Some would continue to use condoms frequently, which would mean PrEP would have an overall positive impact on their sexual health. However, until it can be demonstrated that a small enough proportion of MRIs would engage in CAS when on PrEP to result in a positive average outcome for individuals in this population, the medical harms appear to outweigh the medical benefits.[48] It may be argued it is for individuals to decide whether they prefer the risk of other STIs to HIV, but this is not something for medical actors to enable when

[48] Given the low risk of HIV infection MRIs are at prior to commencing PrEP, the benefits (a reduced risk of HIV infection) are not significant. Further, whilst it is still something to avoid, HIV is no longer life threatening.

condoms are a cheaper and equally efficacious option, and the fact that alternatives are available makes for a lesser insult to the individual's autonomy (see *Chapter III*). Further, it is a proportionate infringement on autonomy which satisfies the conditions previously outlined (Hermerén, 2012); the end goal of preventing the spread of infections is important, denying PrEP in this situation might feasibly achieve this, no less controversial means is available, and denying access to PrEP is not excessive.

The particularly ethically problematic group in terms of individual-level risk compensation is LRIs. There is a reasonable risk these individuals will begin to engage in CAS as a result of being on PrEP, putting them at significantly greater risk than they previously were; from <1% chance of becoming infected with an STI as a result of anal intercourse to having no barrier to infection. There is also potential for them ending up at greater risk of HIV infection if they suffer nonadherence, meaning that second to the significant harm of an increased risk of STIs, such individuals do not experience the intended medical benefit of PrEP.

LRIs have good condom use, meaning they are at a very low risk of HIV infection to begin with. There is no medical need for this population group to use PrEP. Condoms are as efficacious as PrEP in preventing HIV (in addition to preventing against other STIs) and LRIs are likely to do well with event-based usage to ensure effectiveness. To provide them with an unnecessary drug, which they must commit to taking daily, is, as a cumbersome routine alone, a burden. Adherence to daily drugs can be stressful, particularly when individuals miss doses (see *Chapter IV*), and LRIs would be taking on this potential stress without deriving any clear medical benefit.[49] This, in

[49] It is worth noting, even though I am not concerned with the role of sexual liberation, that LRIs would not even benefit from sexual liberation in the way MRIs might. Given the general attitudes of LRIs towards safe sexual practices, risk compensation is extremely unlikely to be an active choice for such individuals.

addition to a potential increased risk of HIV infection and a significantly higher risk of other STIs, makes for an ethically dubious intervention.

There is no ethical basis for providing LRIs with PrEP in terms of risk to benefit ratio; indeed, the opposite is true. The harm risk compensation presents to LRIs is greater than any potential medical benefit. Allowing LRIs access to PrEP is, therefore, ethically irresponsible from a solely medical perspective.

I have assessed the ethical permissibility of providing PrEP to HRIs, MRIs, and LRIs on an individual-level, though there are also population-level implications. I am not referring to prevention optimism as that is a community- rather than population-level issue.[50] When individuals are provided with PrEP and risk compensation ensues, the wider population sees a small increased risk of STI infection without having caused it (and perhaps an increased risk of HIV infection too if PrEP users are not fully adherent, though this would likely be statistically insignificant if it arose at all).

If PrEP users become more susceptible to STIs, they would begin to spread more quickly. This would begin to affect individuals outside the MSM community; MSMW who are either on PrEP themselves or have CAS with PrEP users would become a means for STIs to move from the MSM community to heterosexual and bisexual women initially, and, later, heterosexual men. The extent to which this would arise is difficult to judge. There are several "what ifs" before this point

[50] Prevention optimism is discussed in terms of the effect of PrEP on the MSM and, to a lesser extent, men who have sex with men and women (MSMW), community rather than the wider population. It is possible, however, that someone who is not a member of the MSM(W) population could be affected by prevention optimism.

is reached. However, it is not unrealistic to suggest it could eventually happen. PrEP provision would, indirectly, put members of the wider population at an increased risk of STIs when they are not even aware of it. When the wider population is not sufficiently aware of their increased risk of an STI, their ability to make risk decisions is removed; they are unable to sufficiently exercise autonomy as they would not fulfil the criteria of sufficient understanding. Few are fully aware of the level of risk they are taking when engaging in unprotected sex, and knowledge of this small increase in risk may not affect decisions members of the wider population would make, but it is still contrary to the principle of nonmaleficence at a population-level for individuals to be put at an increased level of risk when unaware, especially when it affords them no benefit.[51] Whilst a key element of population health interventions – limiting individual autonomy in the interests of the health of the population – it does require a significant enough benefit to the overall health of the population. PrEP, as demonstrated, does not present a sufficiently strong health benefit as to permit this stealth increase in the risk of STIs in the wider population, meaning the autonomy of the individual can justifiably be side-lined in pursuit of nonmaleficence at a population-level.

This population-level risk is only applicable when discussing the provision of PrEP to MRIs and LRIs. As HRIs are not affected by risk compensation, they would not be contributing to a greater spread of STIs than they already are. MRIs and LRIs would. We cannot be sure how prevalent this would be. It may be that the benefits gained by the individuals on PrEP are significantly greater than the sum of harm done to the whole population, making a net benefit gain. However, as MRIs and LRIs are not afforded an individual benefit overall, and HRIs are not affected by risk compensation, this seems unlikely.

[51] It is hoped that the provision of PrEP will reduce the spread of HIV which could, eventually, result in everyone's risk of infection being reduced. However, this is an indirect result and is not a significant benefit for heterosexual individuals as they are already at a very low risk of infection.

Ethics and prevention optimism

The debate over prevention optimism concerns all groups – HRIs, MRIs, and LRIs. Prevention optimism seems a likely result of PrEP provision – though the likely extent of the phenomenon is unknown – which is ethically problematic. It sees harm coming to individuals without them benefitting from PrEP. Whilst it is still the individual's actions directly putting them at risk, the provision of PrEP causes the behavioural change responsible. If prevention optimism becomes prevalent, it would constitute a public health concern that may outweigh the benefits of PrEP to users. Victims of prevention optimism may be deemed as having a defect in decision-making in assuming herd immunity – thereby missing a single important fact which can undermine autonomy (see *Chapter III*) – which suggests some action in meeting the demands of nonmaleficence is justified. Though in the case of prevention optimism, it is worth noting that such action would be directed at another; the PrEP user is the subject of the action rather than those who experience prevention optimism, introducing an element of justice as overriding autonomy as the individual would be expected to forego PrEP – which he wants – for the benefit of the wider population.

Prevention optimism would prove a bigger issue for HRIs than anyone else if it resulted in PrEP being made unavailable, as this group stands to gain the most from provision of the drug. HRIs benefit most from PrEP and are least affected by risk compensation. Therefore, PrEP is an intervention which is justified for this group on an individual-level. However, the actions of others not on PrEP could bring into question the appropriateness of such an intervention overall.

If PrEP provision were to result in prevention optimism, it would pose a risk to public health. It then becomes a question of the autonomy of the individual versus the application of nonmaleficence to the wider public. Let us assume that PrEP is only available to HRIs.[52] There is a significant benefit to the health of those individuals, meaning a significant overall benefit to the health of that group. However, prevention optimism introduces a potential risk to the health of a much wider pool of individuals. It could affect those at practically zero risk of HIV infection by introducing this risk, as well as increasing the spread of STIs. This could be the case beyond population groups such as MSM, who are currently most affected by HIV. Heterosexuals could see a heightened risk of infection too. This could result from infections moving from the MSM community via MSMW; whilst this already can, and does, happen, it could happen more frequently if prevention optimism happened as MSMW who currently use condoms may stop doing so and thus increases the potential for carrying infections across.

Antimicrobial resistance is also an issue with prevention optimism, and potentially more significantly so than with risk compensation. In 2015, there was an outbreak of 'super-gonorrhoea'[53] in Leeds (Gallagher, 2015). More recently, in 2018, a heterosexual man presented with a highly resistant strain of gonorrhoea, resulting in a Public Health England (PHE) investigation (Schnirring, 2018). Whilst both situations were dealt with, the risk of drug-resistant infections is a cause for concern throughout healthcare (Viens and Littmann, 2015; Littmann and Viens, 2015), and sexual health is no exception. Prevention optimism, in increasing the spread of STIs, would contribute to this problem; it would cause more individuals to become infected before sexual health services become aware, causing a much more widespread, and thus expensive, problem to deal with.

[52] This is an unlikely reality (see *Chapter VI*) and is raised purely for the sake of discussion.
[53] Strains of Neisseria gonorrhoea which have developed resistance to standard treatment.

As prevention optimism has the potential to cause significant problems at a population-level, it is unethical to permit widespread access to PrEP unless this risk can be either minimised or disproved. Decreasing the already low risk of HIV infection[54] in a small group of individuals is not a significant enough justification for putting the wider population at greater risk of STIs. This is the case for the provision of PrEP to HRIs, MRIs, and LRIs; prevention optimism may be less widespread if PrEP were only available to HRIs as other people would be less inclined to assume enough people are taking the drug, but it would still take place and thus remains as an important consideration in the provision of PrEP.

This debate would be very different if PrEP were the only barrier to HIV. If there was no other way to prevent against the virus (i.e. if condoms did not exist), it may be less clear that population-level risks introduced by prevention optimism outweigh the protection PrEP affords users. However, the fact condoms exist and are freely available cements arguments against PrEP provision based on prevention optimism. We cannot reconcile increasing the risk of both HIV and STI infections throughout the population to lower the risk of HIV infection for a small group of individuals with the principles of nonmaleficence and justice, especially when those individuals could prevent that infection themselves by avoiding CAS.[55]

[54] Whilst HRIs are considered at high risk of HIV infection, their chances of infection are still low due to how difficult it is to spread HIV. Their risk is high relative to others.

[55] At first, it may appear as though the logical extension of this argument would suggest the BCP ought not to be available. There are several reasons why this analogy does not hold and the BCP can remain justified whilst PrEP is not. However, there is not space to explore this fully.

Summary

Risk compensation stands as a valid individual-level argument against the provision of PrEP for MRIs and LRIs, though not for HRIs, and both prevention optimism and the population-level impact of risk compensation provide ethical obstacles to the provision of PrEP for any MSM population group. This is the case assuming PrEP is rolled out with no efforts to counter the effects of risk compensation and prevention optimism, or with efforts that are weak and ineffective. Cassell and colleagues make a very good point on this front:

> 'The prospect of risk compensation should not deter us from pursuing promising methods of prevention or treatment, but it is imperative that we plan ahead to ensure that the benefits will significantly exceed any potentially offsetting limitations.' (Cassell et al., 2006)

Certainly, if appropriate additional measures were in place to prevent, or significantly minimise, risk compensation and prevention optimism it would become ethically permissible to provide PrEP. The problem is in finding measures that will achieve this. Making continued access to PrEP conditional on various forms of health counselling or other methods of changing the views of users towards CAS is one option. This would likely work for some users, but until it can be demonstrated as working for a significant majority it is not grounds for the ethical provision of PrEP. Further, it would do nothing to address prevention optimism. Since prevention optimism arises in those who are not on PrEP, there is no obvious way for these individuals to be targeted with any form of advice or warning. At the very least, efforts to monitor risk compensation in the ongoing international scale-up are necessary (Traeger et al., 2018).

Until approaches to reducing or eradicating risk compensation and prevention optimism are demonstrated to work, PrEP provision cannot be justified as it is irreconcilable with the principles of nonmaleficence and justice even if users are acting sufficiently autonomously. The only point at which risk compensation does not become a barrier to ethical PrEP provision is in the case of HRIs from a solely individual-level perspective. However, for this group, prevention optimism is still a potential issue, thus undermining the benefits gained until prevention optimism can be demonstrated to be minimal.

My conclusions are based on several assumptions. These are necessary due to a lack of available evidence; there are insufficient data on changes to risk behaviour to suggest how widespread risk compensation and prevention optimism would be. It is important to note these assumptions are falsifiable, and if they are demonstrated to be inaccurate my conclusions would be undermined. What is needed are more empirical data so that any conclusions drawn are either supported or shown to be wrong, both normatively and practicably. However, in the absence of such data, the assumptions my conclusions depend on are reasonable and sufficiently justified. Here I invoke the precautionary principle and its focus on pre-damage rather than post-damage control (United Nations Educational, Scientific and Cultural Organization World Commission on the Ethics of Scientific Knowledge and Technology, 2005); it is preferable to wait until we have evidence that PrEP is not harmful rather than introducing it and risking a high prevalence of risk compensation, as to withdraw PrEP provision in the latter scenario would entail significant backlash from the communities that benefit, or at least perceive benefit, from the drug.

Chapter VI: Effective targeting

Having discussed the potential risks associated with PrEP use, particularly in relation to risk compensation in MRIs and LRIs, it is apparent that effective targeting of suitable users is important to minimise harm. The aim should be to ensure only HRIs have access to PrEP because they are the group which can ethically be provided with the drug (see *Chapter V*). However, this may not be a realistic prospect.

I begin this chapter by outlining the target population of the PIT. This model is most likely to reflect the target audience clinical guidelines will stipulate if PrEP is to be made widely available following the conclusion of the trial. The user criteria are much the same throughout the UK, whether as part of a trial or not.

The next section addresses the problem with self-reporting that has been touched on in previous chapters. Given the nature of the eligibility criteria used in the PIT, elements of that eligibility can only be assessed by self-reporting. The problem with self-reporting is that individuals who do not meet eligibility criteria can be assessed as meeting them due to dishonest or mistaken responses from prospective users, granting them access to a drug they ought not to have. I explore the long-term issue of "clinic hopping", whereby users present at clinics to obtain PEP for use as PrEP.

I then outline ethical issues associated with self-reporting as a measure of PrEP eligibility and consider whether they are reconcilable to the point of making effective targeting of PrEP possible. The focus of this discussion is the principle of nonmaleficence and whether it can override autonomy; allowing an LRI access to PrEP, for instance, has the potential to result in significant

harm.[56] It also asks whether it is justifiable to prevent MRIs and LRIs accessing PrEP if they are so determined to.

Finally, I discuss whether the harm caused by PrEP in the absence of effective targeting is great enough to justify making the drug unavailable to the entire population.

PIT target population

An overview of common PrEP eligibility has already been provided, though here it is necessary to provide greater detail on the PIT's access criteria.

To access PrEP through the PIT, individuals must be aged 16 years or over and undergo a clinical risk assessment at a GUM clinic (PrEP Impact Trial, 2017c). The purpose of assessment is to ensure they fit into one of the following three groups:

'a) MSM or trans women who currently test HIV negative, who also tested negative earlier in the previous 12 months, and who report unprotected sex in the previous three months and consider they are likely to have unprotected sex (excluding oral sex) in the next three months.

b) The HIV negative partner of someone with diagnosed HIV, who is not known to be virally supressed and with whom unprotected sex is anticipated.

[56] Where there is some level of nonadherence and/or risk compensation.

c) HIV negative people who are clinically assessed and considered to be at similar high risk of HIV acquisition as those with a partner with HIV who is not known to be virally suppressed. In other words someone who doesn't fall into the criteria set out in a or b but whose situation is assessed to be at a similar level of risk.' (PrEP Impact Trial, 2017c)

These groups are much the same as those deemed eligible in Scotland (NHS Lothian, 2018), Wales (Public Health Wales HIV Expert Group, 2018), and Northern Ireland (Sexual Health NI, 2015). They are also similar characteristics to those used in various other PrEP trials and studies[57] (Molina et al., 2015; Grant et al., 2010; McCormack et al., 2016). My focus is primarily on group A as it concerns MSM, the focus of this thesis. This encompasses individuals who fit group B but are also MSM. Such individuals all fit within the HRI group previously outlined, whilst those who would be classed as LRIs would not fulfil these criteria and MRIs would very rarely (see *Chapter V*).

Reassessment is carried out at quarterly clinic appointments. These visits are also used to assess the effectiveness of PrEP in that individual and will attempt to ascertain adherence and changes to risk behaviour.

HIV status is confirmed by a 4th generation venous blood HIV test. Other criteria – i.e. questions of the potential user's condom use and adherence – are not able to be confirmed through any medical test. It is through conversation with the potential user that this information is obtained. Self-reporting is, therefore, the method of monitoring risk compensation and adherence throughout the trial.

[57] There are some variations, such as the length of time considered when asking about CAS or whether the minimum age is 16 or 18, though they are much the same overall.

The problem with self-reporting

The most important information to obtain in the initial clinical assessment, aside from the HIV status of the potential user, is the history and likely future of CAS. The only way to assess this is through self-reporting, meaning healthcare staff must rely on prospective users being honest. This is an unreliable way to assess eligibility for access to a drug which has such potentially harmful risks associated with it.[58]

Self-reporting is a widely used method of information collection when assessing the health status of individuals, particularly information on health behaviours (Short et al., 2009). However, despite the prevalence of self-reporting, the reliability of this method of data collection is questioned (Saltzman et al., 1987).

The key issue contributing to the unreliability of self-reporting is the fact humans can – and do – lie to serve their own aims. That can be lying to appear in a more positive light, such as claiming full adherence to a drug when you are in fact missing doses,[59] or lying to portray what is generally considered to be a negative characteristic, such as claiming to have regular CAS in order to access PrEP. Both actions are with a view to furthering one's own interests, or perceived interests; appearing in a good light and accessing PrEP respectively. In this discussion it is the latter that I am concerned with highlighting, though the former provides a means of doing so.

[58] Nonadherence (see *Chapter IV*) and risk compensation (see *Chapter V*).
[59] This is otherwise known as social desirability bias and is particularly relevant to questions of adherence in drug trials (see *Chapter IV*).

The PIT eligibility criteria for group A specify that to access PrEP the potential user must have had CAS[60] in the previous three months and be likely to have CAS again in the following three months. Prospective users are not expected to recall frequency, but just answer yes or no to having had CAS in the previous three months. To lie in response to this question is easy; it is a one-word answer rather than requiring the individual to fabricate several untruths coherently in any level of depth. It seems reasonable to assume an individual wanting to access PrEP when ineligible may say yes to having had CAS in the previous three months.

A systematic review of 31 studies which used a social desirability scale[61] found that social desirability affected the results of 43% (van de Mortel, 2008). Whilst 45% of these studies were not influenced by social desirability responding, the fact that nearly the same number were demonstrates the prevalence of social desirability bias. If individuals lie to appear more socially desirable when it benefits them, it seems reasonable to believe they would lie to appear less socially desirable when it furthers their interests. A more content-relevant study of the validity of self-reported condom use in a high-risk population found no association between self-reported condom use and fewer incidences of STIs (Zenilman et al., 1995). This suggests reporting bias in self-reported condom use.

Another way an individual could dishonestly obtain PrEP during a PIT clinical risk assessment is to claim he has an HIV+ partner, thus fulfilling the criteria for group B. This lie could be supported by him asking a friend who is HIV+ to pretend to be his partner, which is feasible for many MSM. Doing so would lead to that individual being deemed eligible for PrEP. Whilst it is not impossible

[60] The criteria specify 'unprotected sex', though I am concerned only with MSM so unprotected sex would entail CAS. Unprotected oral sex is rarely included in such classifications.
[61] A questionnaire that assesses the extent to which respondents are concerned with social approval.

an individual would attempt to obtain PrEP in this way, it seems very unlikely. If an individual ineligible for PrEP wanted to obtain the drug dishonestly, it is far easier to claim to have had CAS in the previous three months than to fabricate a more detailed scenario involving a fake HIV+ partner.

Flaws in self-reporting are not limited to intentional deception by the individual concerned. Human error in the form of forgetfulness and difficulties with recall is also problematic. The National Institute on Drug Abuse's Risk Behaviour Assessment, which seeks to assess an individual's risk of HIV infection, asks questions regarding sexual behaviour and drug use only in the previous 30 days (Alcohol and Drug Abuse Institute). This is because longer recall periods result in less accurate reporting, so an individual being asked about the previous three months is likely to provide less accurate information than if asked about the last month, or even the last fortnight. Whilst these issues, and others, are important when considering self-reporting as a method overall, they are not particularly relevant in the case of clinical risk assessment for PrEP access. Users are asked whether they have engaged in CAS in the previous three months at all rather than how many times they have done so, which is far easier to recall; 100% accuracy of recall in all cases is still not a realistic expectation, but with a binary question concerning an extended time period it is likely to be close to 100%. However, that is close to 100% accuracy of *recall* and does not necessarily mean close to 100% accuracy of *response*.

There is a final and even more unfortunate problem associated with the use of self-reporting. That is the lack of a suitable alternative. For all its flaws, self-reporting is the only method of gathering data such as that required in a clinical risk assessment for PrEP. The only way to obtain entirely reliable data would be surveillance of prospective users, which is a suggestion that need not be entertained. Therefore, we are forced to use self-reporting and hope instances of

dishonesty are minimal. The potential implications of self-reporting are what spark ethical questions, which are explored later in this chapter.

Clinic hopping

One means of deceitful access to PrEP is so-called "clinic hopping", or "PEP as PrEP" (PrEP in Europe Initiative, 2017). This is a practice whereby those who want to access PrEP for free either when PrEP is unavailable or they do not fulfil eligibility criteria do so by presenting at clinics for PEP, falsely claiming a risk of exposure to HIV. This is possible because PEP and PrEP use the same drug. It also takes advantage of the level of confidentiality upheld at GUM clinics; each clinic is independent in terms of patient data, so there is no centralised database. Individuals can visit multiple clinics to obtain enough of the drug to use as PrEP without being flagged as consistently accessing PEP. Blogger Greg Owen notes that some will visit up to three clinics in a single day to obtain enough pills to last three months (Owen, 2015).

Given the nature of clinic hopping, there are no data available on the frequency of the practice. However, it is acknowledged on several PrEP blogs and information sites, suggesting it does happen and may be common. The popular site Prepster cites clinic hopping as a potential means of accessing PrEP (Prepster), whilst Owen's blog states the practice happens in London 'a lot' (Owen, 2015). One individual has even admitted to the practice (Alvarenga, 2017). It is also mentioned in a review by Public Health Wales (Public Health Wales, 2017).

There is no feasible way to stop clinic hopping. It could be achieved by either restricting access to PEP, which would be dangerous as it may harm those who genuinely need PEP, or making PrEP

available to the entire population with no eligibility criteria, which would be very damaging overall in terms of harm to individuals (see *Chapter IV* and *Chapter V*). Clinic hopping may also be stopped by the creation of a centralised database of PEP provision, though this is problematic as the lack of anonymity may deter those who legitimately need PEP.[62] However, what this discussion of clinic hopping has demonstrated is that some people who would be/are looking to access PrEP – some of whom would/do not fit the clinic criteria – are willing to lie to access the drug. If willing to go to the effort clinic hopping requires, it is reasonable to assume they would have no reservations about claiming to have had CAS in the previous three months in order to obtain a much larger supply of PrEP.[63]

Targeting difficulties and ethics

Ethical issues surrounding the difficulty with targeting PrEP access effectively can be separated broadly into two considerations: (1) whether it is ethically justified to attempt to deny MRIs and LRIs access to PrEP, and (2) whether the inability to limit access only to HRIs in practice presents an obstacle to PrEP provision altogether. Both will now be discussed, demonstrating that denying MRIs and LRIs access to PrEP can be ethically justified both clinically in terms of risk and ethically in terms of nonmaleficence, and that difficulties in ensuring only HRIs access PrEP are ethically concerning, but are not so concerning as to suggest PrEP should be entirely inaccessible.

[62] Even if details of PEP access were kept on a separate database to a patient's standard NHS record, there is a risk individuals would fail to realise this. MSM who are not open about their sexuality may fear being 'outed' or stigmatised if information were to leak. This risk would not exist, but if individuals who need PEP think it does then it could prove problematic.
[63] Three months' worth rather than 28 days.

Attempting to deny MRIs and LRIs access to PrEP is only a minor infringement on their autonomy if it is an infringement at all even when they clearly want access to the drug. Some may be considered as exercising insufficient autonomy due to a false pursuit of protection and lack of knowledge of risks, therein failing to fulfil the criteria of intentionality and understanding. For these, the denial of access is an instance of nonmaleficence but does not constitute a denial of autonomy; the failure to fulfil the criteria would make the desire for PrEP among this group insufficiently autonomous. Others will be sufficiently aware of the potential health implications, meaning denial of access would be a significant assault on their autonomy, but this seems likely to be the minority.

Clinically speaking, MRIs and LRIs are not considered high-risk users as they do not fall within the eligibility criteria detailed earlier in this chapter. Even though they are MSM, their risk of HIV infection is low in both the relative and absolute sense. As such, they will derive a negligible clinical benefit from the use of PrEP. The extent of the benefit of PrEP to these individuals is a heightened sense of protection, whereas the purpose of PrEP is to provide actual heightened protection from HIV infection. There is no clinical reason to provide MRIs and LRIs with PrEP based on their current sexual practices.

This sort of justification is routinely used in healthcare. Patients are not able to request any drug they desire, and PrEP should not be an exception. This is partially to do with safety, but also concerns justice in the allocation of healthcare resources; if drugs were available through the NHS by request rather than clinical assessment the cost would be unmanageable, preventing some individuals from accessing drugs they need due to lack of funds.

There is an argument that greater perceived protection is good for mental wellbeing as it can remove the perpetual fear of HIV infection that is verging on unhealthy in some individuals (Alcaraz, 2015). However, this does not change the clinical facts. PrEP will reduce the risk of HIV infection in MRIs and LRIs, but this is by a statistically insignificant amount and is only the case if those users are fully adherent to the drug and do not suffer any risk compensation. The psychological wellbeing PrEP may afford MRIs and LRIs can be considered countered by the increased risk of STIs and the potential increased risk of HIV, making the harms greater than the benefits.

Where an MRI or LRI attempts to access PrEP nonmaleficence can justifiably take priority over respect for autonomy. There is a risk of nonadherence and risk compensation proving damaging to the health of an MRI or LRI if he were to access PrEP (see *Chapter IV* and *Chapter V*). This risk of harm is significant enough that to allow access to PrEP would fail to respect the principle of nonmaleficence.

Further, this particular instance of overriding autonomy is withholding rather than coercion. Denial of autonomy is often thought of in relation to forcing interventions upon those who do not consent, but in many instances, such as the denial of access to PrEP, it is instead a refusal to provide an intervention deemed unnecessary and potentially harmful. Withholding an intervention infringes upon the autonomy of the individual far less than does coercion, making the former less ethically problematic in that it denies only autonomy rather than both autonomy *and* bodily integrity (see *Chapter III*). In this case, the potential harm PrEP can cause MRIs and LRIs is enough to justify this withholding the intervention and the resulting minor infringement of autonomy. As noted by Lepping and colleagues, there is 'no *a priori* reason to focus on any one particular ethical value above others' (Lepping et al., 2016); it is about weighing them up and

following the course of action which is overall most ethically appropriate. In this case, nonmaleficence should be prioritised over autonomy.

I have demonstrated both a clinical and ethical justification for denying MRIs and LRIs access to PrEP. This is consistent with the reality of trials, studies, and programmes of PrEP, whereby only HRIs are deemed eligible. However, preventing MRIs and LRIs who are determined to access PrEP from doing so is almost impossible due to the unreliability of self-reporting as a measure of risk. The more pertinent ethical discussion in terms of practical application, then, is whether this inability to effectively target PrEP access is problematic enough to justify removing access to PrEP altogether.

This discussion again comes down to a question of harm and whether nonmaleficence can override autonomy. It also feeds into my wider discussion of economic considerations, though this is addressed in *Chapter VII*. If ineligible individuals can access PrEP by lying in a clinical risk assessment, it is possible they could come to harm. MRIs and LRIs affected by nonadherence and risk compensation may, depending on the extent the phenomena, find themselves at a greater risk of HIV infection than before they started taking PrEP, not to mention the increased risk of STIs.

Of course, if they were to simply take PrEP as instructed and change nothing else about their sexual risk behaviour then there is no harm to them with which to be concerned. In such a scenario, those users would merely be taking a clinically unnecessary drug with no wider impact on their life than some minor drug side effects. If this were the case, and the case for all MRIs and LRIs, there would be no need to worry about these individuals accessing PrEP in terms of potential

harm; the only issue would be cost, which is discussed in *Chapter VII*. However, this is not a realistic expectation. The extent to which nonadherence and risk compensation would take place is up for debate, but both seem likely to happen to some extent.

The ability of MRIs and LRIs to access PrEP also contributes to prevention optimism (see *Chapter V*). As PrEP becomes more widespread, there may be an increase in individuals who are not on PrEP themselves engaging in more CAS as they feel protected by the prevalence of PrEP in the community. In addition to the harm caused to those inappropriately accessing PrEP themselves, this would harm those affected by prevention optimism. Childress and colleagues write that it is justifiable for society to intervene in areas of public health 'to reduce or prevent the imposition of serious risk on others' (Childress et al., 2002). It is possible, then, if the harm caused to various individuals when MRIs and LRIs access PrEP is great enough, to justify removing access to PrEP for everyone, including HRIs.

However, this harm is not great enough. At least it does not appear to be from existing evidence (see *Chapter V*). Therefore, denying the entire population access to PrEP is not justified in terms of problems with targeting given the current state of knowledge. Further studies are required, however, to assess the extent of these harms discussed. If it were to be found that many MRIs and LRIs are accessing PrEP through deception, and that this is resulting in enough risk compensation and prevention optimism to cause significant harm to the population, it is possible a complete end to the provision of PrEP would be justified. Given the proven efficacy of PrEP, to deny access requires this high standard of justification; as the drug is already available[64] it would be problematic to remove access without good reason, so research is needed to confirm the

[64] In England PrEP is available through the PIT, but this trial is so large it would not be easy to suddenly remove access so it can be considered as *de facto* commissioned.

extent of MRI/LRI access to PrEP and resulting risk compensation and prevention optimism. Until then, however, it is an unfortunate and unintended consequence of PrEP provision that some individuals who do not fit eligibility criteria will be able to access the drug and this may cause some level of harm to them and others. The harm to legitimate users of not being able to access PrEP is greater, making any move to deny access on this basis disproportionate.

Summary

If it were possible to ensure only HRIs had access to PrEP, the whole debate over PrEP provision would be far simpler. However, MRIs and LRIs will access PrEP under current guidelines and practices, and there is no simple remedy to this.

Attempts to deny MRIs and LRIs access to PrEP are justified from both a clinical and ethical perspective. This is based on risk-related need; these individuals are simply not at enough risk for them to derive more benefit than harm from PrEP. Denying access in this situation is a justified in terms of nonmaleficence and is proportionate given the potential harms.

MRIs and LRIs accessing PrEP may cause harm to others as well as themselves as a result of prevention optimism. This harm, however, is not great enough to justify removing all access to PrEP. It is an unfortunate side effect but is not currently a significant enough issue as to tip the balance in the PrEP debate.

Chapter VII: Conclusions

This thesis set out to assess the ethical permissibility of state-funded PrEP for MSM in the UK.[65] It is a pertinent question given the ongoing PIT and surrounding debate, as well as growing international discourse on what role, if any, PrEP ought to have in the fight against HIV. In addressing the ethical concerns, I have also shed more light on the cost-effectiveness of PrEP by highlighting shortcomings of existing analyses based on misunderstandings of such issues.

In this concluding chapter my aim is not simply to summarise what has come before it, but to tie together the individually addressed issues and show what they mean going forward. To this end, this chapter revisits the economic questions outlined towards the beginning of this thesis, further highlighting the shortcomings of existing economic analyses of PrEP provision. Alongside this call for further economic studies, I also present ethically defensible policy suggestions and, most importantly, demonstrate the significant need for greater research in all areas addressed throughout this thesis for policy to be fully informed.

Revisiting economics

As noted in *Chapter II*, the cost-effectiveness of PrEP is a key consideration in commissioning decisions; if it proves too costly given the benefits it affords it will not be deemed an appropriate use of finite resources by NICE (National Institute for Health and Care Excellence, 2008). *Chapter II* also provided an overview of issues with the 'go-to' economic analysis of PrEP in the UK (Cambiano et al., 2018). These were: full adherence, quarterly HIV tests by users, and a mean of

[65] Whilst my initial focus was on the question of state-funded PrEP, many of the issues addressed might be used to support the restriction of privately funded PrEP too. This is touched on later in this chapter.

4.5 years spent on PrEP. Given my subsequent exploration of these issues it is appropriate to now revisit the economic implications.

Full adherence has been demonstrated to be unrealistic in *Chapter IV*. In this thesis I focused on daily PrEP though have also considered event-based usage at times, both of which have been demonstrated to be problematic for users in terms of adherence. Whether this is difficulty establishing a routine for daily usage, partially due to side effects (Grant et al., 2010), or a failure to anticipate an instance of CAS if a user opts for event-based usage (Molina et al., 2015), I have shown that to expect users to be fully adherent to PrEP is unrealistic. This is, however, to be acknowledged alongside the fact that for nonadherence to prove problematic to the extent of being clinically concerning, it would need to be severe, verging on discontinuation. At least that is the case for daily PrEP. For event-based usage nonadherence can be more problematic, hence my assertion that only daily usage ought to be presented as an option – this is revisited shortly.

The role of adherence in the question of the cost-effectiveness of PrEP is not all that important when considering daily PrEP. It is unlikely to make a huge difference to financial considerations. Adherence still ought to be encouraged, but nonadherence alone is unlikely to tip the balance with regards to the cost-effectiveness of the drug, or indeed its ethical defensibility.

Next is the expectation of quarterly HIV testing. This ties in with the issue of risk compensation explored in *Chapter V*, as quarterly testing should partially control the increased spread of STIs that may arise due to risk compensation. However, given the fact risk compensation can have an impact on the spread of STIs beyond the MSM community it is not unrealistic to assume the increase in treatment costs will be significant. Potentially significant enough to bring the cost-

effectiveness of PrEP into question. Whilst quarterly testing is enforceable by making it a condition of access, it may be limited in its ability to counter the effects of risk compensation should the phenomenon arise.

Finally, the question of time spent on PrEP by the average user. This is likely to be one of the biggest factors affecting the cost-effectiveness of PrEP as the drug itself is the main cost. The 4.5 years suggested by the Cambiano study, in addition to being wholly unexplained, seems to be far too short for the reasons outlined. As highlighted in *Chapter II*, the most likely reason a PrEP user would stop taking the drug would be entering a closed, monogamous sexual relationship with a partner who is either HIV- or HIV+ but virally suppressed. It seems unlikely this would be the reality for the majority of PrEP users after 4.5 years, particularly since it is not uncommon for MSM couples to maintain open relationships (Levine et al., 2018). There is insufficient evidence to accurately suggest the average length of time a user may spend on PrEP, but it is best considered an open-ended need that may continue past 4.5 years. The failure of the Cambiano study to perform sensitivity analysis to this effect is problematic, so in addition to the need for further research into average time until discontinuation it is also important that further economic analysis is carried out with this in mind.

Many issues raised with the Cambiano study, and, by extension, those explored throughout this thesis, are not hugely problematic in terms of cost-effectiveness when taken alone. It is when they occur contemporaneously, as is at least possible, that costs rise and benefits decline. Take, for example, a scenario whereby: PrEP users remain on the drug for an average of 10 years; MRIs and LRIs access PrEP and suffer risk compensation, before some struggle with adherence and eventually discontinue PrEP without reverting to the use of condoms; those in the MSM community not on PrEP experience prevention optimism; and the increased spread of STIs and

HIV reaches heterosexual individuals. This may sound an almost dystopian worst-case scenario whereby all the possible issues associated with PrEP arise at once, but it is not all that unrealistic. If these things happen at once the cost-effectiveness of PrEP is far less clear. It would be difficult to account for these eventualities fully in sensitivity analyses, but that does not mean efforts should not be made.

It is possible even this worst-case scenario could be softened by developments such as LAI-PrEP and new methods of effective targeting. Until these happen, however, it seems realistic that PrEP could prove cost-ineffective. Nonetheless, what is vital is a new cost-effectiveness study which takes these issues into account as best it can. Only with such a study can the discussion of PrEP commissioning take place in an informed manner with regards to cost-effectiveness.

Policy implications

I asserted early in this thesis that cost-effectiveness is not the sole factor that ought to be considered in commissioning decisions. Its importance is understandable in a system of finite resources. However, a cost-effective intervention is not necessarily appropriate, just as a cost-ineffective intervention is not necessarily inappropriate.

Given the shortcomings of the Cambiano study, it seems a definitive answer as to the cost-effectiveness of PrEP in the UK is not yet available. Based on currently available information I suggest it seems unlikely it will be cost-saving to the extent suggested by the Cambiano study, but future studies may nonetheless demonstrate cost-effectiveness. For the purposes of this

discussion, let us assume PrEP is demonstrated to be cost-effective and consider what ought to be the next steps based on the ethical debate in this thesis.

To begin with potential users, I have argued only HRIs can ethically be provided with PrEP (as is in keeping with official access guidelines). The overall harms that would result from PrEP use for MRIs and LRIs are such that it would be ethically unjustifiable to allow. The question of whether this insults the autonomy of MRIs and LRIs is an interesting point. The withholding-coercion distinction becomes relevant here and denying access is justified on the grounds of nonmaleficence – allowing these users access to PrEP would cause more harm than benefit.

This raises the question of effective targeting as explored in *Chapter VI*. It seems almost impossible to prevent those who are not considered eligible from accessing PrEP. Whether through falsely reporting their risk in a clinical risk assessment, or clinic hopping, when the drug remains available *at all* it will always be available to those who are willing to lie to access it. Before the drug was ever available as PrEP, clinic hopping meant individuals were able to access it for such a use. As such, clinic hopping cannot be deemed a legitimate objection to the provision of PrEP as it would in fact be an objection to the provision of PEP; clinic hopping would continue if PrEP were not available. It is an unfortunate truth that there will always be individuals happy to cheat the system for their own benefit (perceived or real), but this cannot justify a blanket removal of PrEP access. In terms of policy, PrEP access can justifiably be made available to HRIs. Whilst problematic, MRIs and LRIs accessing the drug as a result can be marked an unfortunate side effect and hopefully be minimised through more effective clinical risk assessment.

The next policy consideration is mode of dosing; whether we should allow users to choose between daily and event-based PrEP. Based on adherence concerns, I have argued for daily PrEP to be the default. Alternative approaches – such as event-based and *Ts an Ss* – make adherence far more difficult for users due to the lack of a simple routine. As the insult to autonomy that is limiting dosing options is a lesser harm than the risk posed by nonadherence, putting all PrEP users on daily PrEP is a proportionate denial of autonomy. This is common practice in medicine whereby drugs are prescribed to be taken a certain way; we are not offered different courses of antibiotics to suit our routine but are expected to adhere to the most effective dose/routine combination to ensure maximum effectiveness. Of course, there must be clinical discretion to permit event-based PrEP. This, however, should be used sparingly and only when necessary, such as the example given of the man who very occasionally engages in risky sexual activity at bathhouses (see *Chapter V*).

If daily PrEP is to become the default because it is preferential in terms of adherence, current research into LAI-PrEP becomes a serious policy discussion. For the same reason of improved adherence, I believe it would be ethically justifiable for LAI-PrEP to become the default means of administering the drug if introduced. Not only would LAI-PrEP aid users in adherence – the extent of effort required on the part of the user is limited to attending a clinic once every 2-3 months – but it would also assist healthcare staff in monitoring users. It will be impossible for a user to discontinue PrEP without doctors knowing as failure to attend an appointment for the next dose would be flagged, enabling efforts to prevent discontinuation.

By only providing users with daily PrEP – or LAI-PrEP if and when the time comes – we are giving an immediate boost to adherence. Whilst nonadherence is not necessarily problematic with PrEP, it is worth making such a simple move to prevent users reaching the point of discontinuation. To

aid this adherence further it is important in initial consultations that users are made aware of what side effects to expect, and for clinicians to identify users who may require additional support. The potential for SMS services to support adherence has been discussed (Liu et al., 2018), and it is important this idea is further explored and implemented if appropriate.[66]

Dealing with risk compensation and prevention optimism is a far more complex issue. Similarly to nonadherence, risk compensation might be mitigated by effective consultations. It is important users have explained to them the consequences of risk compensation and that they be provided with condoms and encouraged to use them. Unfortunately, this will not work for all users; there are those who view PrEP as a reason not to use condoms and sufficiently acknowledge the risk, and for these individuals nothing can be done. However, it is possible appropriate counselling may work for some, so it is important to consider the potential benefits and weigh them against cost implications.

When it comes to prevention optimism, counselling has little scope to help. As individuals affected by prevention optimism are, by definition, not on PrEP themselves they are not easily reached as a group. Some will attend GUM clinics for check-ups, so providing some level of counselling to all who attend – as is routine anyway – may mitigate prevention optimism slightly but is not getting to the root of the problem. Perhaps the best way to address the issue is to focus on effective targeting of PrEP provision as herd immunity may be assumed by fewer individuals if there are fewer people on PrEP. This, however, brings us back to the difficulty in effectively targeting PrEP at HRIs only. It seems for now prevention optimism must, much like clinic hopping, exist as an unfortunate side effect of PrEP provision. There is a clear need to research ways of

[66] This would include cost considerations, though it is likely to be a negligible additional cost as SMS services are already used by GUM clinics.

effective targeting in order to prevent the issues associated with it, and this should be the focus of efforts in this area.

One final policy consideration is the question of privately funded PrEP. Whilst some of the ethical issues arise from widespread availability of PrEP, some are just as problematic when only a small number of users access the drug. For instance, an MRI or LRI purchasing PrEP online may still suffer both nonadherence and risk compensation. The question then arises over whether efforts should be made to prevent access to PrEP entirely. There is not space to fully explore this in this thesis, though it is an interesting question. There are many points to consider: would permitting private purchase but not state provision create a socioeconomic divide in PrEP access?; if PrEP were restricted entirely should those who still manage to obtain it receive support from GUM clinics?;[67] if PrEP restriction were sought, would it be enough to discourage individuals or would criminalisation be appropriate? These are interesting and important questions to explore, but it is not possible in this thesis.

Limitations

All conclusions reached and suggestions made are based on currently available evidence and the theoretical foundations outlined in *Chapter III*. There are, therefore, potential limitations to this thesis.

[67] Currently, and prior to the start of the PIT, those who purchased PrEP online were still able to seek support and advice from their local GUM clinic.

Firstly, the question of the theoretical positions adopted throughout. There are myriad conceptions of each principle and value outlined and applied, meaning some readers will inevitably disagree with my usage. In particular, the distinction between coercion and withholding does rely on agreement with certain fundamental ideas concerning bodily integrity and a somewhat quantitative consideration of values (i.e. only undermining autonomy is preferable to undermining both autonomy and bodily integrity).

There is also the issue of limited evidence. As I have highlighted throughout this thesis, my arguments are based on currently available evidence. This has, in many cases, been limited. In some cases this is simply due to no research having yet been done on the issues I touch on, and in others it is owing to the practical and methodological difficulties in obtaining the relevant data. For example, evidence of risk compensation among LRIs is limited to personal testimonies as trials have sought to recruit primarily HRIs. Some data is also unavailable at present due to its longitudinal nature (i.e. how long the average user spends on PrEP).

In a similar vein, any future evidence contrary to the premises central to this thesis may raise valid objections to my arguments. For instance, the average PrEP user in the UK may end up being on the drug for the 4.5 years suggested by Cambiano and colleagues (Cambiano et al., 2018). If this proves to be the case it means the base cost of PrEP will be lower than I have suggested. It may also transpire that risk compensation is minimal and users are mostly fully adherent. Whilst I consider it unlikely such evidence will arise, it remains a possibility and must be acknowledged.

Finally, there is the limitation of international applicability. I have written this thesis based almost entirely on the UK healthcare system. Much of the discussion will be relevant in other jurisdictions

but will not be a perfect fit owing to a variety of country-specific factors. Particularly where the means of dispensing HIV drugs is concerned; clinic hopping may not be possible, or at least may be significantly more difficult, in a country that restricts access to PEP.

These limitations do not immediately question the contribution of this thesis. Most are *potential* limitations as a result of future research. The only limitation that is currently relevant – in terms of questioning the contribution of this thesis – is the potential for individuals to disagree with my theoretical stances. This is to be expected in the field of bioethics and, therefore, does not undermine the value of this thesis to the ongoing debate. Indeed, drawing on Ives' fallibilistic conception of bioethics, the purpose of research in this field is not to find *the* solution, but *a* solution which 'goes some way towards resolving the problem we currently have' (Ives, 2014). This, I have done.

Concluding remarks

The key takeaway from this thesis is that we need more evidence and a greater focus on mindful deliverance. I am concerned about the implications of the rush to make PrEP available and think it important to take a step back and consider how we can best utilise the drug in reducing the spread of HIV.

To suggest PrEP is inherently unethical would be a strong and frankly unsupportable claim. Rather, I hold that the nature of PrEP provision as it stands is such that many ethical issues arise which, in combination, suggest the provision of PrEP as per the PIT model is ethically problematic. It is my hope that future research will answer many of the remaining empirical questions, allowing

better informed ethical analysis and commissioning decisions. Only then might PrEP be made available in an ethically appropriate manner, with due attention to potential pitfalls. PrEP undoubtedly has a role to play in the future of HIV prevention, but the hurried nature of current discourse is problematic and runs the risk of doing more harm than good.

Bibliography

Alcaraz J. 2015. Joel – “I was still scared, but something funny happened…”. My PrEP Experience. Available at: http://myprepexperience.blogspot.com/ [Accessed 05 November 2018].

Alcohol and Drug Abuse Institute. Risk Behavior Assessment (RBA). Available at: http://lib.adai.washington.edu/dbtw-wpd/exec/dbtwpub.dll?BU=http%3A//lib.adai.washington.edu/instrumentsearch.htm&TN=Instruments&CS=0&QY=find%20(AccessNo%20ct%20385)&RF=Full&DF=Full&MR=&NP=3&RL=0&DL=0&XC=&ID=&AC=QBE_QUERY [Accessed 30 January 2019].

Alvarenga G. 2017. I Couldn't Get PrEP, and Now I'm Living With HIV. Available at: http://www.thebody.com/content/80623/i-couldnt-get-prep-and-now-im-living-with-hiv.html [Accessed 29 January 2019].

Ammassari A, Murri R, Pezzotti P, et al. 2001. Self-reported symptoms and medication side effects influence adherence to highly active antiretroviral therapy in persons with HIV infection. Journal of Acquired Immune Deficiency Syndrome 28(5): 445-449.

Anderson PL, Glidden DV, Liu A, et al. 2012. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. Science Translational Medicine 4(151): 151ra125.

Autier P, Mezzetti M, Doré J-F, et al. 1998. Sunscreen use, wearing clothes, and number of nevi in 6- to 7-year-old European children. European Organization for Research and Treatment of Cancer Melanoma Cooperative Group. Journal of the National Cancer Institute 90(24): 1873-1880.

Axelsson M. 2013. Report on personality and adherence to antibiotic therapy: a population-based study. BMC Psychology 1(1): 24.

Axelsson M, Brink E, Lundgren J, Lötvall J. 2011. The influence of personality traits on reported adherence to medication in individuals with chronic disease: an epidemiological study in West Sweden. PLoS One 6: e18241.

Beauchamp TL, Childress JF. 2013. Principles of Biomedical Ethics. New York: Oxford University Press.

Beauchamp TL, Rauprich O. 2016. Principlism. In ten Have H (ed.) Encyclopedia of Global Ethics. Cham: Springer International Publishing.

Beymer MR, DeVost MA, Weiss RE, et al. 2018. Does HIV pre-exposure prophylaxis use lead to a higher incidence of sexually transmitted infections? A case-crossover study of men who have sex with men in Los Angeles, California. Sexually Transmitted Infections 94(6): 457-462.

Borland S, Spencer B, Robinson M. 2016. NHS fights back against ruling forcing it to hand out 'promiscuity pill' that prevents HIV as the £20m cost will hit its ability to treat cancer and give limbs to amputees. The Daily Mail. Available at: https://www.dailymail.co.uk/news/article-3720706/What-skewed-sense-values-NHS-told-5-000-year-lifestyle-drug-prevent-HIV-vital-cataract-surgery-rationed.html [Accessed 24 October 2018].

Brennan RO, Durack DT. 1981. Gay compromise syndrome. Lancet 2(8259): 1338-1339.

Brooks RA, Landovitz RJ, Kaplan RL, et al. 2012. Sexual risk behaviors and acceptability of HIV pre-exposure prophylaxis among HIV-negative gay and bisexual men in serodiscordant relationships: a mixed methods study. AIDS Patient Care and STDs 26: 87-94.

Buchanan DR. 2008. Autonomy, paternalism, and justice: ethical priorities in public health. American Journal of Public Health 98(1): 15-21.

Calabrese SK, Underhill K. 2015. How Stigma Surrounding the Use of HIV Preexposure Prophylaxis Undermines Prevention and Pleasure: A Call to Destigmatize "Truvada Whores". American Journal of Public Health 105(10): 1960-1964.

Callahan D. 2003. Principlism and communitarianism. Journal of Medical Ethics 29(5): 287-291.

Cambiano V, Miners A, Dunn D, et al. 2018. Cost-effectiveness of pre-exposure prophylaxis for HIV prevention in men who have sex with men in the UK: a modelling study and health economic evaluation. Lancet Infectious Diseases 18(1): 85-94.

Cassell MM, Halperin DT, Shelton JD, Stanton D. 2006. Risk compensation: the Achilles' heel of innovations in HIV prevention? British Medical Journal 332(7541): 605-607.

Centers for Disease Control and Prevention. 1982. Epidemiologic Notes and Reports Pneumocystis carinii Pneumonia among Persons with Hemophilia A. Morbidity and Mortality Weekly Report. Available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/00001126.htm [Accessed 06 November 2018].

Chen Y-H, Snowden JM, McFarland W, et al. 2016. Pre-exposure Prophylaxis (PrEP) Use, Seroadaptation, and Sexual Behavior Among Men Who Have Sex with Men, San Francisco, 2004-2014. AIDS and Behavior 20(12): 2791-2797.

Childress JF, Faden RR, Gaare RD, et al. 2002. Public health ethics: mapping the terrain. Journal of Law, Medicine and Ethics 30(2): 170-178.

Clouser KD, Gert B. 1990. A critique of principlism. Journal of Medicine and Philosophy 15(2): 219-236.

Collins S. 2015. PrEP to be available free in France from January 2016. Available at: http://i-base.info/htb/29311 [Accessed 25 October 2018].

Crepaz N, Hart TA, Marks G. 2004. Highly active antiretroviral therapy and sexual risk behavior: a meta-analytic review. Journal of the American Medical Association 292(2): 224-236.

Cresswell F, Waters L, Briggs E, et al. 2016. UK guideline for the use of HIV Post-Exposure Prophylaxis Following Sexual Exposure, 2015. International Journal of STD and AIDS 27(9): 713-738.

Dawson A. 2010. The future of bioethics: three dogmas and a cup of hemlock. Bioethics 24(5): 218-225.

Duran D. 2016. Truvada Whores? Huffington Post. Available at: https://www.huffingtonpost.com/david-duran/truvada-whores_b_2113588.html?guccounter=1 [Accessed 19 November 2018].

Dworkin G. 1988. The Theory and Practice of Autonomy. New York: Cambridge University Press.

Elford J, Bolding G, Sherr L. 2002. High-risk sexual behaviour increases among London gay men between 1998 and 2001: what is the role of HIV optimism? AIDS 16(11): 1537-1544.

Evans D. 2014. Monthly or quarrterly injectable PrEP continues to wow researchers. Available at: https://www.projectinform.org/news/croi-monthly-or-quarterly-injectable-prep-continues-to-wow/ [Accessed 25 October 2018].

Faria NR, Rambaut A, Suchard MA, et al. 2014. The early spread and epidemic ignition of HIV-1 in human populations. Science 346(6205: 56-61.

Feldman D. 2002. Civil Liberties and Human Rights in England and Wales. Oxford: Oxford University Press.

Ford N, Irvine C, Shubber Z, et al. 2014. Adherence to HIV postexposure prophylaxis: a systematic review and meta-analysis. AIDS 28(18): 2721-2727.

Frankena W. 1973. Ethics. Englewood Cliffs, NJ: Prentice Hall.

Gallagher J. 2015. 'Super-gonorrhoea' outbreak in Leeds. BBC News. Available at: https://www.bbc.co.uk/news/health-34269315 [Accessed 14 November 2018].

Gilead Sciences. 2018. Truvada for PrEP Important Facts. Available at: https://services.gileadhiv.com/content/pdf/TRUVADA_for_PrEP_Important_Facts.pdf [Accessed 25 October 2018].

Gilead Sciences. What are possible side effects of TRUVADA for PrEP? Available at: https://www.truvada.com/what-is-truvada/side-effects [Accessed 10 January 2019].

Gillon R. 1985. "Primum non nocere" and the principle of non-maleficence. British Medical Journal (Clinical Research Ed.) 291: 130-131.

Gillon R. 2003. Ethics needs principles--four can encompass the rest--and respect for autonomy should be "first among equals". Journal of Medical Ethics 29(5): 307-312.

Grace D, Jollimore J, MacPherson P, et al. 2018. The Pre-Exposure Prophylaxis-Stigma Paradox: Learning from Canada's First Wave of PrEP Users. AIDS Patient Care STDS 32(1): 24-30.

Grant RM, Anderson PL, McMahan V, et al. 2014. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. Lancet Infectious Diseases 14(9): 820-829.

Grant RM, Lama JR, Anderson PL, et al. 2010. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. New England Journal of Medicine 363: 2587-2599.

Greene GJ, Swann G, Fought AJ, et al. 2017. Preferences for Long-Acting Pre-exposure Prophylaxis (PrEP), Daily Oral PrEP, or Condoms for HIV Prevention Among U.S. Men Who Have Sex with Men. AIDS and Behavior 21(5): 1336-1349.

Hermerén G. 2012. The principle of proportionality revisited: interpretations and applications. Medicine, Health Care and Philosophy 15(4): 373-382.

Herring J, Wall J. 2017. The Nature and Significance of the Right to Bodily Integrity. Cambridge Law Journal 76(3): 566-588.

Holt, M, Lea T, Mao L, et al. 2018. Community-level changes in condom use and uptake of HIV pre-exposure prophylaxis by gay and bisexual men in Melbourne and Sydney, Australia: results of repeated behavioural surveillance in 2013-17. Lancet HIV 5(8): e448-e456.

Holt M, Murphy DA. 2017. Individual Versus Community-Level Risk Compensation Following Preexposure Prophylaxis of HIV. American Journal of Public Health 107(10): 1568-1571.

Hosein SR. 2016. Truvada. Canadian AIDS Treatment Information Exchange. Available at: https://www.catie.ca/en/fact-sheets/co-formulations/truvada [Accessed 11 November 2018].

Huebner DM, Gerend MA. 2001. The relation between beliefs about drug treatments for HIV and sexual risk behavior in gay and bisexual men. Annals of Behavioral Medicine 23(4): 304-312.

Husereau D, Drummond M, Petrou S, et al. 2013. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. British Medical Journal 346: f1049.

I Want PrEP Now a. I Want PrEP Now. Available at: https://www.iwantprepnow.co.uk/ [Accessed 25 October 2018].

I Want PrEP Now b. All about PrEP. Available at: https://www.iwantprepnow.co.uk/about/ [Accessed 01 May 2019].

I Want PrEP Now c. How to take PrEP. Available at: https://www.iwantprepnow.co.uk/how-to-take-prep/ [Accessed 17 December 2018].

Intarcia. 2016. Intarcia Secures Second Close of the Series EE Equity Financing for an Additional $206M; As Part of the Financing and a New Strategic Initiative, Intarcia Now Aims Its Medici Technology Towards Preventing HIV. Available at: https://www.intarcia.com/media/media-archive/press-releases/intarcia-secures-second-close-of-the-series-ee-equity-financing-.html [Accessed 21 June 2019].

Irish Department of Health. 2019. Ministers for Health Commit to Delivering a PrEP HIV Prevention Programme in the Autumn. Available at: https://health.gov.ie/blog/press-release/ministers-for-health-commit-to-delivering-a-prep-hiv-prevention-programme-in-the-autumn/ [Accessed 14 June 2019].

Ives J. 2014. A method of reflexive balancing in a pragmatic, interdisciplinary and reflexive bioethics. Bioethics 28(6): 302-312.

Jameton A. 1984. Nursing Practice: The Ethical Issues. Englewood Cliffs, NJ: Prentice-Hall.

Jecker NS, Schneiderman LJ. 1993. Medical futility: the duty not to treat. Cambridge Quarterly of Healthcare Ethics 2(2): 151-159.

Kaltwasser J. 2018. Long-Acting Injectable PrEP Shows Promise in Reducing HIV Transmision. Available at: https://www.mdmag.com/medical-news/longacting-injectable-prep-shows-promise-in-reducing-hiv-transmission [Accessed 25 October 2018].

Kant I. 2011. Groundwork of the Metaphysics of Morals: A German-English edition. Cambridge: Cambridge University Press.

Kruger J. 2015. PrEP is about HIV prevention, not good or bad behavior. WHYY. Available at: https://whyy.org/segments/choosing-prep-is-actually-about-hiv-prevention-not-good-or-bad-behavior/ [Accessed 16 June 2019].

Lepping P, Palmstierna T, Raveesh BN. 2016. Paternalism v. autonomy - are we barking up the wrong tree? British Journal of Psychiatry 209(2): 95-96.

Levine EC, Herbenick D, Martinez O, et al. 2018. Open Relationships, Nonconsensual Nonmonogamy, and Monogamy Among U.S. Adults: Findings from the 2012 National Survey of Sexual Health and Behavior. Archives of Sexual Behavior 47(5): 1439-1450.

Littman J, Viens AM. 2015. The Ethical Significance of Antimicrobial Resistance. Public Health Ethics 8(3): 209-224.

Liu AY, Vittinghoff E, von Felten P, et al. 2018. Randomized Controlled Trial of a Mobile Health Intervention to Promote Retention and Adherence to Pre-exposure Prophylaxis among Young People at Risk for Human Immunodeficiency Virus: The EPIC Study. Clinical Infectious Diseases 68(12): 2010-2017.

Mabire X, Puppo C, Morel S, et al. 2019. Pleasure and PrEP: Pleasure-Seeking Plays a Role in Prevention Choices and Could Lead to PrEP Initiation. American Journal of Men's Health 13(1): 1557988319827396.

McCormack S, Dunn DT, Desai M, et al. 2016. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet 387(10013): 53-60.

Mill JS. 2006. On Liberty and the Subjection of Women. London and New York: Penguin.

Molina J-M, Capitant C, Spire B, et al. 2015. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. New England Journal of Medicine 373: 2237-2246.

Molloy GJ, Graham H, McGuinness H. 2012. Adherence to the oral contraceptive pill: a cross-sectional survey of modifiable behavioural determinants. BMC Public Health 12: 838.

Moreau C, Bouyer J, Gilbert F, et al. 2006. Social, demographic and situational characteristics associated with inconsistent use of oral contraceptives: evidence from France. Perspectives on Sexual and Reproductive Health 38(4): 190-196.

Munro S, Lewin S, Swart T, Volmink J. 2007. A review of health behaviour theories: how useful are these for developing interventions to promote long-term medication adherence for TB and HIV/AIDS? BMC Public Health 7: 104.

Myers JE, Sepkowitz KA. 2013. A pill for HIV prevention: deja vu all over again? Clinical Infectious Diseases 56(11): 1604-1612.

National Health Executive. 2018. Welsh government agree to start PrEP trials in summer. Available at: http://www.nationalhealthexecutive.com/Health-Care-News/welsh-government-agree-to-start-prep-trials-in-summer- [Accessed 05 November 2018].

National Health Service. 2017a. HIV prevention drug could save NHS £1 billion over 80 years. NHS. Available at: https://www.nhs.uk/news/medication/hiv-prevention-drug-could-save-nhs-1-billion-over-80-years/ [Accessed 04 April 2019].

National Health Service. 2017b. Your contraception guide. Available at: https://www.nhs.uk/conditions/contraception/male-condoms/ [Accessed 30 April 2019].

National Health Service Lothian. 2018. PrEP. Available at: http://www.lothiansexualhealth.scot.nhs.uk/STIHIV/InformationOnHIV/PreP/Pages/default.aspx [Accessed 24 October 2018].

National Institute for Health and Care Excellence. 2008. Social Value Judgements: Principles for the development of NICE guidance. Available at: https://www.nice.org.uk/about/who-we-are/our-principles [Accessed 10 April 2019].

National Institute for Health and Care Excellence. 2016. Pre-exposure prophylaxis of HIV in adults at high risk: Truvada (emtricitabine/tenofovir disoproxil). Available at: https://www.nice.org.uk/advice/esnm78/resources/preexposure-prophylaxis-of-hiv-in-adults-at-high-risk-truvada-emtricitabinetenofovir-disoproxil-pdf-1502681172406981 [Accessed 22 October 2018].

National LGBTQ Task Force Action Fund. 2016. 10 Key LGBTQ Health Advocacy Issues. Available at: https://3i7oz02sfzeyh36i1zm0kttf-wpengine.netdna-ssl.com/wp-content/uploads/sites/84/2020/02/10-key-lgbtq-health-advocacy-issues.pdf [Accessed 25 October 2018].

Newcomb ME, Moran K, Feinstein BA, et al. 2018. Pre-Exposure Prophylaxis (PrEP) Use and Condomless Anal Sex: Evidence of Risk Compensation in a Cohort of Young Men Who Have Sex with Men. Journal of Acquired Immune Deficiency Syndrome 77(4): 358-364.

Nguyen V-K, Greenwald ZR, Trottier H, et al. 2018. Incidence of sexually transmitted infections before and after preexposure prophylaxis for HIV. AIDS 32(4): 523-530.

Nyamweya S, Hegedus A, Jaye A, et al. 2013. Comparing HIV-1 and HIV-2 infection: Lessons for viral immunopathogenesis. Reviews in Medical Virology 23(4): 221-240.

Office for National Statistics. 2019. Sexual orientation, UK: 2017. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/culturalidentity/sexuality/bulletins/sexualidentityuk/2017 [Accessed 11 February 2019].

Ong KJ, Desai S, Field N, et al. 2017. Economic evaluation of HIV pre-exposure prophylaxis among men-who-have-sex-with-men in England in 2016. Euro Surveillance 22(42).

Osterberg L, Blaschke T. 2005. Adherence to medication. New England Journal of Medicine 353: 487-497.

Owen G. 2015. Get free P(r)EP on the NHS - NOW. Available at: https://gregowenblog.wordpress.com/tag/clinic-hopping/ [Accessed 29 January 2019].

Potter L, Oakley D, de Leon-Wong E, Cañamar R. 1996. Measuring compliance among oral contraceptive users. Family Planning Perspectives 28(4): 154-158.

PrEP Impact Trial. 2017a. About PrEP. Available at: https://www.prepimpacttrial.org.uk/ [Accessed 01 May 2019].

PrEP Impact Trial. 2017b. About the PrEP Impact Trial. Available at: https://www.prepimpacttrial.org.uk/about-prep [Accessed 24 October 2018].

PrEP Impact Trial. 2017c. Frequently asked questions. Available at: https://www.prepimpacttrial.org.uk/faqs [Accessed 10 December 2018].

PrEP in Europe Initiative. 2017. PrEP Access in Europe. Available at: https://www.avac.org/sites/default/files/u3/PEI_Report_May2017.pdf [Accessed 22 October 2018].

Prepster. Buying PrEP online? Here's how to do it safely. Available at: https://prepster.info/buying-prep-online/ [Accessed 25 October 2018].

Public Health England. 2018. Trends in new HIV diagnoses and people receiving HIV-related care in the United Kingdom: data to the end of December 2017. London: Public Health England.

Public Health Wales. 2017. 'Preparing for PrEP?' A Review of the Current Evidence for Pre-Exposure Prophylaxis (PrEP) to prevent HIV infection in Wales. Available at: http://www.wales.nhs.uk/sitesplus/documents/888/FINAL%20%20-%20Preparing%20for%20PrEP%20Main%20Report%20March%202017.pdf [Accessed 28 October 2018].

Public Health Wales. 2018. PrEPARED in Wales. Available at: www.friskywales.org/wales-prep-project.html [Accessed 30 April 2019].

Public Health Wales HIV Expert Group. 2018. Pre-Exposure Prophylaxis (PrEP) for HIV - Service Guide. Available at: http://www.wales.nhs.uk/sitesplus/documents/888/Prep%20Wales%20Service%20Guide%20June%202018.pdf [Accessed 11 November 2018].

Richens J, Imrie J, Copas A. 2000. Condoms and seat belts: the parallels and the lessons. Lancet 355(9201): 400-403.

Rodger AJ, Cambiano V, Bruun T, et al. 2019. Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study. Lancet 393(10189): 2428-2438.

Rosenberg MJ, Waugh MS, Burnhill MS. 1998. Compliance, counseling and satisfaction with oral contraceptives: a prospective evaluation. Family Planning Perspectives 30(2): 89-92.

Ryan B. 2018. Truvada and the truth: is HIV prevention propelling the STI epidemic? The Guardian. Available at: https://www.theguardian.com/society/2018/oct/21/truvada-prep-hiv-prevention-sti-msm [Accessed 01 February 2019].

Saltzman SP, Stoddard AM, McCusker J, et al. 1987. Reliability of self-reported sexual behavior risk factors for HIV infection in homosexual men. Public Health Reports 102(6): 692-697.

Schnirring L. 2018. In world first, UK reports high-level gonorrhea resistance. Available at: http://www.cidrap.umn.edu/news-perspective/2018/03/world-first-uk-reports-high-level-gonorrhea-resistance [Accessed 14 November 2018].

Schröder-Bäck P, Duncan P, Sherlaw W, et al. 2014. Teaching seven principles for public health ethics: towards a curriculum for a short course on ethics in public health programmes. BMC Medical Ethics 15: 73.

Sexual Health Northern Ireland. 2015. Pre-exposure prophylaxis (PrEP) for HIV. Available at: https://www.sexualhealthni.info/pre-exposure-prophylaxis-prep-hiv [Accessed 25 January 2019].

Short ME, Goetzel RZ, Pei X, et al. 2009. How accurate are self-reports? Analysis of self-reported health care utilization and absence when compared with administrative data. Journal of Occupational and Environmental Medicine 51(7): 786-796.

Stolte IG, Dukers NHTM, Geskus RB, et al. 2004. Homosexual men change to risky sex when perceiving less threat of HIV/AIDS since availability of highly active antiretroviral therapy: a longitudinal study. AIDS 18(2): 303-309.

Thomas R, Galanakis C, Vézina S, et al. 2015. Adherence to Post-Exposure Prophylaxis (PEP) and Incidence of HIV Seroconversion in a Major North American Cohort. PLoS One 10(11): e0142534.

Traeger MW, Schroeder SE, Wright EJ, et al. 2018. Effects of Pre-exposure Prophylaxis for the Prevention of Human Immunodeficiency Virus Infection on Sexual Risk Behavior in Men Who Have Sex With Men: A Systematic Review and Meta-analysis. Clinical Infectious Diseases 67(5): 676-686.

Treibich C, Lépine A. 2018. Estimating misreporting in condom use and its determinants among sex workers: Evidence from the list randomisation method. Health Economics 28(1): 144-160.

Trussell J. 2004. Contraceptive failure in the United States. Contraception 70(2): 89-96.

United States Food and Drug Administration. 2004. Drug Approval Package: Truvada (Emtricitabine and Tenofovir Disoproxil Fumarate) Tablets. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021752s000_TruvadaTOC.cfm [Accessed 10 May 2019].

Umbrella. 2017. How to take Pre-exposure Prophylaxis (PrEP). Available at: https://www.uhb.nhs.uk/Downloads/pdf/PiUmbrellaPrep.pdf [Accessed 22 October 2018].

United Nations Educational, Scientific and Cultural Organization World Commission on the Ethics of Scientific Knowledge and Technology. 2005. The Precautionary Principle. Paris: United Nations Educational, Scientific and Cultural Organization.

van de Mortel TF. 2008. Faking it: social desirability response bias in self-report research. Australian Journal of Advanced Nursing 25(4): 40-48.

Varelius J. 2006. The value of autonomy in medical ethics. Medicine, Health Care and Philosophy 9(3): 377-388.

Viens AM, Littmann J. 2015. Is Antimicrobial Resistance a Slowly Emerging Disaster? Public Health Ethics 8(3): 255-265.

Weller C. 2016. Norway just became the first country to offer the leading HIV prevention drug for free. Available at: http://uk.businessinsider.com/norway-offers-hiv-drug-prep-free-2016-10 [Accessed 25 October 2018].

Welsh D. 2018. 'Bohemian Rhapsody' Premiere Crashed By Protesters With message About HIV Prevention. Available at: https://www.huffingtonpost.co.uk/entry/bohemian-rhapsody-hiv-protesters_uk_5bd0358de4b0d38b587dfddc?guccounter=1&guce_referrer_us=aHR0cHM6Ly93d3cuZ29vZ2xlLmNvbS91cmw_c2E9dCZyY3Q9aiZxPSZlc3JjPXMmc291cmNlPXdlYiZjZD0zJnZlZD0yYWhVS0V3alczYVNBaEtMZUFoV0wzS1FLSFJINkNsNFFGakFDZWdRSUNSQUImdXJsPWh0dHBzJTNBJTJGJTJGd3d3Lmh1ZmZpbmd0b25wb3N0LmNvLnVrJTJGZW50cnklMkZib2hlbWlhbi1yaGFwc29keS1oaXYtcHJvdGVzdGVyc191a181YmQwMzU4ZGU0YjBkMzhiNTg3ZGZkZGMmdXNnPUFPdlZhdzF4NVE1MVpISFR1MkZCZGJEalZCRnU&guce_referrer_cs=LuSwkEFMb5r6Ptiojoz3xA [Accessed 25 October 2018].

Wilde GJS. 1982. The Theory of Risk Homeostasis: Implications for Safety and Health. Risk Analysis 2(4): 209-225.

Wilton J. 2012. Putting a number on it: The risk from an exposure to HIV. Canadian AIDS Treatment Information Exchange. Available at: https://www.catie.ca/en/pif/summer-2012/putting-number-it-risk-exposure-hiv [Accessed 9 November 2018].

World Health Organization. 2014. Post-exposure prophylaxis to prevent HIV infection. Available at: https://www.who.int/hiv/topics/prophylaxis/info/en/ [Accessed 26 October 2018].

World Health Organization. 2016. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Available at: https://apps.who.int/iris/bitstream/handle/10665/208825/9789241549684_eng.pdf?sequence=1 [Accessed 25 October 2018].

World Health Organization. 2015. Sexual health, human rights and the law. Available at: https://apps.who.int/iris/bitstream/handle/10665/175556/9789241564984_eng.pdf?sequence=1 [Accessed 26 October 2018].

Zenilman JM, Weisman CS, Rompalo AM, et al. 1995. Condom use to prevent incident STDs: the validity of self-reported condom use. Sexually Transmitted Diseases 22(1): 15-21.