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HIV pre-exposure prophylaxis: additional insights through secondary analyses of the PROUD trial

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Declaration

I, Ellen White confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed: Date:

Use of own published work:

Part of the work presented in Chapter 2 was published in the journal of Sexually Transmitted Infections, doi:10.1136/sextrans-2018-053808. This published article is included in the appendix (Appendix 1).

Part of the work presented in Chapter 5 has been submitted to the Journal of Viral Hepatitis and the submitted version is included in the appendix (Appendix 2).

Abstract

This thesis utilises data from PROUD, a randomised controlled trial to evaluate pre-exposure prophylaxis (PrEP) for HIV prevention. PROUD randomised 544 HIV-negative men who have sex with men (MSM) to receive PrEP immediately or deferred for a year. The trial demonstrated that PrEP was highly effective at preventing HIV transmission. In this thesis, I consider four further questions: (1) Who should access PrEP? (2) How appropriate are epidemiological measures that are commonly used for PrEP and other prevention strategies? (3) Is PrEP-use associated with an increased risk of sexually transmitted infections (STIs)? and (4) What is the risk of hepatitis C (HCV) among PrEP-users?

The highest risk of HIV acquisition was associated with a rectal STI or syphilis diagnosis in the previous year, or reporting condomless receptive intercourse with two or more partners in the previous three months. MSM meeting these criteria are therefore in most need of PrEP.

STI diagnoses were more common among PrEP-users, found in both the randomised and pre-/post-PrEP comparisons. It was unclear whether this was driven by a difference in screening or sexual behaviour. Regardless, PrEP-using MSM are at high risk of STIs, and frequent screening in a PrEP programme would likely help control onward transmission.

HCV incidence was high and increased during the four-year period of follow-up, doubling in the final year. Risk varied according to reported risk factors. Thus, the current recommendation of quarterly HCV screening for all PrEP-using MSM may not be appropriate unless there is a localised epidemic.

My findings show that MSM seeking PrEP have a high but heterogeneous risk of sexually transmitted diseases, with variation according to individual- and population-level risk factors. PrEP programmes need to allocate sufficient provisions to screen for and treat other clinical outcomes, including STIs and HCV.

Impact statement

Between 2008 and 2015, the number of new HIV diagnoses among men who have sex with men (MSM) in the UK remained constant, at around 3000 per year. PROUD was a high-profile randomised controlled trial, conducted between 2012 and 2016, which showed that pre-exposure prophylaxis (PrEP) was highly effective at preventing HIV acquisition when used by MSM attending sexual health clinics in England. In 2015, a reduction in HIV diagnoses among MSM was observed, with a 17% fall overall in England and 32% in London. This was attributed to a combination of prevention efforts, including access to PrEP via PROUD and the purchase of generic PrEP online. In 2018, PrEP guidelines were released by the British HIV Association (BHIVA) and the British Association for Sexual Health and HIV (BASHH). These guidelines set out broad eligibility criteria for PrEP initiation in MSM and recommended quarterly STI screening including for hepatitis C (HCV) in this population.

My work used PROUD data to assess whether these guidelines are appropriate, by: (1) identifying who should access PrEP; (2) evaluating the risk of STIs among PrEP-users; and (3) quantifying the risk of HCV among PrEP-users. PROUD had similarly broad eligibility criteria and quarterly screening for the majority of the trial and my conclusions are likely to be applicable to the wider MSM population attending sexual health clinics.

I identified that a rectal STI or syphilis diagnosis in the previous year, or reporting condomless receptive intercourse with two or more partners in the previous three months were associated with the highest risk of HIV acquisition. This work was cited in the BHIVA/BASHH guidelines for PrEP initiation, and has been published in the Journal of Sexually Transmitted Infections. Whilst the eligibility criteria should remain broad, my work enables commissioners and service providers to more accurately target MSM most in need of PrEP.

I found that MSM using PrEP had a higher rate of STIs compared to those not on PrEP. It was unclear whether this was driven by a difference in screening or sexual behaviour.

Regardless, MSM using PrEP are at high risk of STIs. This work supports the BHIVA/BASHH recommendation for quarterly screening, and suggests to commissioners that sufficient provisions should be allocated to STI screening and treatment in a PrEP programme. Results were presented at both the European AIDS Conference and the International Clinical Trial and Methodology Conference, and have contributed to a systematic review of STI rates among PrEP-users conducted by the World Health Organization.

I showed that HCV incidence was high among PROUD participants, and increased during the trial. However, HCV risk varied according to reported risk-factors. In the absence of a HCV epidemic, targeted screening for HCV may be more appropriate than uniform quarterly screening. This work was particularly important because the HCV risk among MSM on PrEP in the UK was unknown. Therefore, from a public health perspective, my findings inform the need for HCV screening, contact tracing and treatment for MSM accessing PrEP. This work has been submitted to the Journal of Viral Hepatitis.

Acknowledgements

I would like to thank my supervisors, Professor David Dunn and Professor Sheena McCormack, for their guidance and support throughout my PhD. Thank you so much for your insightful comments and expertise. I would especially like to thank David, who has been my line manager during my time as a Statistician at the MRC CTU, and has always supported me. Thank you to the PROUD trial team, led by Sheena, for showing that anything is possible when working together in such a special team. A huge thank you to the PROUD participants, without whom the trial would not have been possible (Appendix 3).

Thank you very much to Deborah Ford and Claire Vale for providing moral and academic support, your words of encouragement meant a lot. I owe a lot to Chris J, Chris R, Claire, Debbie, Hibo, Jenna, Lizzie, Louise, Marie, and Ruth for looking over my work with a fresh pair of eyes – thank you all.

Thank you to Gilead Sciences plc. for funding my tuition fees and stipend during my PhD.

Thank you to my fellow PhD students: Alex, Andy, Hibo, Jenna, Leanne, Lizzie C, Lizzie G, Marthe, Merry, Nuru and Theodosia for their daily encouragement in and out of the office. The promise of tea, biscuits and Prosecco in the park with you all made my PhD all the more enjoyable. Thank you to Ashley, Chris and Ruth for your invaluable friendship and encouragement. In addition, thanks to my school friends (Emily, Hollie, Jade, Kat, Meg and Sophie) who remind me on a daily basis that life is too short to be worrying about work, and more about laughter.

Finally, I would like to thank my family, for their endless support in everything I do. Thank you to Rory, for always being by my side and making life all the better. Thank you to my sister, Louise, who is the most intelligent and selfless person I know. The biggest thanks goes to my Mum and Dad who encouraged me and Louise to not only search for happiness, but most importantly, to always be ourselves.

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Abbreviations

Abbreviation	Definition
Ab	Antibody
Ag	Antigen
AI	Anal intercourse
AIDS	Acquired immune deficiency syndrome
aIRR	Adjusted incidence rate ratio
ALT	Alanine transaminase
aOR	Adjusted odds ratio
ART	Antiretroviral therapy
BASHH	British Association for Sexual Health and HIV
BHIVA	British HIV Association
BIC	Bayesian information criteria
CDC	Center for Disease Control and Prevention
CI	Confidence interval
CRF	Case report form
CROI	Conference on Retroviruses and Opportunistic Infections
CT	Chlamydia
DEF	Deferred arm
DOB	Date of birth
EACS	European AIDS Clinical Society
FDA	Food and Drug Administration
FTC	Emtricitabine
GC	Gonorrhoea
GEE	Generalised estimated equation
GHB	Gamma-hydroxybutyrate
GLMM	Generalised linear mixed model
HARS	The HIV and AIDS Reporting System
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
IAI	Insertive anal intercourse
IDU	Injection drug use
IMM	Immediate arm
IQR	Interquartile range
IRR	Incidence rate ratio
Key STI	Rectal chlamydia, rectal gonorrhoea or syphilis
LTFU	Lost to follow-up
MPR	Medication possession ratio
MSM	Men who have sex with men
NA	Not applicable
NAAT	Nucleic acid amplification tests
NAT	National AIDS Trust
NBREG	Negative-binomial regression
ncAI	Anal intercourse without a condom

ncIAI	Insertive anal intercourse without a condom
ncRAI	Receptive anal intercourse without a condom
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NNT	Number needed to treat
NYC	New York City
OR	Odds ratio
p	*p*-value
PAF	Population attributable fraction
PAR	Population attributable risk
PEP	Post-exposure prophylaxis
PHE	Public Health England
PHQ-9	Patients health questionnaire
PPAI	Proportion of potential averted infections
PrEP	Pre-exposure prophylaxis
PY	Person-years
RAI	Receptive anal intercourse
RNA	Ribonucleic acid
RR	Rate ratio
RPR	Rapid plasma regain
STI	Sexually transmitted infection
TAF	Tenofovir Alafenamide
TasP	Treatment as prevention
TDF	Tenofovir Disoproxil Fumerate
TMG	Trial Management Group
TPHA	Treponema pallidum haemagglutination
UCL	University College London
UK	United Kingdom
USA	United States of America
VL	Viral load
WHO	World Health Organization
ZINB	Zero-inflated negative-binomial regression
ZIP	Zero-inflated Poisson regression

1 Background

Since the beginning of the human immunodeficiency virus (HIV) epidemic in the 1980s, men who have sex with men (MSM) have been disproportionality affected by the disease [1]. A number of socio-behavioural and biological factors have driven this, including the density of sexual networks [2]. The success of antiretroviral therapy (ART), introduced in the 1990s, has resulted in increased life expectancy, and as rates of new HIV infections arising in the UK MSM population have remained fairly constant this century, prevalence has continued to rise [3, 4].

1.1 HIV prevention strategies

A range of tools are available to reduce the likelihood of HIV transmission:

Condoms prevent HIV transmission by providing a physical barrier to prevent the transmission of bodily fluids. Condoms continue to play an important role in the prevention of HIV and other sexually transmitted infections [5].

Circumcision reduces the surface area for the virus to enter by removing the foreskin of the male penis. Voluntary medical male circumcision has been shown to reduce the risk of aquiring HIV in heterosexual men and in MSM who exclusively perform the insertive role in anal intercourse (AI) [6].

Sero-sorting/sero-positioning is the practice of choosing sexual partners, sexual position or condom-use based on their partner's HIV status [7]. For instance, an individual may only partake in condomless receptive anal intercourse (ncRAI) with a partner who they know to be HIV-negative.

Treatment of STIs may reduce HIV transmission by reducing HIV viral load shed by an individual living with HIV or by reducing the surface area or target cells for HIV acquisition in an HIV-negative individual [8].

Increase in HIV testing enables individuals to be diagnosed earlier [9]. By knowing their HIV-positive status, they are likely to adapt sexual behaviour to reduce the likelihood of transmission.

Treatment as prevention (TasP) involves providing ART to a HIV-positive individual with the intention of reducing their viral load to undetectable so that they are no longer infectious [10].

Post-exposure prophylaxis (PEP) is a method which involves taking a combination of ART for 28 days after a potential exposure to a HIV-positive source [11]. This is an emergency HIV prevention tool and should be started within 72 hours of a potential exposure in order to prevent an established infection.

Pre-exposure prophylaxis (PrEP), like PEP, this involves taking a combination of ART prior to, during and after exposure during periods of HIV risk (Section 1.2).

1.2 Oral pre-exposure prophylaxis

PrEP is a HIV prevention method, used by HIV-negative individuals, which involves taking one or two antiretroviral drugs, to prevent infection upon exposure to the virus. Truvada is the most common form of PrEP; this is a co-formulated pill containing two drugs: emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF). FTC and TDF belong to the Nucleos(t)ide reverse transcriptase inhibitors (NRTI) class of ART, and work by preventing the virus from making copies of itself through blocking the enzyme used in reverse transcription.

PrEP is most commonly prescribed as a daily pill taken during periods of high HIV risk. However, high efficacy has also been shown in MSM using an "on-demand" strategy during the IPERGAY trial (Section 1.3)[12]. This involves taking two pills 24 hours before sex, one single pill 24 hours later and another pill 48 hours after the first dose.

1.3 Summary of oral PrEP efficacy trials to end of 2016

Since 2010, there have been eight completed oral PrEP efficacy trials, three among MSM [12-14], two among women in Africa [15, 16], two among heterosexual men and women in Africa [17, 18], and one in injecting drug users in Thailand [19]. An overview of the eight oral PrEP trials identified in a review by Nugent and Gilson can be seen in Table 1.1 [20].

The first trial to report benefit in 2010, the iPrEx study, randomised 2499 MSM in four continents (North America, South America, Asia and Africa) to receive daily oral Truvada (TDF-FTC) or placebo. They demonstrated a 44% (95% CI: 15-63, p=0.005) reduction in HIV incidence. However, among a subgroup with detectable study-drug levels, the relative risk reduction in HIV infections was 92% (95% CI: 40-99) [14].

A further three studies were published in 2012, the Partner's PrEP study, FEM-PREP, and TDF2 [15, 17, 18]. The Partner's PrEP study randomised 4747 serodiscordant heterosexual couples in Kenya and Uganda to TDF, TDF-FTC or placebo. They showed efficacy of PrEP in preventing HIV, with 67% (95% CI: 44-81%, p<0.001) and 75% (95% CI: 55-87%, p<0.001) reduction for TDF and TDF-FTC compared to placebo, respectively [17]. The TDF2 study in Botswana randomised 1219 men and women to TDF-FTC or placebo and demonstrated a 62% (95% CI: 22-83%, p=0.03) reduction in HIV diagnoses [18]. The FEM-PrEP trial, aimed to estimate the efficacy of PrEP in heterosexual women. 2120 women in Kenya, South Africa, and Tanzania were randomised to daily TDF-FTC vs. placebo, however due to low adherence in this population the study failed to show efficacy (HR=0.94 [95% CI: 0.59-1.52], p=0.81). Based on the results of the iPrEx and Partner's PrEP studies, the US Food and Drug

Administration (FDA) approved daily oral TDF-FTC for use in individuals who are at high risk of acquiring HIV in July 2012 [21].

The Bangkok tenofovir study, published in 2013, randomised 2413 injection drug users to receive either TDF or placebo, resulting in a 48.9% (95% CI: 9.6-72.%, p=0.01) reduction in HIV incidence [19].

In 2015, VOICE, IPERGAY, and PROUD were published. VOICE targeted heterosexual women in Africa (South Africa, Uganda, and Zimbabwe) and randomised participants to receive one of five regimens: oral TDF; oral TDF-FTC; oral placebo; vaginal tenofovir (TFV) gel; or vaginal placebo gel. The results of this trial failed to demonstrate the efficacy of TDF-FTC (VOICE -4.4% for TDF-FTC, HR=1.04 [95% CI: 0.73-1.49]) due to low adherence, similar to FEMPrEP [15]. These results conflicted the Partner's PrEP study which showed a 75% (95% CI: 55-87) efficacy compared to placebo, and higher level of adherence [17].

The PROUD and IPERGAY trials, both in MSM, were conducted in the UK and France (and Canada) respectively, and both reported 86% effectiveness [12, 13]. PROUD randomised 544 MSM to receive either daily oral TDF-FTC immediately (IMM) or were deferred initiation for a further 12 months (DEF) (Section 1.4). IPERGAY assessed the use of an on-demand regimen, rather than daily. Participants in IPERGAY were randomised 1:1 to receive TDF-FTC or placebo and were encouraged to take two pills in the 2-24 hours before sex, one pill 24 hours after the first dose, and the fourth 24 hours later. The median number of pills taken per-month in each trial arm was 15. For both PROUD and IPERGAY, the deferred arm within PROUD, and the placebo arm in IPERGAY, were closed early (and offered PrEP) as a result of the high efficacy of PrEP and the high HIV risk in those not receiving PrEP.

Table 1.1: Overview of oral PrEP efficacy trials

Study, year	Population	Randomisation	Trial findings
iPrEx, 2010 [14]	2499 men or transgender women who have sex with men in four continents*	Daily oral TDF-FTC vs. placebo	44% (95% CI: 15-63%, p=0.005) reduction in the incidence of HIV compared to placebo
FEM-PREP, 2012 [15]	2120 women in Kenya, South Africa, Tanzania	Daily TDF-FTC vs. placebo	The HR for HIV acquisition in the TDF-FTC group compared to placebo was 0.94 (95% CI: 0.59-1.52, p=0.81)
Partners PrEP, 2012 [17]	4747 HIV-1 serodiscordant heterosexual couples in Kenya and Uganda	Daily oral TDF-FTC, TDF or placebo	67% (95% CI: 44-81%, p<0.001) reduction in TDF and 75% (95% CI: 55-87%, p<0.001) reduction in TDF-FTC compared to placebo
TDF2, 2012 [18]	1219 heterosexual men and women in Botswana	Daily TDF-FTC vs. placebo	62.2% (95% CI: 21.5-83.4%, p=0.03) reduction in HIV diagnoses in TDF-FTC compared to placebo
Bangkok tenofovir study, 2013 [19]	2413 injection drug users in Bangkok	TDF vs. placebo	48.9% (95% CI: 9.6-72.2, p=0.01) reduction in HIV incidence in TDF compared to placebo
VOICE, 2015 [16]	5029 women in South Africa, Uganda and Zimbabwe	Daily oral TDF-FTC, daily oral TDF, oral placebo, TFV vaginal gel, or vaginal gel placebo	The HR for HIV acquisition in TDF group was 1.49 (95% CI: 0.97-2.29), 1.04 (95% CI: 0.73-1.49) for TDF-FTC group, and 0.85 (95% CI: 0.61-1.21) for TFV gel group compared to placebo
PROUD, 2015 [13]	544 men or transgender women who have sex with men in England	Immediate daily oral TDF-FTC vs deferred TDF-FTC	86% (90% CI: 64-96%, p=0.0001) reduction in the incidence of HIV in IMM compared to DEF
IPERGAY, 2015 [12]	400 men who have sex with men in France and Canada	TDF-FTC vs. placebo before and after sexual activity	86% (95% CI: 40-98%, p=0.002) reduction in the incidence of HIV in TDF-FTC compared to placebo

TDF-FTC, tenofovir disproxil fumerate/emtricitabine; TDF, tenofovir disproxil fumerate; CI, confidence intervals; HIV, human immunodeficiency virus; HR, hazard ratio; *p*, p-value; TFV, tenofovir. *iPrEx recruited in Peru, Ecuador, South Africa, Brazil, Thailand and the United States

1.4 The PROUD study

1.4.1 Background

It was clear from iPrEx and the Partner's PrEP trial that PrEP was effective at preventing HIV when taken [14, 17]. But these were blinded placebo-controlled trials with monthly visits and it was very difficult to ascertain what the effect would be in real life, with no placebo, less frequent support and the knowledge that PrEP reduces HIV.

PROUD was designed as a pragmatic trial to mirror how PrEP could be used in clinic. Participants were aware of their treatment status because they were randomised to either receive the drug immediately or after a 12 month delay. The trial was carried out in sexual health clinics in England, a setting where PrEP was likely to be prescribed if commissioned, and the eligibility criteria for the trial were broad and reflected the majority of MSM attending sexual health clinics.

1.4.2 PROUD trial design

The PROUD trial was a randomised controlled trial (RCT) conducted among MSM in 13 sexual health clinics in England. Eligibility criteria specified participants were HIV-negative according to a routinely used assay, male at birth, aged 18 years or older, attended the clinic previously, and reported condomless anal sex in the three months prior to enrolment and stated it likely that this would happen again in the next three months. Participants were excluded if they had an acute viral illness possibly related to HIV seroconversion, a contraindication for TDF-FTC or were being treated for hepatitis B. Recruitment ran from November 2012 to April 2014, and participants were randomised to receive PrEP immediately (IMM) or after twelve months of follow-up (DEF), the study period referred to as the deferred phase. Study visits occurred every three months, which involved HIV and STI tests, risk reduction counselling as well as pill dispensing, and safety monitoring, with

creatinine annually for those on PrEP. Participants had an additional visit a month after initiating PrEP in order to review safety and adherence.

Based on the estimated incidence of HIV amongst MSM attending sexual health clinics, a trial of 5000 men was required to determine if PrEP would reduce HIV by 50% (with 85% power and 5% significance). Due to restricted funding, PROUD was set up as a smaller pilot study to assess the feasibility of the larger trial, with the primary outcomes recruitment and retention. However, in October 2014, the Independent Data Monitoring Committee (IDMC) met and subsequently informed the Trial Steering Committee (TSC) of the significantly increased risk of HIV infection in the DEF arm, and the highly effective reduction in HIV in the IMM arm. A joint recommendation was made to offer PrEP to all participants including those that had yet to complete one year of follow-up (*n*=163).

Every effort was made to continue the trial until PrEP was available on the NHS, but this was not possible due to lack of funding, and the last visit was in October 2016.

1.4.3 Summary of PROUD results reported in The Lancet

In February 2015, the main results from the deferred phase of the PROUD trial were presented at the annual Conference for Retroviruses and Opportunistic Infections (CROI) and later published in The Lancet in September 2015 [13].

544 MSM were randomised, with 275 in IMM and 269 in DEF. Two participants were enrolled twice (co-enrollers) and were analysed according to their original assignment (DEF arm). Although negative on a point-of-care test, three HIV infections were subsequently diagnosed at baseline (two IMM and one DEF respectively). Follow up was high, with 94% and 90% of the expected person-years of follow-up in the IMM and DEF group respectively. In the IMM arm, sufficient PrEP was prescribed to cover 88% of the days during the deferred phase. Over 243 person-years (PY) of follow-up, three infections were observed in the IMM arm, giving an incidence of 1.2 per 100 PY. Despite a large number of

PEP prescriptions (*n*=174), 20 infections occurred over 222 PY of follow up in the DEF arm, with an incidence of 9.0 per 100 PY. The effectiveness of PrEP was high, with a proportionate reduction of 86% (90% CI: 64-96). On average, 13 (90% CI: 9-23) men in a similar population would need to be treated with PrEP for a year in order to avert one additional infection (number needed to avert [prevent/delay]).

A higher proportion of the IMM arm were diagnosed with at least one bacterial STI during the deferred phase (IMM 57% vs. DEF 50%). This was attributed to the difference in the number of STI screens between trial arms (mean: IMM 4.2 vs. DEF 3.6). After adjustment for the number of screens, there was no difference in STI positivity between the trial arms for individual STIs or overall (odds ratio (OR)=1.33, adjusted odds ratio (aOR)=1.07 [90% CI: 0.78-1.46], *p*=0.74). Six hepatitis C (HCV) infections occurred during the deferred phase; three in each trial arm. For three participants, injecting drug use was the potential route of transmission.

All five participants diagnosed with a HIV infection in the IMM arm (two at baseline and three during follow-up) received a drug resistance test. Of the infections identified at enrolment or at the four week visit (one participant), two had a mutation at position 184 of the reverse transcriptase gene (M184IM, M184IVM), possibly selected due to exposure to FTC. However, there was no resistance mutations detected in the two participants acquiring HIV later on in the trial, which was expected given their non-adherence to PrEP.

At twelve months, there was no significant difference in the total number of anal sex partners between the two groups (*p*=0.57). However, there was some indication that participants in the IMM arm had a greater number of receptive anal intercourse partners without a condom (ncRAI) (*p*=0.03) compared to the DEF arm; 21% of the IMM arm reported ten or more ncRAI partners vs. 12% in the DEF arm.

In terms of safety within the IMM arm, 8% (21/275) of participants missed or interrupted PrEP due to adverse events[1] (28 distinct episodes); 13 of these were deemed to be related to Truvada. 20 of the 21 participants restarted PrEP. There were 29 serious adverse events during the deferred phase within 27 participants, but none were attributed to PrEP.

1.5 Implementation of PrEP in the UK

In September 2014, NHS England (NHSE) convened a group to gather the evidence required to inform a commissioning recommendation for a national PrEP programme (Table 1.2). After the PROUD results were presented at CROI in February 2015, the NHSE group accelerated activities, meeting monthly to assemble the evidence base to present for public consultation so that the policy could be part of the annual prioritisation exercise in June 2016. However, in March 2016, NHSE unexpectedly announced that HIV prevention was not their responsibility, but rather that of local authorities' [22, 23]. After a successful legal challenge brought by the National AIDS Trust (NAT), NHSE announced that they would fund a trial of 10,000 individuals on PrEP over 3 years (PrEP Impact trial) [24]. PrEP IMPACT was designed to assess the eligibility, uptake and duration of PrEP-use in sexual health clinic attendees in England and 2000 places were reserved for populations other than MSM. The study began recruiting in October 2017 and quickly filled the places for MSM. The sample size was revised and increased to 26000 [25].

Although there was no commissioning policy, individuals were able to purchase their own PrEP from online pharmacies and from September 2015 from NHS trusts via private prescriptions at a list price of £355.73 for 30 pills [26, 27]. At a similar time, community activists set up two websites: Prepster to raise awareness about PrEP and I Want PrEP Now

[1] An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

to facilitate individuals seeking PrEP online in some cases for prices as low as £19 per month [28, 29].

PrEP access on the NHS is different for individuals living in Scotland or Wales. Since July 2017, PrEP has been available for those MSM at risk of HIV on the NHS in Scotland [30, 31]. In Wales, PrEP has been made available via the PrEPARED project run from a number of sexual health clinics. Unlike the PrEP Impact trial, there is no cap on the numbers of participants enrolled [32].

Table 1.2: PrEP timeline in the UK (until end of 2017)

Date		Event
2004		FDA approved Truvada for treatment of HIV-positive patients [33]
2010	November	iPrEx announced results [14]
2012	July	FDA approved Truvada for pre-exposure prophylaxis [21]
	November	PROUD began recruiting [13]
2014	September	NHS England (NHSE) convened a group to scope and collate the evidence required to support commissioning of a national PrEP programme.
	October	PROUD deferred arm closed and all participants given access to PrEP [13]
2015	February	PROUD results presented at CROI [34]
	October	NHSE evidence review group meet monthly
	September	PROUD published in The Lancet [13] NHS Trust private clinic opens at 56 Dean Street [27]
	October	PrEPster and IwantPrEPNow websites launch [28, 29]
2016	March	NHSE stated that HIV prevention was not their remit and rather local authorities responsibility but would fund pilot of 500 men (£2 million) [22, 23]
	April	NAT legally challenge NHS [35]
	May	After reconsidering, NHSE confirmed their decision that PrEP was out of their remit
	August	Judicial review outcome. NHSE appeal, but also launch public consultation
	October	PROUD follow-up ends
	November	Judgement upheld: NHSE can provide PrEP [36]
	December	NHSE announce the PrEP Impact trial – 10,000 individuals to be provided with PrEP over 3 years [24]
2017	April	NHS approved provision of PrEP in Scotland [30, 31]
	April	All Wales Medicines Strategy Group announce Wales will trial PrEP [32, 37]
	June	FDA approved generic Truvada for PrEP [33]
	October	PrEP Impact started recruiting [38]

1.6 PrEP recommendations

There have been a number of published clinical guidelines for PrEP initiation (Table 1.3).

In 2016, the World Health Organization (WHO) published guidelines recommending PrEP for populations with an annual incidence of 3% or higher [39]. This cut-off aims to target populations where access to PrEP would be cost-effective, or even cost-saving. However, individual risk of acquiring HIV infection is highly heterogeneous and implementation of this recommendation, especially on a patient-by-patient basis, is not straightforward.

For MSM, the European AIDS Clinical Society (EACS) guidelines (version 9.0) focus on the inconsistent condom use with casual partners or HIV-positive partners not on treatment, regardless of sexual position [40]. The guidelines also suggest that a recent STI, PEP use or chemsex may be a marker for increased HIV risk. However, a time frame in which these have occurred is not specified.

The Center for Disease Control and Prevention (CDC) are more explicit in the time-frames for particular characteristics [41]. They recommend PrEP in MSM reporting receptive or insertive anal intercourse in the past six months in a non-monogamous partnership and/or a diagnosis of a bacterial STI in the past six months.

MSM guidelines from the British HIV Association (BHIVA) and British Association of Sexual Health and HIV (BASHH) did not focus solely on condomless sex in the past six months but also whether the individual thought it would occur again [42]. Further, guidelines state that a number of other factors should be considered in combination: bacterial STI diagnosis in the year prior; PEP use in the year prior; sexual partners of unknown HIV status; and factors relating to the injection of drugs. Among persons with HIV-positive partners, PrEP should only be considered if the viral load of the partner is detectable.

Table 1.3: PrEP guidelines for MSM

Organisation	Recommendation
WHO [39]	Populations with HIV incidence ≥3%
CDC [41]	1. Anal sex without a condom (receptive or insertive) outside of an monogamous relationship in past 6 months with a recently tested HIV-negative man 2. Diagnosed with a bacterial STI in past 6 months
BHIVA [42]	1. Reporting anal intercourse without a condom in the last six months and likely to occur again 2. HIV positive partner with detectable viral load 3. Or a combination of factors including: a. A bacterial STI in the previous year b. PEP use in the previous year c. High risk sexual behaviour with partners of unknown HIV status or high HIV risk d. High risk injection drug use
EACS [40]	1. Inconsistent condom use with casual partners 2. Inconsistent condom use with HIV-positive partners who are not on treatment 3. A recent STI, use of PEP or chemsex

WHO, World Health Organization; HIV, human immunodeficiency virus; CDC, Center for Disease Control and Prevention; STI, sexually transmitted infection; BHIVA, British HIV Association; PEP, post-exposure prophylaxis; EACs, European AIDS Clinical Society.

1.7 Clinical monitoring on PrEP within the UK

In 2018, BHIVA/BASHH updated their guidance relating to the use of PrEP [42]. Their guidance on PrEP initiation has been described in Section 1.6. The recommendations also include screening for HIV (point-of-care or antigen(Ag)/antibody(Ab) test in the four weeks prior to PrEP initiation, unless the individual has been at a particularly high risk of HIV during this period. In this case, a HIV viral load is recommended. BHIVA/BASHH recommend that STI screening should be carried out for syphilis and at each anatomical site of sexual exposure (rectal, urethral or oral), in accordance with national guidance [43]. In addition, hepatitis B (HBV) and C (HCV) screening is recommended at PrEP initiation.

Guidelines suggest a 90-day supply for the first prescription of PrEP, with a follow-up appointment four weeks later to review adherence and side effects. Daily PrEP is recommended for all populations at risk of HIV, including MSM, trans-women, and

heterosexual men and women [12, 13]. In addition, an on-demand regimen can be recommended to MSM; individuals take two tablets 2-24 hours prior to sex, a third tablet 24 hours later and fourth 24 hours after that [44].

Once the participant has initiated PrEP, regardless of dosing, the guidelines recommend quarterly follow-up visits where individuals should be screened for HIV, bacterial STIs and HCV at each visit.

Individuals are recommended to continue accessing PrEP whilst their HIV risk is ongoing.

1.8 HIV diagnoses and incidence in the UK – early signs of an impact

MSM account for half of the HIV diagnoses in the UK [45], with the number of new HIV diagnoses remaining relatively constant at around 3000 per year between 2008 and 2015 (Figure 1.1) [4]. During this period, a number of strategies were developed to reduce the number of HIV diagnoses in this and other populations. Guidelines were introduced for three-monthly HIV screens for those at high HIV risk [46]. In addition, recommendations described that individuals diagnosed with HIV, regardless of CD4 count, could access ART immediately to prevent onward transmission, regardless of CD4 count [47]. Also, PROUD participants had access to PrEP via the study [13].

In December 2016, four large London sexual health clinics reported up to a 50% reduction in new HIV diagnoses on social media [48]. In a subsequent letter to The Lancet HIV, Nwokolo et al. reported that 56 Dean Street (London's largest sexual health clinic) had seen an 80% reduction in diagnoses between October 2015 and September 2017 [49]. Nationally, Brown et al. reported that new HIV diagnoses fell by 17% overall between October 2014-September 2015 and October 2015-September 2016, and by 32% in five London clinics [50].

Reductions in diagnoses were attributed to a combination of the HIV prevention efforts described above, including PrEP [49, 50]. A later report by Public Health England (PHE) in 2018 suggested that the drop in new infections (rather than diagnoses) had been occurring since 2012 (Figure 1.2), and therefore PrEP was unlikely to have contributed [4, 51]. However, this has been debated since the number of PrEP-users in the UK is unknown [27, 49]. In contrast, a PrEP roll-out programme in New South Wales (Australia), where 90-90-90 targets were surpassed in 2016, showed a reduction of 25.1% in HIV diagnoses at the MSM population level, comparing 12 months before and 12 months after PrEP roll-out [27, 52].

Figure 1.1: HIV diagnoses by exposure group from 2017 PHE report (image redacted due to copyright)

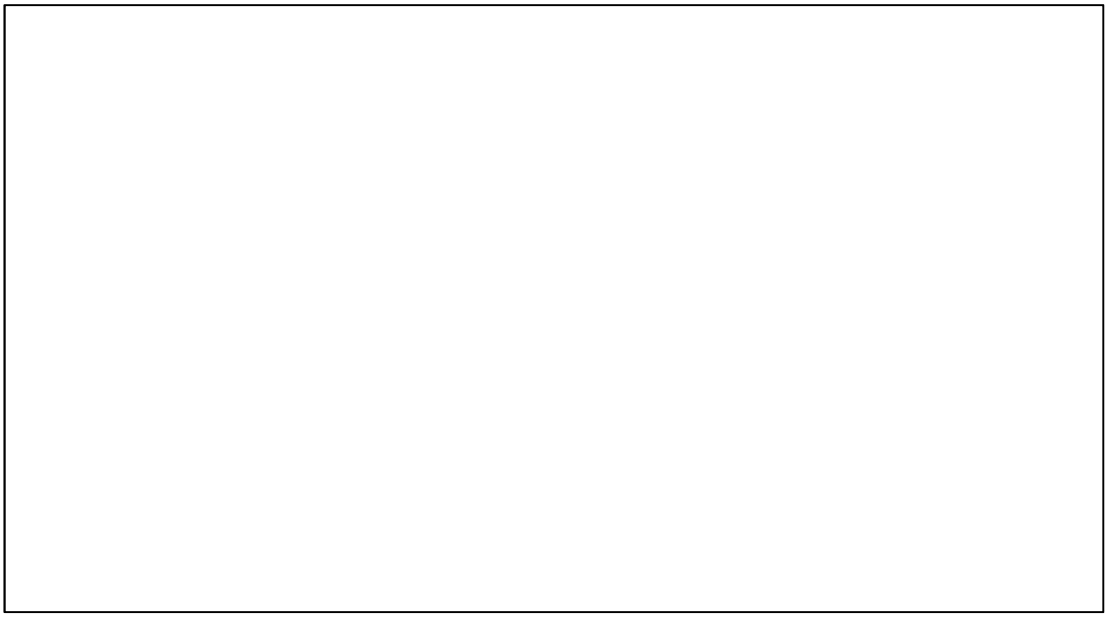


Figure footnote: *Figure from Trends in new HIV diagnoses and people receiving HIV-related care in the UK: data to end of December 2017 Health Protection Report Volume 12 Number 32 [4].*

Figure 1.2: Estimates of HIV incidence in gay and bisexual men from 2017 PHE report (image redacted due to copyright)

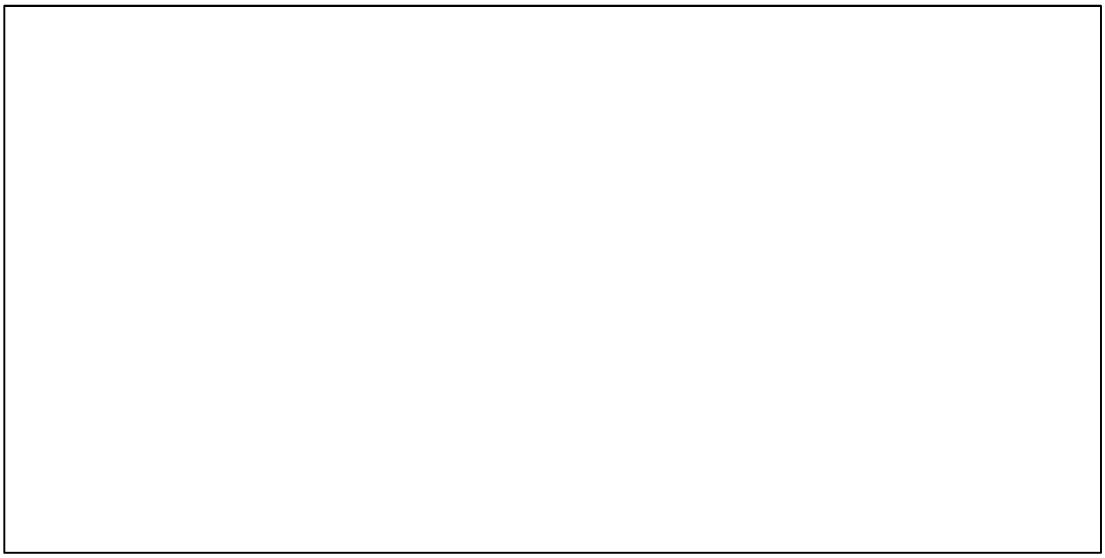


Figure footnote: *Figure from Trends in new HIV diagnoses and people receiving HIV-related care in the UK: data to end of December 2017 Health Protection Report Volume 12 Number 32 [4].*

1.9 Focus of thesis

The PROUD study was pivotal in demonstrating the high effectiveness of PrEP for preventing HIV in MSM. By performing secondary analyses, this thesis addresses a number of epidemiological and public health questions related to the use of PrEP, not explored in the primary trial results, with a focus on the methodological issues underlying these.

Given the broad PrEP criteria for initiating PrEP in MSM, and the limited PrEP availability, Chapter 2 aims to identify MSM at the highest risk of HIV. Looking at the deferred group before they had access to PrEP provides an opportunity to examine the relative importance of the recommended eligibility criteria for PrEP, identify any other risk factors and identify subgroups that are at lower risk of HIV.

A number of other HIV prevention studies have aimed to identify individuals most in need of PrEP by estimating the number needed to treat (NNT) and the population attributable fraction (PAF). Considering these, in Chapter 3, I discuss the relevance of such measures for

PrEP. I make suggestions on the calculation, presentation and interpretation of NNT and propose an alternative to PAF.

The main results of PROUD indicated that participants in the immediate group were more likely to obtain a bacterial STI diagnosis compared to those in the deferred arm. However, this difference was attributed to more frequent clinic attendance in those receiving PrEP. In Chapter 4, I present methodological considerations and challenges when analysing and interpreting these data. Given these considerations, I present a re-analysis of the deferred phase, a new analysis of the deferred and post-deferred phase comparison (when all participants had access to PrEP), and an analysis of STI incidence over calendar time. BHIVA/BASHH currently recommend quarterly STI screening for MSM accessing PrEP, and these analyses provide an opportunity to assess whether the recommended screening frequency is appropriate.

BHIVA/BASHH also currently recommend quarterly HCV screening for MSM using PrEP, however, HCV risk among PrEP-users in the UK is unknown. In March 2015, funding was acquired to screen PROUD participants quarterly for HCV and capture additional data on HCV risk factors at every visit. Using these data, in Chapter 5, I present estimates of HCV seroprevalence, incidence and risk factors of acquiring HCV to inform the frequency of HCV screening for PrEP-using MSM.

A final summary of my work is presented in Chapter 6.

2 Baseline predictors of HIV incidence among men not allocated to PrEP in the PROUD study

2.1 Introduction

An important unresolved question for PrEP programmes is eligibility. As the amount of PrEP available is generally limited, it is important that it is offered to those at the highest risk of acquiring HIV and not provided to those at negligible risk. This chapter utilises the data from PROUD to identify baseline predictors of acquiring HIV and to examine the extent to which these discriminate between individuals at low and high risk. The analysis includes data on additional HIV infections identified through matching with the national HIV database. This raises some methodological issues, particularly around censoring, which are discussed.

2.2 Background

An important issue in a PrEP rollout programme is patient eligibility since cost-effectiveness is critically dependent on HIV incidence in the target population [53, 54]. From a clinical perspective, the risk:benefit ratio of PrEP may be disadvantageous in individuals at low risk of HIV infection. For instance, there are specific concerns about renal toxicity, impact on bone density [55] and developing ART resistance in breakthrough infections [56]; however, studies have shown these are rare [57, 58].

Several organisations have issued PrEP guidelines, which include eligibility criteria for MSM (Section 1.6) [39-42]. WHO guidelines are the only to specify HIV incidence, and recommend PrEP in populations with an annual incidence greater than 3% [39]. However, individual risk of acquiring HIV infection is highly heterogeneous and implementation of this recommendation is not straightforward. Other PrEP guidelines are based on reported behaviours or clinical data [40-42]. The central criterion for MSM in all guidelines is

reported anal intercourse without a condom, although with no explicit reference to the number of partners or the position (insertive/receptive) of sex. Other criteria include the use of PEP, a recent diagnosis with a bacterial STI, and a history of sexualised drug use ("chemsex").

Uncertainty remains around the optimal eligibility criteria for PrEP, specifically whether there are subgroups at low risk of HIV for whom PrEP might not be warranted. A literature review described in this chapter found that a number of studies have considered the risk factors for the acquisition of HIV infection among cohorts (mainly of sexual health clinic attenders) in several countries (Section 2.4). Some of these aimed to inform eligibility criteria for PrEP or identify individuals at particularly high risk of infection who could potentially be targeted for other HIV prevention strategies. The wait-listed design of PROUD provides an ideal opportunity to analyse the baseline risk factors for HIV acquisition among MSM randomised to the deferred group before they had access to PrEP.

2.3 Aims

The aims of this chapter are:

1. Conduct a literature review of predictors of HIV in MSM populations (Section 2.4)
2. Describe the matching process with a national database of HIV diagnoses and consider how to incorporate censoring in analyses of HIV incidence (Section 2.5.4)
3. Examine the relative importance of the recommended eligibility criteria for PrEP, identify any other risk factors and identify subgroups that are at a lower risk of HIV (Section 2.6)
4. Explore whether STI acquisition can be used as a marker for HIV risk (Section 2.7).

2.4 Literature review: HIV predictors in MSM

This section contains a review of the literature to assess the predictors of acquiring HIV in the MSM population.

2.4.1 Study selection

I used a combination of terms to search PubMed for publications which identify predictors ("incidence", "incident", "predict*", associat*, "risk factor*") of acquiring HIV ("HIV", "human immunodeficiency virus") in MSM ("men who have sex with men", "MSM", "gay", "homosexual") (Table 2.1) [59]. The publication date was restricted between Jan 1, 2012 until Dec 31, 2017 i.e. after the year PrEP was approved by the FDA [21].

I reviewed and excluded irrelevant papers using a sequential approach: first reviewing the titles; then the remaining abstracts; and then the full text. Papers were included if the study: (1) was set in a high income country (defined as Europe [excluding Eastern Europe], North America, or Australasia); (2) was a cohort study of HIV-negative individuals; (3) reported on incident HIV infections; (4) considered predictors of HIV acquisition; or (5) included individuals who were not receiving PrEP. Cross-sectional studies and studies based on simulated data were excluded.

Table 2.1: PubMed search terms for HIV predictors in MSM

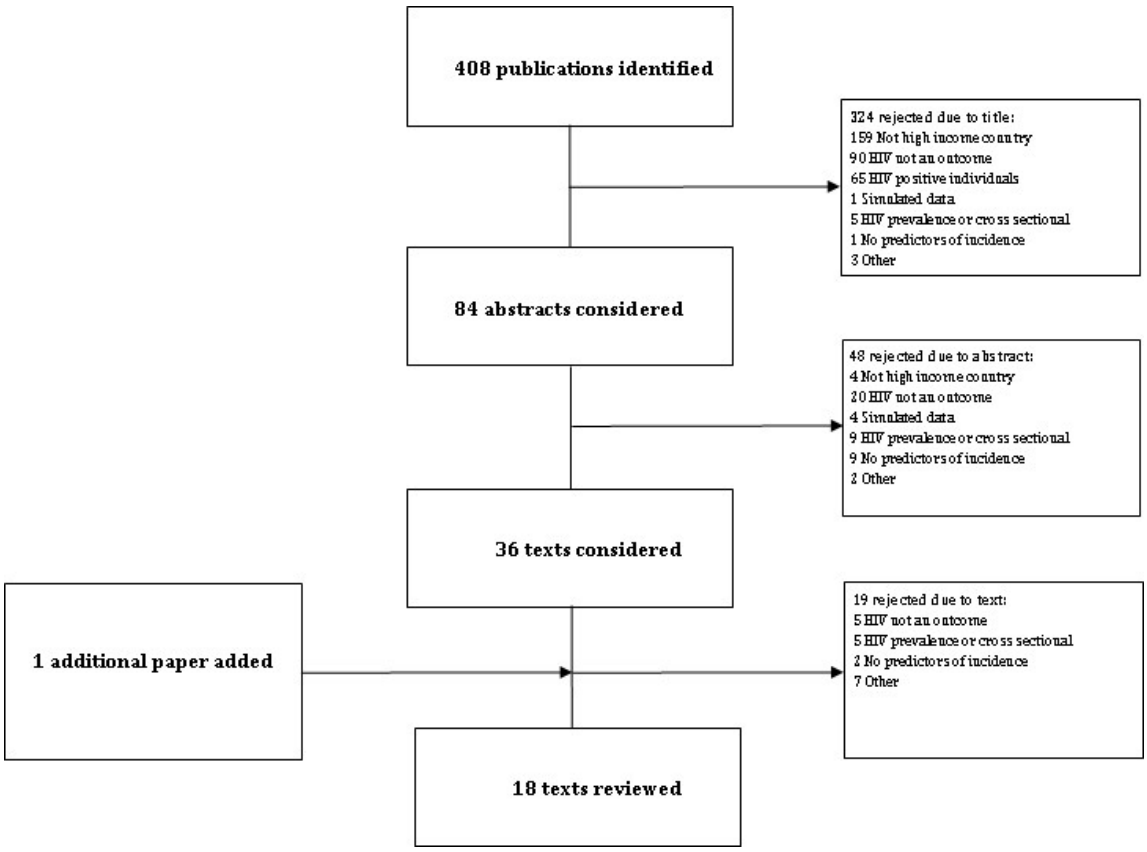
	Topic of interest	Location in paper	Search term used
1	MSM	Title	("men who have sex with men"[ti] OR "MSM"[ti] OR "gay"[ti] OR "homosexual"[ti])
2	HIV	Title	("HIV" [ti] OR "human immunodeficiency virus" [ti])
3	Predictors	Title	(incidence[ti] OR incident[ti] OR predict*[ti] OR associat*[ti] OR "risk factors"[ti] OR "risk factor"[ti])
4	Paper published since PrEP approved by FDA (2012)	Date of publication	("2012/01/01"[PDat] : "2017/12/31"[PDat])

MSM, men who have sex with men; HIV, human immunodeficiency virus; FDA, Food and Drug Administration

Search used: 1 AND 2 AND 3 AND 4

I identified 408 publications. On review of the titles, 324 were rejected, with a further 48 rejected after reviewing the abstract, and 19 rejected upon reviewing the methods section of the paper (Figure 2.1). The remaining 17 were included in the review [59-75]. An additional study, not captured by the search criteria, was included because it was particularly relevant to the aim of this chapter [76]. The iPrEx study was not entirely conducted in a resource rich setting, however, it is of particular relevance because it was also a PrEP trial with a no-PrEP arm [76].

Figure 2.1: Flow chart of selection of paper from literature review of HIV predictors



Risk factors mentioned in the 18 papers identified in the literature review, and which were also collected by PROUD at baseline, are presented in Table 2.2. Other risk factors, not collected by PROUD, are discussed in Section 2.4.4. If studies did not report confidence intervals for incidence estimates, they were calculated using the *cii* command in Stata. An association between a predictor and incident HIV infection was considered significant if the *p*-value<0.05. Although an arbitrary cut-off, this enabled a systematic approach over the studies. If a multivariable approach was used, only variables included in the multivariable

model were considered as predictors, due to the difficulty in comparing the unadjusted and adjusted effect measures.

Table 2.2: HIV predictors in MSM (selected papers published between 2012 and 2017)

Author, year	Country	HIV incidence per 100 PY (95% CI)	Total partners	ncAI	ncRAI	ncIAI	ncAI with unknown or +ve HIV statsus	STIs	Sex related drugs* or alcohol before sex	Injection drug use	PEP use	Age	Number of HIV tests	Race or place of birth	Circumcision	Employment	Education	Location	Depression
Bedoya, 2012 [60]	USA	2.1 (1.9-2.4)	---	---	---	---		---			---	---	---		---	---	---	---	
Beymer, 2016 [59]	USA	3.6 (3.1-4.2)		---			---			---	---		---		---	---	---	---	---
Beymer, 2017 [61]	USA	2.6 (1.9-3.5)		---			---			---	---		---	---	---	---	---	---	---
Buchbinder, 2014 [76]	4 continents**	3.9 (3.2-4.9)								---	---		---		---	---		---	
Cheung, 2016 [62]	Australia	1.3 (1.0-1.6)			---	---	---		---				---	---	---	---	---	---	
Desai, 2017 [63]	UK	2.0 (1.8-2.2)	---	---	---	---	---		---	---					---	---	---		
Ferrer, 2015 [64]	Spain	2.4 (1.9-2.9)			---	---				---	---				---			---	
Garofalo, 2016 [65]	USA	4.1 (2.8-6.0)			---	---				---	---				---	---		---	---
Halkitis, 2015 [66]	USA	2.8 (2.1-3.8)	---		---	---	---	---	---	---	---	---	---		---	---			---
Hoenigl, 2015 [67]	USA	2.3%(2.0-2.6)***				---					---		---		---	---	---	---	---
Irvin, 2015 [68]	USA	3.2 (2.1-4.7)	---	---		---		---	---	---	---	---	---	---	---	---	---	---	---
Jin, 2013 [69]	Australia	0.8 (0.6-1.0)	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	
Kelley, 2015 [70]	USA	3.8 (2.6-5.4)	---	---	---	---	---		---	---	---	---	---	---	---	---	---	---	---
Meireles, 2015 [71]	Portugal	2.8 (1.9-4.1)								---					---	---		---	---
Pathela, 2017 [72]	USA	2.4 (2.2-2.7)							---	---	---		---		---	---	---	---	---
Schilder, 2014 [73]	Canada	5.8%(3.3-9.2)***		---		---	---	---	---		---		---		---			---	
Smith, 2012 [74]	USA	1.3%(1.2-1.5)***		---						---	---		---	---	---	---	---	---	
Sullivan, 2015 [75]	USA	3.8 (2.6-5.4)			---	---		---	---		---		---						

HIV, human immunodeficiency virus; PY, person-years; CI, confidence intervals; ncAI, anal intercourse without a condom; ncRAI, receptive anal intercourse without a condom; ncIAI, insertive anal intercourse without a condom; STIs, sexually transmitted infections; PEP, post-exposure prophylaxis; USA, United States of America; UK, United Kingdom

*Poppers, methamphetamine or erectile dysfunction medication, ** North America, South America, Africa and Asia, ***Proportion with infection, incidence not presented.

Shaded grey indicates that the characteristic was observed as being associated with HIV, --- indicates that the characteristic was not explored as a potential HIV predictor.

2.4.2 HIV incidence

Twelve of the studies were based in North America [59-61, 65-68, 70, 72-75], two were in Australia [62, 69], and three in Europe (UK, Spain and Portugal) [63, 64, 71]. iPrEX was an exception because it was an international clinical trial based in four continents (North America, South America, Africa and Asia) [76]. HIV incidence varied widely between studies, ranging from 0.8 per 100 PY (95% CI: 0.6-1.0) to 4.1 per 100 PY (95% CI: 2.8-6.0) [65, 69]. Three studies did not report the incidence, and instead reported the percentage of participants who acquired HIV over follow-up (1.3% [95% CI: 1.2-1.5] and 2.3% [95% CI: 2.0-2.6] in USA and 5.8% [95% CI: 3.3-9.2] in Canada) [67, 73, 74].

2.4.3 Statistical methodology

The fact that different studies used different definitions of variables (e.g. STIs, number of partners etc.) and collected information over different time frames (the previous 3 months, 6 months etc.) complicates the comparison of studies (Table 2.2). For instance, Buchbinder et al. did not specify how they defined a self-reported STI [76], whereas Beymer et al. distinguished between chlamydia, gonorrhoea and syphilis [59].

17 of the 18 studies used either Poisson or Cox proportional hazard models to compare HIV risk according to reported characteristic [59-73, 75, 76], with one using propensity-score-weighted Cox regression [70]. In contrast, Smith et al. developed a risk score by fitting a logistic regression model with cumulative incidence as the outcome and scaling the coefficients to develop a scoring system [74]. Fifteen studies used multivariable analyses to account for confounding, although the factors adjusted for varied by study [59-61, 63-68, 70-74, 76]. Ten studies used time-updated techniques to account for possible changes in risk factors within individuals [60, 62, 64, 65, 67-70, 74, 75]. Two studies collected longitudinal data but combined the time-varying data into composite variables from a

number of time points [71, 72]. The remaining six studies analysed HIV risk according to factors collected at study enrolment [59, 61, 63, 66, 73, 76].

Population attributable fraction (PAF) was used in four studies to illustrate those who would most benefit from a HIV prevention strategy [62, 63, 70, 76]. Buchbinder et al. combined PAF with number needed to treat (NNT) and argued that PrEP should be focused towards populations with factors that predicted a high PAF and low NNT [76]. These epidemiological measures are discussed further in Chapter 3.

2.4.4 HIV predictors identified

Seven studies found that the recent history of an STI was associated with HIV risk [61-63, 67, 70-72]. Fourteen studies identified an association with at least one sexual behaviour: total number of partners [59, 61, 64, 72, 74]; condomless anal intercourse (ncAI) [62, 64, 71, 72, 75]; condomless receptive anal intercourse (ncRAI) [59, 61, 67, 72-74, 76]; condomless insertive anal intercourse (ncIAI)[72]; and ncAI with a HIV-positive or unknown HIV status partner [60, 64, 65, 67, 68, 71, 72, 74].

Younger age was associated with a higher HIV risk in four studies [59, 72, 74, 75]. Seven studies identified a relationship between ethnicity or place of birth and HIV acquisition; black, Asian, and minority ethnicities (BAME) or participants born in a foreign country (according to the area of study) were at a higher risk [59, 60, 64-66, 75]. Drug use, whether sex related or injecting, was found to be associated with HIV in five studies [59, 60, 62, 64, 74]. Three studies found an increased risk among participants screening more frequently for HIV [64, 65, 71]. Other studies reported an association with PEP use [62], education [73, 75] and the location of the attending clinic or residence [63, 75]. One study considered the effect of circumcision, but found no protective effect [75].

Some predictors of HIV which were not collected by PROUD at baseline were identified. Several were based on the participant's sexual partner's demographics or behaviour,

including: ethnicity of partner [59, 75]; age of partner or age difference compared to participant [59, 69, 75]; concurrency of partner [65]; and ncRAI with a partner who injects drugs [67]. Other factors relating to the participant themselves were: childhood abuse [73]; age at sexual debut [66]; intimate partner violence [61]; health insurance (or lack of) [75]; and economic status [66].

2.4.5 Summary

Analyses of risk factors for the acquisition of HIV infection among cohort studies (sexual health clinic attenders) have been conducted in several countries. Risk factors ranged between demographic, clinical, and sexual. These factors included reporting a history of STIs, ncRAI, ncAI with a partner who was HIV-positive or unknown HIV status, and being BAME or from a foreign origin. It was not possible to combine the information collected in studies because studies had used such different definitions, and therefore, it was difficult to ascertain the most important parameters.

The generalisability of these analyses is questionable for ascertaining PrEP eligibility since not all individuals within these studies would be interested in taking PrEP or knew their PrEP status (i.e. iPrEX). The wait-listed design of PROUD provides an ideal opportunity to identify risk factors for HIV in MSM seeking PrEP.

2.5 Methods

Details on PROUD eligibility and randomisation were described in Section 1.4.

2.5.1 Baseline questionnaire

At enrolment, participants self-completed a questionnaire on: demographic characteristics, including age, education, employment, country of birth, whether they had been circumcised, and relationship status; sexually transmitted infections, use of post-exposure prophylaxis

(PEP) and the number of HIV/STI screens in the previous twelve months; and sexual behaviour in the previous three months (Appendix 3). Sexual behaviour included the use of poppers and chemsex-associated drugs (defined in the footnote of Table 2.9) and the number of anal sex partners (total, receptive sex, insertive sex, receptive/insertive sex without a condom, receptive/insertive sex without a condom and partner known to be HIV-infected).

Questionnaires were sent to the Medical Research Council Clinical Trials Unit at UCL (MRC CTU at UCL) for data entry.

2.5.2 HIV testing

HIV tests were performed at each follow-up visit, which were scheduled to occur every three months, structured to mirror the frequency of sexual health clinic visits for those at high risk of HIV transmission [46]. HIV infection was defined as a reactive HIV Ag–Ab test result (confirmed by the detection of HIV RNA) in participants who were HIV-negative at enrolment.

2.5.3 Deferred phase

Originally, PrEP was planned to be offered to participants randomised to the DEF arm at the twelve month scheduled visit. However, in October 2014, based on an interim efficacy analysis, the IDMC recommended that all participants should be offered PrEP. Due to the change in protocol, the analyses comparing the HIV incidence between the two arms needed to be adapted to make the time comparable. In general terms, the deferred phase is defined as the period in which individuals randomised to the IMM group have access to PrEP and the DEF group do not. The deferred phase for each participant (including those in the IMM arm) was defined as the interval between randomisation and the first HIV test after 48

weeks or after 13 October 2014[2] at one of the PROUD clinics, whichever time point was the earliest. This time-point represents the earliest time when participants randomised to the deferred arm were able to access PrEP via the trial. The main PROUD publication was based on this definition of the deferred phase.

Loss to follow-up (LTFU) in the trial was low during the deferred phase, with HIV status defined in 89.2% (485/544) of participants [13]. However, as the trial went on, this became more of a concern, with clinics only able to confirm HIV status for 72.8% (396/544) of PROUD participants at the end of the trial[3]. We therefore performed matching with the Public Health England (PHE) national database of new HIV diagnoses (performed by Peter Kirwan), which collects information on all new diagnoses in England, Wales and Northern Ireland (and Scotland annually), to ascertain HIV diagnoses not already identified through the PROUD clinics as part of the trial procedures [77].

2.5.4 Public Health England (PHE) matching

PHE matching exercise

Matching was performed twice: the first in September 2016 and again in the following year (September 2017), using The HIV and AIDS Reporting System (HARS) dataset, which, in principle, contained complete HIV diagnoses until the end of 2015 and 2016, respectively. The data sent to PHE included: soundex[4]; initials; date of birth (DOB); clinic number; PROUD site; last date of HIV screen in PROUD; and gender. In September 2016, information was sent on participants who had not attended a PROUD study visit in the previous six months (*n*=181). In order to assess the validity of the process, information on individuals who were

[2] The date when the decision to close the deferred arm was communicated to the site Principle Investigators
[3] Defined as either HIV-positive at any point during the study or a negative test from March 2016 onwards.
[4] Soundex is a four digit string which is composed of the first letter of the surname along with three numbers based on the phonetic spelling of the surname.

known to have acquired HIV during the study were also sent (*n*=32 at this point), although the HIV-status was not indicated to PHE. In the September 2017 dataset, data were sent on all participants other than those who had tested positive during the trial and a few participants whose HIV status was inconsistent between the results obtained from the 2016 matching and information given by PROUD clinics.

Table 2.3 describes the thirty-nine matches identified between PROUD and PHE. Thirty participants matched on all identifiers and nine participants matched on three or more variables. At the time of the first matching, soundex was missing for a proportion of participants but, after querying with clinics, this was rectified for the second match. In the PROUD database, the last initial did not always correspond to the first letter of the soundex. This was presumably due to double-barrel surnames or different initial recording (e.g. Ellen Marie White as EMW or Ellen White-Holmes as EWH), as participants did not always have consistent surnames or initials across clinical records. However, this was not a concern for the PHE matching exercise as combinations of different initials and soundex were considered in the matching exercise (e.g. E W300, EH, EWH). In the event an infection was identified by PHE but unknown to PROUD, reporting clinics were asked to confirm the date of diagnosis and provide a date of their last negative test. These details were then added to the PROUD database by the team at MRC CTU.

Table 2.3: Matching identifiers for individuals acquiring HIV between PHE data and PROUD

Matching identifiers	**Number of infections**	
	Known to PROUD	**Identified by PHE**
Soundex, DOB, first initial, sex	25	5
DOB, first & last initials, sex	3	---
DOB, date of HIV test, last initial, sex	2	---
First & last initials, sex, clinic number	1	---
Soundex, month & year of birth, first initial, sex	1	---
Soundex, DOB, sex	1	---
DOB, first initial, middle initial matched to surname initial, sex	---	1

PHE, Public Health England; soundex, encoded surname; DOB, date of birth; HIV, human immunodeficiency virus

A total of 33 infections were identified through trial follow-up procedures: 11 in the IMM arm and 22 in the DEF group; three of these were reported at baseline (2 IMM and 1 DEF). Matching to the PHE database was successful for all 33 cases.

In addition, PHE identified an additional six participants who appeared to have seroconverted during the trial (3 IMM, 3 DEF). After liaising with the sexual health clinics, it was confirmed that all but one were in fact PROUD participants (2 IMM, 3 DEF) (Table 2.3). The discrepant match was based on a partial match: DOB; sex; first initial; and the middle initial matching the last initial. However, the reporting clinic was contacted by the PROUD team and stated that this was not the same participant. The second matching exercise in 2017 also identified this infection as a potential match, and was again checked and refuted by the clinic.

Assigning HIV infections to trial phase

Inclusion of PHE data complicates the definition of the deferred phase for two reasons: (1) the definition of the deferred phase was defined by the date of HIV screens (positive and negative) in the trial. Unfortunately, PHE were unable to provide a history of the participants' screening prior to diagnosis. We attempted to rectify this by asking reporting clinics to provide the date of the participants' last negative HIV screen, but clearly, this did not provide a full testing history. (2) The definition of the deferred phase was driven by the assumption that participants had access to PrEP if they received a HIV screen after week 48 or October 2014. However, given that some screens had occurred at a clinic not involved in PROUD, this was not always the case. Despite these considerations, infections identified by PHE were attributed to the deferred/post-deferred phase using the same approach as the original analysis.

A final 38 participants were thought to have acquired HIV during the course of PROUD. This meant that, according to the deferred phase definition, there was an additional infection in each arm during the randomised period compared to that reported in the main Lancet paper

(one due to a late diagnosis and one via the PHE matching), giving a total of 4 in IMM and 21 in DEF (Table 2.4) [13]. In the post-deferred phase, seven infections were identified in IMM and three in DEF. However, the analysis of predictors of incident HIV infection presented in this chapter is based on the deferred phase. HIV infections occurring during the post-deferred phase are not analysed as part of this thesis and have been presented elsewhere [78].

Table 2.4: Total HIV infections by phase and trial arm, according to PHE matching

	Total HIV infections in PROUD					
	Immediate arm			**Deferred arm**		
Phase	Total	Known to PROUD	Identified by PHE	Total	Known to PROUD	Identified by PHE
Baseline	2	2	0	1	1	0
Deferred	4	4	0	21	20	1
Post-deferred	7	5	2	3	1	2

HIV, human-immunodeficiency virus; PHE, Public Health England

Incorporating PHE matching into HIV incidence calculation

Incorporating individuals who were LTFU in the analysis is not straightforward. Incorporating only those individuals identified as positive introduces bias into the analysis because the denominator does not account for the individuals who remained HIV-negative (which is the majority). The PHE matching exercise identified additional HIV infections that are included in the numerator of estimates of HIV incidence. However, it is imperative to also inflate the denominator to account for the additional follow-up. As discussed above, this is challenging since the definition of the deferred phase is based on the assumption of access to PrEP (Section 2.5.3).

Table 2.5 and Figure 2.2 presents five different approaches for defining censoring at the end of the deferred phase for participants LTFU. The aim was to identify the strategy that avoided disproportionate weighting of those LTFU by censoring these individuals at a comparable time-point to those remaining in the trial. Considering the strengths and

limitations of each, I decided strategy 3 was the most appropriate. Therefore, in the analysis presented in Section 2.6, follow-up was censored at the first visit either when a participant was actually offered PrEP (if they remained in follow-up) or when a participant would have been offered PrEP within the trial (if they experienced early loss to follow-up).

Figure 2.2: Censoring approaches for the deferred phase for PROUD participants LTFU

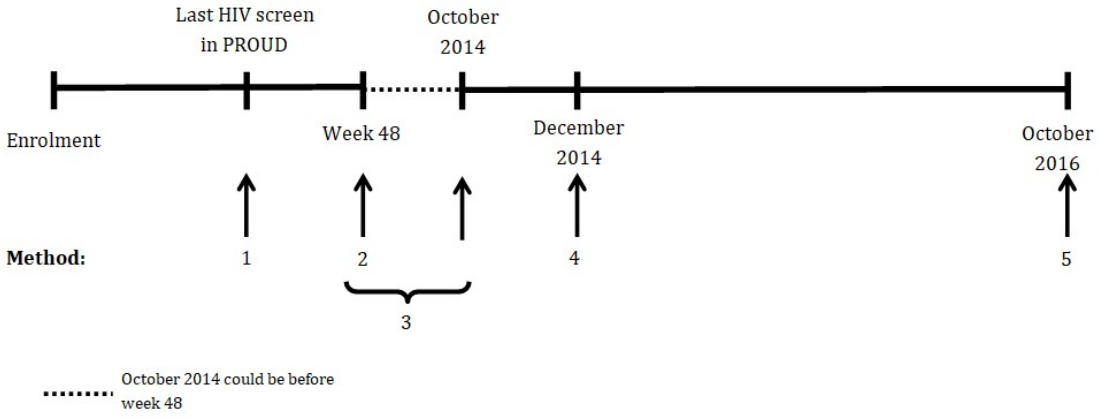
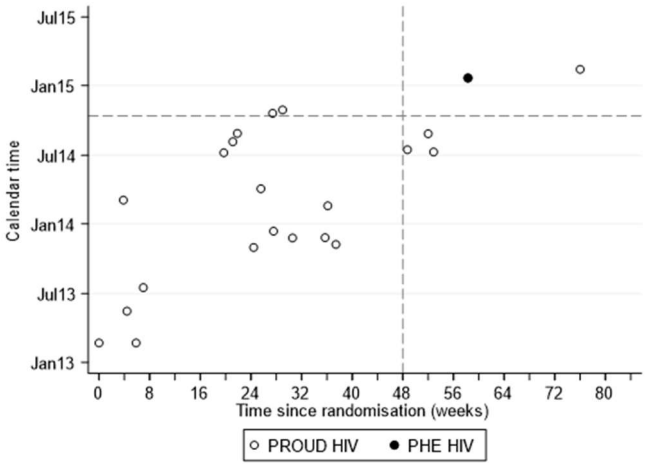


Figure 2.3 demonstrates the censoring dates during the deferred phase according to these rules. As described in Table 2.5, this illustrates the individuals LTFU and remaining HIV-negative (black crosses) are likely under-represented in the denominator because they are censored at the earliest date they could have accessed PrEP (if they had continued to attend PROUD clinic). Whereas, those returning to a PROUD clinic later than intended are likely over-represented because they are censored at the date they returned, rather than the earliest date they could have accessed PrEP.

Figure 2.3: HIV infection and censor dates identified by PROUD and PHE



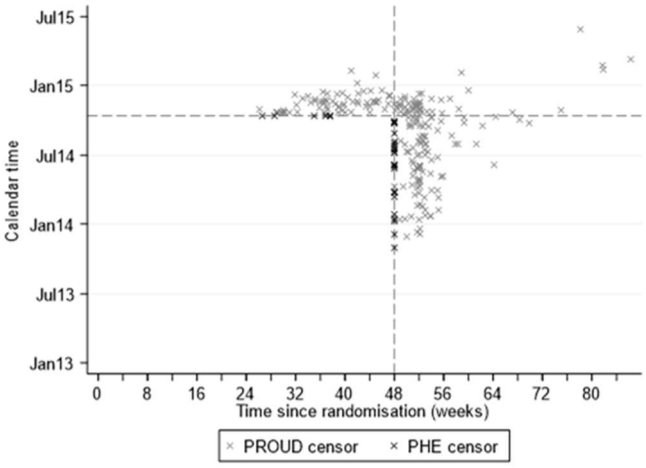


Figure legend: *Line intersecting the y-axis denotes October 2014, when all participants had access to PrEP. Line intersecting the x-axis denotes 48 weeks after randomisation.*

Table 2.5: Comparison of censoring approaches for the deferred phase for PROUD participants who were LTFU

Method	Description	Discussion
1	Censor at the last HIV test during the deferred phase	**Strengths:** -: Reflects analysis in the main Lancet paper -: Can be sure that individuals were actually in HIV prevention care and receiving HIV testing **Weaknesses:** -: Is based only on HIV testing, therefore excludes individuals who did not test for the rest of the study -: Ignores PHE matching HIV-negatives buts incorporates the positives identified, therefore incorporating bias
2	Censor at week 48 – when participants thought they were eligible for PrEP based on the information given at enrolment	**Strengths:** -: Incorporates participants who were LTFU **Weaknesses:** -: Participants could have got PrEP much earlier than week 48, therefore gives a larger weighting to participants who were LTFU
3	Censor at week 48/October 2014 – when participants were eligible for PrEP base on the changed in protocol in October 2014	**Strengths:** -: Incorporates participants who were LTFU -: Reflects the follow-up in the deferred phase for participants who continued to attend **Weaknesses:** -: Censoring at this date might be weighting the LTFU group too small as this is the earliest opportunity they could have received PrEP
4	Censor at the end of 2014 – when most participants should have attended clinic for PrEP if they wanted access	**Strengths:** -: Incorporates participants who were LTFU -: Reflects the time that it takes for participants to return to clinic for PrEP given the change in the protocol **Weaknesses:** -: Participants could have got PrEP much earlier than the end of 2014, therefore gives a larger weighting to participants who were LTFU
5	Censor at the end the trial (October 2016) for participants who did not attend clinic once eligible for PrEP	**Strengths:** -: Incorporates participants who were LTFU -: Reflects the period in which the LTFU did not have access to PrEP as they had not returned to a PROUD clinic to obtain drug **Weaknesses:** -: Censoring at this date weights the LTFU group to big as could have up to four years of follow-up -: This period does not reflect the (approximately) year long period after the participant as considered to be at high sexual risk and therefore might not be particularly useful in informing whether someone needs access to PrEP.

HIV, human immunodeficiency virus; PHE, Public Health England; PrEP, pre-exposure prophylaxis; LTFU, lost-to-follow-up.

2.5.5 Statistical analysis

Within the DEF arm, HIV incidence was compared between different subgroups according to baseline data during the period they did not have access to PrEP. For participants who acquired HIV, date of infection was taken to be the date of the first reactive test.

In addition, two participants enrolled twice in the trial (first to DEF and then to IMM). In the main analysis, their entire follow-up was assigned according to their original randomisation allocation (intention to treat); in the present analysis, their follow-up is censored on the date of second randomisation (when they were offered PrEP) [13]. For the small number of cases (n=9) where PrEP was initiated just before the end (typically, a few days) of their defined deferred phase, follow-up was censored at the date of PrEP initiation. This occurred when a participant had a HIV test just before PrEP initiation but the HIV test did not fit the criteria for deferred phase because it occurred just before week 48 or the 13th October 2014. These censoring strategies are presented in Table 2.6.

Table 2.6: Censoring method for HIV incidence analysis

Description of testing/follow-up	**Censored:**	*n*
HIV test after eligible for PrEP	Date of PrEP eligibility (first HIV test after week 48/October 2014)	205
HIV-positive during deferred phase	Date of first positive test result	21
Last HIV test before eligible for PrEP	Date of PrEP eligibility (week 48/October 2014)	19
Last HIV test at baseline	Date of PrEP eligibility (week 48/October 2014)	12
Initiated PrEP before eligible	Date of PrEP initiation	9
Co-enrollers	Date of randomisation to IMM arm	2
HIV-positive at baseline	Excluded from analysis	1
Total		**269**

n, number of participants; HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; IMM, immediate

The number of sexual partners in the three months prior to enrolment was categorised as 0, 1, 2-4, 5-9, 10-19, 20+. Grouping continuous variables in this way was deemed acceptable due to the clear rounding by participants (Section 2.6.1, Figure 2.4). HIV incidence was calculated stratified by rectal chlamydia, rectal gonorrhoea and syphilis infection in the

twelve months prior to enrolment. Rectal infections are associated with risky sex, and syphilis is associated with mixing in risky networks, usually including HIV-positive individuals. Therefore, rectal infections and syphilis may provide a useful measure of HIV risk; this is subsequently referred to as "key STI". The effects of oral and urethral infections were also considered by excluding those reporting a key STI.

For each baseline characteristic, incidence was calculated as the total number of HIV infections divided by the total person-years of follow-up. Ideally, given a very large sample, a multivariable model would be fitted to identify those subgroups at the highest risk; however, due to the small number of HIV infections during PROUD, this was not feasible. Exact Poisson models (**expoisson** command in Stata) were fitted to the data, and reference groups were chosen to be the category with the most person-years in order to have the most stable estimates of the rate ratio (RR). **midp** option in Stata was specified in order to give mid-p values and confidence intervals for RRs [79]. For ordered categorical variables, the *p*-value presented is for trend. The upper 97.5% confidence limit was presented when a category had no HIV infections. To assess whether the HIV rates changed over follow-up (due to attrition/losing the high risk individuals), a Weibull model was fitted and compared against an exponential model.

Given the small number of HIV outcomes, an additional analysis explored the use of key STI diagnosis as a proxy for HIV risk. This is described in Section 2.7.

2.6 Results

2.6.1 Participants

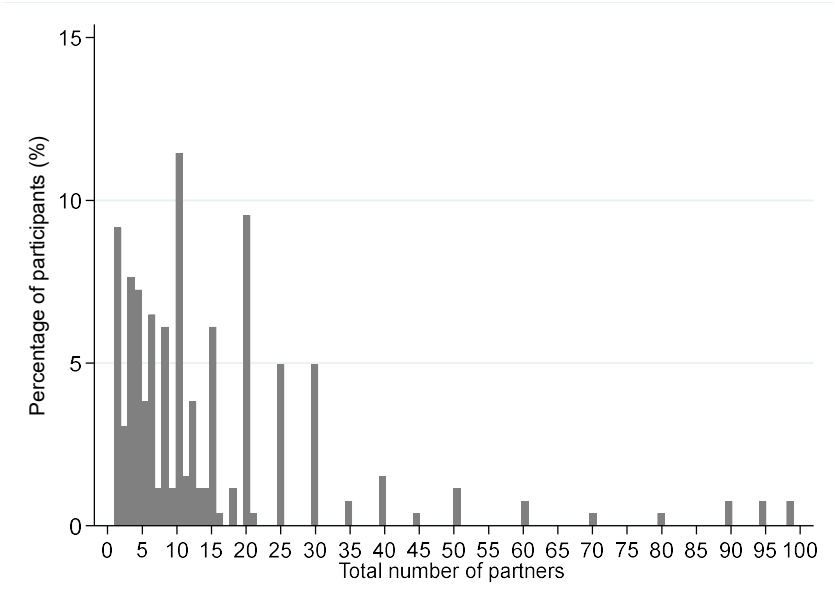
Five hundred and forty four individuals were randomised to PROUD. The deferred arm included 269 participants who were due to access PrEP after a deferral period of 12 months. 268 participants from the DEF arm were included in the analysis; one participant was

excluded from the analysis due to a reactive HIV Ag-Ab test at enrolment, despite a non-reactive point-of-care test. Baseline questionnaires were not completed by two individuals and responses were occasionally missing for some questions for others (maximum 6.3% missing, Table 2.9, footnote).

At enrolment, median age was 35 years (interquartile range (IQR): 28-41), 40.2% were born outside the UK, 69.8% were recruited through a London clinic, and 55.1% identified themselves as single (Table 2.9). In the previous twelve months, 39.5% reported they had been diagnosed with a key STI, and 36.7% had received at least one PEP prescription.

There was wide variability in the reported number of anal sex partners in the three months prior to enrolment. Participants appeared to round the number of sexual partners to multiples of 3 and 10, especially for high values (Figure 2.4). 9.2% reported a single partner, while 27.5% reported 20 or more, with a median of 10 (IQR: 4-20). A high proportion reported ncRAI, as expected in light of the inclusion criteria; 87.5% at least once and 11.7% reported 10 or more such partners. Insertive anal intercourse without a condom (ncIAI) was also common and was reported by 85.5% of participants.

Figure 2.4: Distribution of total number of sexual partners reported in three months prior to enrolment



2.6.2 HIV incidence

20 HIV infections were directly identified in the DEF arm during the deferred phase. In addition, the PHE matching exercise identified one additional HIV infection that had occurred in this group during this period (Section 2.5.4). For individuals who were LTFU, matching with PHE provided an additional 19.4 person-years of follow-up from 31 participants who were HIV-negative at the end of PROUD.

Overall, 21 participants acquired HIV infection over 239.3 person-years (PY) follow-up, yielding an incidence rate of 8.8 per 100 PY (95% CI: 5.4-13.4). Figure 2.5 illustrates the interval between the last negative and the first positive HIV test. During the relatively short period of follow-up, HIV incidence increased (shape parameter (Weibull model)=1.4 [95% CI: 0.9-2.1]), although, this change was not statistically significant (p=0.13). However, there may not have been sufficient power to detect changes, due to the low number of infections.

Figure 2.5: Time between last negative and first positive HIV tests for incident HIV infections

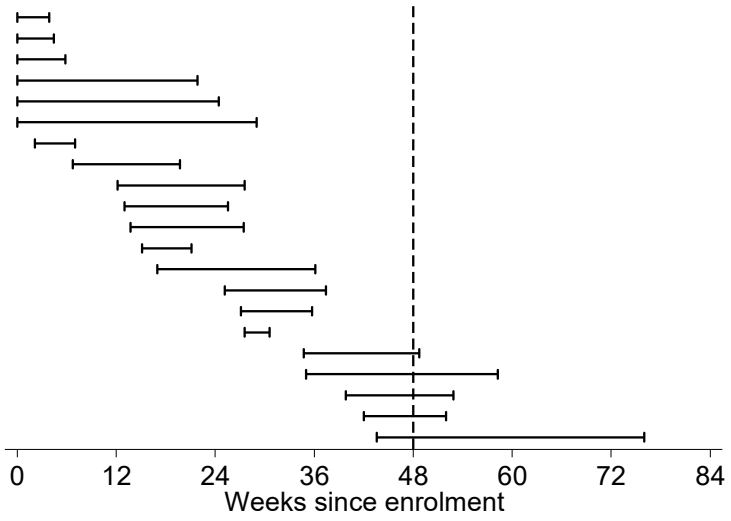


Figure legend: *Left bound for each HIV case represents last non-reactive HIV test; right bound represents first reactive HIV test. The dotted line represents time when participants in the deferred group became eligible for pre-exposure prophylaxis under the original protocol*

2.6.3 HIV risk factors: STIs and number of sexual partners

The diagnosis of a key STI in the previous 12 months was a highly significant predictor for HIV acquisition. The incidence rate in this subgroup was 17.2 per 100 PY (95% CI: 9.7-28.5), 4.8-fold higher (95% CI: 1.8-14.9) than the rate for men without such a diagnosis. Table 2.7 shows HIV incidence according to the specific STI that was diagnosed. The rate was the highest among participants reporting syphilis (HIV incidence 20.8 per 100 PY [95% CI: 6.8-48.6]), although incidence was high amongst individuals reporting any of the three key STIs. Table 2.7 also shows that HIV incidence was relatively low amongst participants reporting an oral or urethral STI (without a rectal STI), although estimates are very imprecise.

Table 2.7: Associations between STIs and HIV incidence rate

	Participants, *n*(%)	**PY**	**HIV infections, *n***	**Incidence rate (per 100 PY)**	**95% CI**
Rectal CT/GC or syphilis (key STI)	101 (39.4)	87.0	15	17.2	9.7-28.5
Syphilis	30 (11.7)	24.0	5	20.8	6.8-48.6
Rectal CT/GC	83 (32.4)	72.9	12	16.5	8.5-28.8
Rectal CT	56 (21.9)	49.8	8	16.1	6.9-31.6
Rectal GC	62 (24.2)	54.0	8	14.8	6.4-29.2
Excluding participants reporting rectal infection or syphilis					
Pharyngeal infection	25 (16.1)	23.5	0	0	0-15.7*
Urethral infection	33 (21.3)	30.6	1	3.3	0.08-18.2

n, number of participants; PY, person years; HIV, human immunodeficiency virus; CI, confidence interval; CT, chlamydia; GC, gonorrhoea STI, sexually transmitted infection;
*one-sided, 97.5% confidence interval

The other strong predictive factor was the number of self-reported anal sex partners in the previous 90 days. In general, for each type of sexual behaviour, as the number of partners increased, so did the HIV risk (Table 2.8).

Although the clearest gradient in risk was seen for the number of partners when the participant was receptive without a condom, these variables are highly correlated and therefore the effects are difficult to separate. A threshold effect was evident, with HIV risk sharply elevated for men reporting two or more ncRAI partners; HIV incidence in this subgroup was 13.6 per 100 PY (RR=4.6 [95% CI: 1.5-19.8]), compared to 2.9 per 100 PY

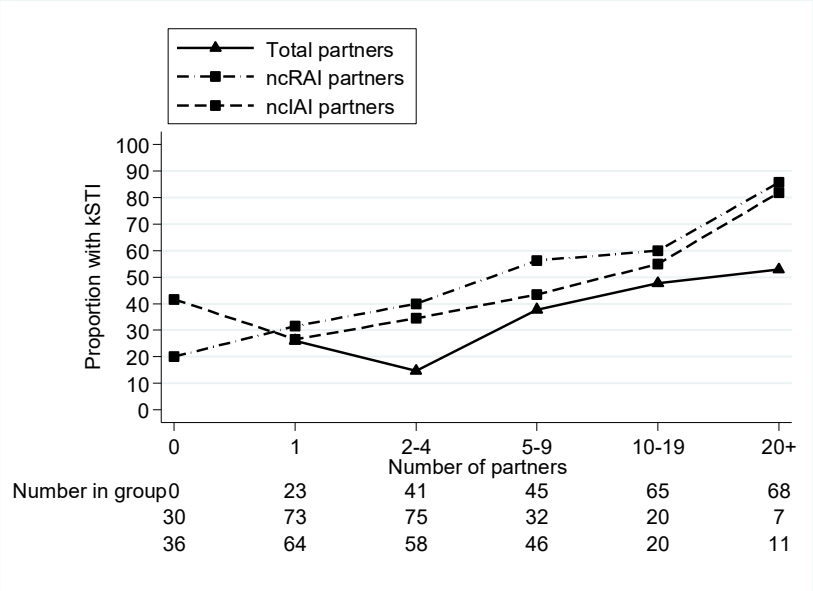
[95% CI: 0.6-8.6] for those with one or fewer ncRAI partners. 31 participants reported the only condomless sex they had was insertive, none of whom acquired HIV during follow-up (95% CI: 0-12.3 per 100 PY). Although, it is important to note that these analyses are based on small numbers.

Whilst there was a threshold effect for HIV risk in participants reporting two or more ncRAI partners, the relationship for total number of partners and ncIAI was not as clear (Table 2.8). For instance, individuals reporting only one sexual partner were at a higher risk of HIV compared to those reporting 2-4 partners (4.5 vs. 0 per 100 PYs). In addition, individuals reported zero ncIAI partners were at a higher risk compared to those reporting 1, 2-4 and 4-9 partners (10.2 vs. 4.8, 4.1 and 8.1 per 100 PY, respectively). This suggests that the relationships with HIV risk were possibly driven by other sexual behaviour, such as ncRAI.

The diagnosis of a key STI in the year prior to enrolment was closely related to the number of reported ncRAI partners, for those with 0, 1, 2-4, 5-9, and 10+ partners, 23%, 31%, 40%, 55%, and 67% reported a key STI in the previous year, respectively (Figure 2.6). In a bivariable model that included both ncRAI and key STI, the relative risk estimates for two or more ncRAI partners attenuated (RR 4.6 to 2.9) but the estimate for the diagnosis of a key STI was largely unchanged (RR 4.8 to 4.7). All but one[5] (20/21, 95%) of the HIV infections occurred among the 177 participants who reported either a key STI or ncRAI with two or more partners; the person-years observed in the group reporting either of these characteristics comprised 63.4% (151.6/239.3) of the overall follow-up. The incidence rate among participants lacking both of these risk factors was 1.1 per 100 PY (1/87.6, 95% CI: 0.02-6.4).

[5] 15 participants were missing data for the composite variable of ncRAI and key STI. Permutations of this were: ncRAI value- key-STI value (N. participants, N. participants with HIV diagnosis): N-? (4, 0), ?-N (6,1), ?-? (5, 0). Details in Appendix 5.

Figure 2.6: Relationship between number of sexual partners and key STI reported at baseline



2.6.4 HIV risk factors: other variables

There was an indication that HIV risk varied according to the number of HIV tests in the year prior to enrolment (p=0.13); participants reporting five or more HIV tests showed an increased risk compared to those reporting the recommended quarterly screening frequency (p=0.08). Non-significant trends in the expected direction were seen for other variables, including PEP use, use of chemsex drugs, the number of HIV/STI screens, and age (younger men at higher risk), Table 2.9. Participants in full-time employment were at higher risk of HIV compared to those not in full-time employment. There was no evidence of an effect of the location of the clinic (London vs. non-London), or whether the participant was born in the UK, although these are widely perceived to have an impact on HIV risk.

Participants in a relationship but who were not cohabiting were at a lower risk of HIV infection than either single men or men in a cohabiting relationship, although this difference was not significant (p=0.47 and p=0.32 respectively).

Table 2.8: HIV incidence by sexual partners at baseline

Characteristic		Participants, *n* (%)	Total PY	HIV infections	Incidence rate (per 100 PY)	95% CI	RR	95% CI	*p*-value*
Number of AI partners	1	24 (9.2)	22.3	1	4.5	0.1-24.9	0.3	0.01 -1.7	0.01
	2-4	47 (17.9)	41.7	0	0	0-8.9**	0.1	0-0.5**	
	5-9	49 (18.7)	43.8	4	9.1	2.5-23.4	0.6	0.2-1.8	
	10-19	70 (26.7)	61.7	6	9.7	3.6-21.2	0.6	0.2-1.7	
	20+	72 (27.5)	63.4	10	15.8	7.6-29.0	1.0	---	
Number of IAI partners	0	23 (8.9)	19.7	2	10.2	1.2-36.7	1.3	0.2-7.1	0.12
	1	45 (17.5)	41.4	2	4.8	0.6-17.4	0.6	0.1-3.4	
	2-4	55 (21.4)	48.6	2	4.1	0.5-14.9	0.5	0.1-2.9	
	5-9	54 (21.0)	49.6	4	8.1	2.2-20.6	1.0	---	
	10-19	45 (17.5)	37.9	5	13.2	4.3-30.8	1.6	0.4-6.8	
	20+	35 (13.6)	32.2	5	15.5	5.0-36.2	1.9	0.5-8.1	
Number of RAI partners	0	18 (7.0)	17.7	0	0	0-20.8**	0.6**	0-3.7**	0.02
	1	40 (15.5)	37.2	2	5.4	0.7-19.4	0.8	0.1-4.4	
	2-4	68 (26.4)	58.2	4	6.9	1.9-17.6	1.0	---	
	5-9	47 (18.2)	42.2	2	4.7	0.6-17.1	0.7	0.1-3.9	
	10-19	62 (24.0)	54.1	9	16.6	7.6-31.6	2.4	0.8-9.0	
	20+	23 (8.9)	20.1	3	14.9	3.1-43.6	2.2	0.4-10.5	
Number of ncIAI partners	0	37 (14.5)	32.3	3	9.3	1.9-27.2	2.9	0.4-24.3	0.03
	1	69 (27.1)	62.3	2	3.2	0.4-11.6	1.0	---	
	2-4	65 (25.5)	60.5	3	5.0	1.0-14.5	1.5	0.2-13.0	
	5-9	50 (19.6)	42.3	6	14.2	5.2-30.8	4.4	0.9-31.8	
	10+	34 (13.3)	30.0	6	20.0	7.3-43.6	6.2	1.3-44.9	
Number of ncRAI partners	0	32 (12.5)	29.8	1	3.4	0.1-18.7	1.2	0.04-16.0	0.01

Table continued on following page

	1	78 (30.5)	72.5	2	2.8	0.3-10.0	1.0	---	
	2-4	81 (31.6)	68.7	8	11.6	5.0-22.9	4.2	1.0-29.1	
	5-9	35 (13.7)	30.9	5	16.2	5.3-37.8	5.9	1.2-43.7	
	10+	30 (11.7)	25.7	4	15.6	4.2-39.9	5.7	1.0-44.1	
Number of ncIAI HIV +ve partners	0	142 (58.2)	128.0	9	7.0	3.2-13.4	1.0	---	0.04
	1	49 (20.1)	45.2	2	4.4	0.5-16.0	0.6	0.1-2.6	
	2-4	27 (11.1)	24.0	5	20.9	6.7-48.7	3.0	0.9-8.9	
	5-9	16 (6.6)	11.4	2	17.5	2.1-63.2	2.5	0.4-10.4	
	10+	10 (4.1)	9.1	2	22.0	2.7-79.4	3.1	0.5-13.1	
Number of ncRAI HIV +ve partners	0	141 (57.8)	128.1	9	7.0	3.2-13.3	1.0	---	0.03
	1	58 (23.8)	50.5	3	5.9	1.2-17.4	0.8	0.2-3.0	
	2-4	23 (9.4)	19.9	3	15.1	3.1-44.2	2.2	0.5-7.6	
	5-9	14 (5.7)	10.7	4	37.4	10.2-95.7	5.3	1.4-17.0	
	10+	8 (3.3)	7.4	1	13.4	0.3-74.8	1.9	0.1-11.6	

n, number of participants; PY, person years; HIV, human immuno-deficiency virus; CI, confidence interval; RR, rate ratio; AI, anal intercourse; IAI, insertive anal intercourse; RAI, receptive anal intercourse; ncIAI, insertive anal intercourse without a condom; ncRAI, receptive anal intercourse without a condom;

Missing data (Total, events lost due to missing exposure data) for AI (6, 0); IAI (11, 1); RAI (10, 1); ncIAI (13, 1); ncRAI (12, 1); ncIAI with HIV +ve partner (24, 1); ncRAI with HIV +ve partner (24, 1).

**p*-value for trend

**one-sided, 97.5% confidence interval

Table 2.9: HIV incidence by baseline characteristics

Characteristic		Participants, *n* (%)	Total PY	HIV infections	Incidence rate (per 100 PY)	95% CI	RR	95% CI	*p*-value*
Total		268 (100.0)	239.3	21	8.8	5.4-13.4	---	---	---
Age, years	18-24	27 (10.1)	24.6	3	12.2	2.5-35.7	1.4	0.3-4.8	0.26
	25-34	104 (38.8)	94.5	9	9.5	4.4-18.1	1.1	0.4-2.8	
	35-49	116 (43.3)	101.0	9	8.9	4.1-16.9	1.0	---	
	50+	21 (7.8)	19.1	0	0	0-19.3**	0.4	0-2.1**	
University degree	No	101 (38.0)	90.6	6	6.6	2.4-14.4	1.0	---	0.38
	Yes	165 (62.0)	146.7	15	10.2	5.7-16.9	1.5	0.6-4.3	
Full-time employment	No	68 (25.8)	63.1	3	4.8	0.9-13.9	1.0	---	0.20
	Yes	196 (74.2)	173.0	18	10.4	6.2-16.4	2.2	0.7-9.3	
Born in UK	No	107 (40.2)	91.5	9	9.3	4.3-17.7	1.0	---	0.84
	Yes	159 (59.8)	140.7	12	8.5	4.4-14.9	0.9	0.4-2.3	
Ethnicity	White	218 (82.6)	192.3	19	9.9	5.9-15.4	1.0	---	0.32
	Black, Asian and minority	46 (17.4)	42.8	2	4.7	0.6-16.9	0.5	0.07-1.8	
London site	No	81 (30.2)	71.8	6	8.4	3.1-18.2	1.0	---	0.91
	Yes	187 (69.8)	167.4	15	9.0	5.0-14.8	1.1	0.4-3.0	
Circumcised	No	185 (70.1)	166.2	17	10.2	6.0-16.4	1.0	---	0.30
	Yes	79 (29.9)	69.8	4	5.7	1.6-14.7	0.6	0.2-1.6	
Relationship status	Living with partner	73 (27.5)	66.9	6	9.0	3.3-19.5	0.9	0.3-2.3	0.32
	Not living with partner	46 (17.4)	42.1	2	4.7	0.6-17.2	0.5	0.1-1.8	
	Single	146 (55.1)	127.3	13	10.2	5.4-17.5	1.0	---	
High depression score[A]	No	233 (92.1)	205.1	19	9.3	5.6-14.5	1.0	---	0.68
	Yes	20 (7.9)	18.5	1	5.4	0.1-30.2	0.6	0.03-3.2	
No. of HIV tests[B]	0-2	91 (35.5)	82.4	5	6.1	2.0-14.2	0.7	0.2-2.1	0.13

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	3-4	122 (47.7)	106.1	9	8.5	3.9-16.1	1.0	---	
	5+	43 (16.8)	38.1	6	15.7	5.8-34.2	1.9	0.6-5.3	
Key STI[B]	No	155 (60.5)	140.4	5	3.6	1.2-8.3	1.0	---	0.001
	Rectal CT/GC or syphilis	101 (39.5)	87.0	15	17.2	9.7-28.5	4.8	1.8-14.9	
PEP use[B]	No	159 (63.3)	142.3	11	7.7	3.9-13.8	1.0	---	0.41
	Yes	92 (36.7)	80.3	9	11.2	5.1-21.3	1.4	0.6-3.6	
Number of ncRAI partners[C]	0	32 (12.5)	29.8	1	3.4	0.1-18.7	1.2	0.04-16.0	0.01
	1	78 (30.5)	72.5	2	2.8	0.3-10.0	1.0	---	
	2-4	81 (31.6)	68.7	8	11.6	5.0-22.9	4.2	1.0-29.1	
	5-9	35 (13.7)	30.9	5	16.2	5.3-37.8	5.9	1.2-43.7	
	10+	30 (11.7)	25.7	4	15.6	4.2-39.9	5.7	1.0-44.1	
Drug use associated with chemsex[C, D]	No	135 (52.3)	121.9	7	5.7	2.3-11.8	1.0	---	0.17
	Yes	123 (47.7)	108.1	12	11.1	5.7-19.4	1.9	0.8-5.2	
Poppers[C]	No	129 (50.0)	117.9	10	8.5	4.1-15.6	1.0	---	0.91
	Yes	129 (50.0)	112.1	9	8.0	3.7-15.2	0.9	0.4-2.4	

PY, person years; HIV, human immuno-deficiency virus; CI, confidence interval; RR, rate ratio; kSTI, key sexually transmitted infections (rectal chlamydia (CT), rectal gonorrhoea (GC) or syphilis); AI, anal intercourse; ncRAI, receptive anal intercourse without a condom; ncIAI, insertive anal intercourse without a condom; PEP, post exposure prophylaxis.

[A] Defined by the PHQ-9 score, high score ≥10

[B] Occurred in 12 months prior to baseline visit

[C] Occurred in the 90 days prior to baseline visit

[D] Chemsex associated drugs defined as the use of methamphetamine, GHB, mephedrone or ketamine

Missing data (Total, events lost due to missing exposure data) for education (2, 0); employment status (4, 0); born in UK (2, 0); ethnicity (4, 0); circumcised (4, 0); relationship (3, 0); depression (15, 0); No. of HIV tests (12, 1); key STI (12, 1); PEP (17, 1); ncRAI (12, 1); chemsex (10, 2); poppers (10, 2);.

*p-value for trend calculated for ordered categorical variables: ncRAI partners, AI partners, age and HIV tests. p-value for relationship status compares single vs. not living with partner. P-value for ethnicity compares white against all other categories combined.

**one-sided, 97.5% confidence interval

Quantitative variables were grouped according to clinical considerations

2.7 Using STI infection as a marker for HIV risk

The analysis in Section 2.6 demonstrated that individuals reporting a key STI in the previous twelve months and two or more ncRAI partners in the past three months were at extremely high risk of acquiring HIV. Key STIs are indicative of engaging in risky sex or in high risk sexual networks. Also, key STIs occur at a much higher rate than HIV, and, therefore, acquisition of a key STI is a possible proxy for high HIV risk (i.e. greater power). The aim in this section was to use the acquisition of a key STI to identify other markers of high HIV risk, which may not have been identified in the previous analysis.

2.7.1 Methods

Information on the number of STI screens and the number of infections since the last visit were collected using the laboratory case report forms (CRF, Appendix 6, described further in Section 4.4).

For this analysis, the outcome was defined as acquiring at least one key STI (rectal chlamydia, rectal gonorrhoea or syphilis) during the deferred phase. Individuals who acquired HIV were also defined as having an outcome. 11 participants were excluded from the analysis as they had not been screened for a key STI during this phase.

Statistical analysis

Logistic regression models were used to examine the association between baseline characteristics and key STI acquisition. A multivariable model was fitted and the covariates were selected by using a backwards stepwise selection approach, variables with a P-value>0.1 were removed from the model according to Wald tests. To avoid collinearity[6], the

[6] Collinearity was not assessed formally due to the clear intrinsic relationship between sexual partner variables, e.g. ncRAI cannot be more than total number of partners.

number of ncRAI partners was the only sexual behaviour variable considered for entry into the model because the sexual behaviour variables are highly correlated and this was the most powerful predictor of HIV risk.

2.7.2 Results

In total, there were 993 screens (in 252 participants) for key STIs during the deferred phase, with a median of four screens per participant (IQR: 2-5). 140 key STIs were reported in 94 individuals during this period. In addition, 9 individuals acquired HIV. Therefore, over the course of the deferred phase, 103 (40.1%) individuals acquired a key STI or HIV.

The multivariable analysis highlighted a number of independent characteristics associated with the acquisition of a key STI (Table 2.10). The backward stepwise selection procedure selected: ncRAI; full-time employment; chemsex-associated drug use; poppers; relationship status; born in the UK; and younger age. The odds of a key STI increased in those reporting chemsex-associated drug use (aOR=2.4 [95% CI: 1.2-4.6], p=0.01) and poppers (aOR=2.1 [95% CI: 1.1-4.0], p=0.03) in the three months before enrolment. Risk was three-fold higher in those in full-time employment (aOR=3.0 [95% CI: 1.3-7.2], p=0.01). Younger participants were at an increased risk of a key STI, with 18-24 years at a three-fold higher risk compared to 35-49 years (aOR=3.3 [95% CI: 1.0-11.0], p=0.05). Participants reporting living with their partners were at a higher risk than single individuals (aOR=2.1 [95% CI: 1.0-4.4], p=0.05).

Overall, most variables seemed to be correlated between the HIV and STI predictors analyses (Figure 2.7). Two or more ncRAI partners had a much stronger relationship with HIV compared to key STI. This is possibly the result of a cumulative effect between a high number of partners and HIV risk; as the number of partners increase, the HIV risk increases with it. Whereas key STIs are much more common and therefore the relationship with sexual partners will eventually reach a plateau. Another possibility is that due to the small number of HIV infections, one additional infection can have a significant impact on the effect estimate.

Figure 2.7: Unadjusted odds ratio from STI analysis vs. rate ratio from HIV incidence analysis by baseline characteristics

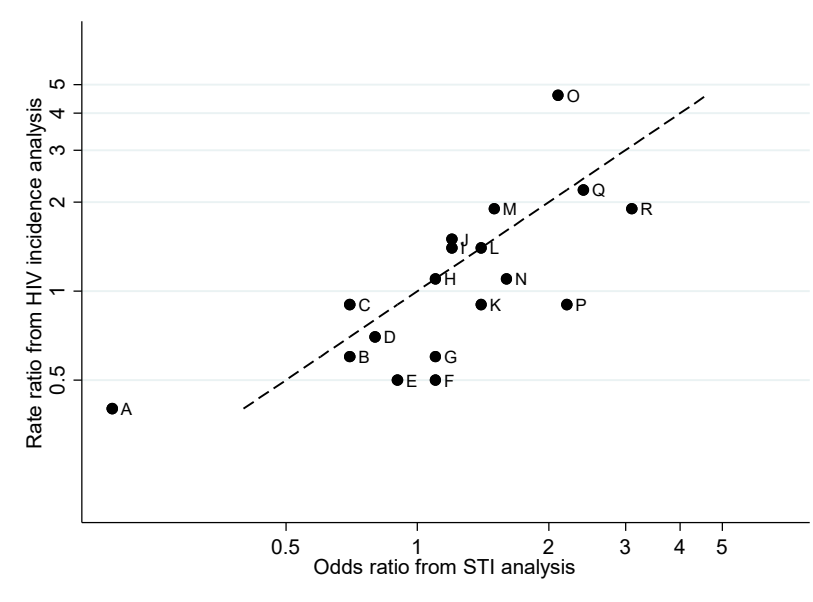

Figure legend: *A, Age, 50+; B, high depression score; C, born in UK; D, no. of HIV tests, 0-2; E, relationship status - not living with partner; F, ethnicity (BAME); G, circumcised; H, London site; I, age, 18-24; J, university degree; K, relationship status - living with partner; L, PEP use; M, no. of HIV tests, 5+; N, age, 25-34; O, ncRAI with 2 or more partners; P, poppers; Q, full-time employment; R, chemsex. Line represents rate ratio=odds ratio.*

Table 2.10: Association between baseline characteristics and diagnoses of key STI during deferred phase

Characteristic		Participants, *n* (%)	*n* (%) with key STI*	OR	95% CI	*p*-value**	aOR***	95% CI	*p*-value**
Age at randomisation, years	18-24	26 (10.1)	11 (42.3)	1.2	0.5-2.9	0.01	3.3	1.0-11.0	0.001
	25-34	99 (38.5)	48 (48.5)	1.6	0.9-2.8		2.2	1.1-4.2	
	35-49	113 (44.0)	42 (37.2)	1.0	---		1.0	---	
	50+	19 (7.4)	2 (10.5)	0.2	0.04-0.9		0.3	0.1-1.6	
University degree	No	93 (36.5)	34 (36.6)	1.0	---	0.45			
	Yes	162 (65.5)	67 (41.4)	1.2	0.7-2.1				
Full-time employment	No	66 (26.1)	17 (25.8)	1.0	---	0.007	1.0	---	0.01
	Yes	187 (73.9)	84 (44.9)	2.4	1.3-4.4		3.0	1.3-7.2	
Born in UK	No	104 (40.8)	46 (44.2)	1.0	---	0.21	1.0	---	0.07
	Yes	151 (59.2)	55 (36.4)	0.7	0.4-1.2		0.6	0.3-1.0	
Ethnicity	White	208 (82.2)	82 (39.4)	1.0	---	0.84			
	Black, Asian and other minority	45 (17.8)	17 (37.8)	1.1	0.6-2.1				
London site	No	76 (29.6)	29 (38.2)	1.0	---	0.68			
	Yes	181 (70.4)	74 (40.9)	1.1	0.6-1.9				
Circumcised	No	176 (69.6)	68 (38.6)	1.0	---	0.66			
	Yes	77 (30.4)	32 (41.6)	1.1	0.7-1.9				
Relationship status	Living with partner	70 (27.6)	32 (45.7)	1.4	0.8-2.5	0.28	2.1	1.0-4.4	0.05

Table continued on following page

	Not living with partner	44 (17.3)	16 (36.4)	0.9	0.5-1.9		0.7	0.3-1.6	
	Single	140 (55.1)	53 (37.9)	1.0	---		1.0	---	
High depression score[D]	No	223 (92.1)	89 (39.9)	1.0	---	0.48			
	Yes	19 (7.9)	6 (31.6)	0.7	0.3-1.9				
No. of HIV tests[B]	0-2	87 (35.5)	30 (34.5)	0.8	0.5-1.4	0.24			
	3-4	117 (47.8)	46 (39.3)	1.0	---				
	5+	41 (16.7)	20 (48.8)	1.5	0.4-1.0				
PEP use[B]	No	153 (63.5)	55 (36.9)	1.0	---	0.20			
	Yes	88 (36.5)	39 (44.3)	1.4	0.8-2.4				
ncRAI with 2 or more partners	No	108 (43.9)	31 (28.7)	1.0	---	0.005	1.0	---	0.007
	Yes	138 (56.1)	64 (46.4)	2.1	1.3-3.7		2.4	1.3-4.6	
Drug use associated with chemsex[A, C]	No	126 (51.0)	33 (32.4)	1.0	---	<0.001	1.0	---	0.01
	Yes	121 (49.0)	63 (50.5)	3.1	1.8-5.2		2.4	1.2-4.6	
Poppers[A]	No	122 (49.4)	36 (26.2)	1.0	---	0.003	1.0	---	0.03
	Yes	125 (50.6)	60 (52.1)	2.2	1.3-3.7		2.1	1.1-4.0	

n, number of participants; STI, sexually transmitted infections; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; UK, United Kingdom; ncRAI, receptive anal intercourse without a condom; PEP, post-exposure prophylaxis; HIV, human immunodeficiency virus.

*Note that denominator may be different to total number due to missingness of key STI and baseline characteristics

***p*-value for trend calculated for ordered categorical variables: age and HIV tests. *p*-value for relationship status compares single vs. living with partner.

***Adjusted OR presented for variables selected by backwards selection

[A]Occurred in the 90 days prior to baseline visit

[B]Occurred in 12 months prior to baseline visit

[C]chemsex defined as the use of methamphetamine, GHB, mephedrone or ketamine and assuming drug taking occurred in the context of chemsex

[D]Defined by the PHQ-9 score, high score ≥10

Table 2.11: Association between baseline sexual behaviour and diagnoses of key STI during deferred phase

Characteristic		Participants, *n*	*n* (%) with key STI	OR	95% CI	*p*-value*
Number of AI partners[A]	1	21 (8.4)	7 (33.3)	0.5	0.2-1.4	<0.001
	2-4	46 (18.3)	10 (21.7)	0.3	0.1-0.6	
	5-9	47 (18.7)	10 (21.3)	0.3	0.1-0.6	
	10-19	68 (27.1)	37 (54.4)	1.2	0.6-2.3	
	20+	69 (27.5)	35 (50.7)	1.0	---	
Number of IAI partners[A]	0	22 (8.9)	10 (45.5)	1.1	0.4-3.1	0.09
	1	42 (17.0)	12 (28.6)	0.5	0.2-1.3	
	2-4	54 (22.0)	16 (29.6)	0.6	0.3-1.3	
	5-9	52 (21.1)	22 (42.3)	1.0	---	
	10-19	44 (17.9)	20 (45.5)	1.1	0.5-2.6	
	20+	32 (13.0)	16 (50.0)	1.4	0.6-3.3	
Number of RAI partners[A]	0	18 (7.3)	2 (11.1)	0.3	0.1-1.2	<0.001
	1	38 (15.3)	9 (23.7)	0.6	0.3-1.6	
	2-4	64 (25.8)	21 (32.8)	1.0	---	
	5-9	46 (18.5)	18 (39.1)	1.3	0.6-2.9	
	10-19	61 (24.6)	37 (60.7)	3.2	1.5-6.6	
	20+	21 (8.5)	10 (47.6)	1.9	0.7-5.1	
Number of ncIAI partners[A]	0	36 (14.8)	18 (50.0)	2.3	1.0-5.3	0.68
	1	66 (27.1)	20 (30.3)	1.0	---	
	2-4	63(25.8)	22 (34.9)	1.2	0.6-2.6	
	5-9	48 (19.7)	21 (43.8)	1.8	0.8-3.9	

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	10+	31 (12.7)	14 (45.2)	1.9	0.8-4.6	
Number of ncRAI partners[A]	0	31 (12.6)	8 (25.8)	0.8	0.3-2.1	0.003
	1	77 (31.3)	23 (29.9)	1.0	---	
	2-4	76 (30.9)	32 (42.1)	1.7	0.9-3.3	
	5-9	35 (14.2)	17 (48.6)	2.2	1.0-5.1	
	10+	27 (11.0)	15 (55.6)	2.9	1.1-6.9	
Number of ncIAI HIV +ve partners[A]	0	137 (58.6)	50 (36.5)	1.0	---	0.16
	1	47 (20.1)	15 (31.9)	0.8	0.4-1.7	
	2-4	26 (11.1)	11 (42.3)	1.3	0.5-3.0	
	5-9	16 (6.8)	6 (37.5)	1.0	0.4-3.0	
	10+	8 (3.4)	6 (75.0)	5.2	1.0-26.8	
Number of ncRAI HIV +ve partners[A]	0	138 (59.0)	51 (37.0)	1.0	---	0.07
	1	55 (23.5)	13 (23.6)	0.5	0.3-1.1	
	2-4	21 (9.0)	12 (57.1)	2.3	0.9-5.8	
	5-9	13 (5.6)	9 (69.2)	3.8	1.1-13.1	
	10+	7 (3.0)	3 (42.9)	1.3	0.3-5.9	

PY, person years; HIV, human immuno-deficiency virus; CI, confidence interval; RR, rate ratio; AI, anal intercourse; IAI, insertive anal intercourse; RAI, receptive anal intercourse; ncIAI, insertive anal intercourse without a condom; ncRAI, receptive anal intercourse without a condom

[A]Occurred in the 90 days prior to baseline visit
*p-value for trend
*one-sided, 97.5% confidence interval

2.8 Discussion

2.8.1 Key findings

- Matching with the national database of HIV diagnoses enhanced the analysis of HIV incidence
- MSM seeking PrEP are at high risk of acquiring HIV
- Highest HIV risk was amongst MSM reporting a rectal STI or syphilis diagnosis in the previous twelve months, or reporting condomless receptive anal intercourse with two or more partners in the past three months
- Participants reporting neither of these risk factors were at substantially lower risk of HIV
- Other baseline characteristics, such as: full-time employment; chemsex; poppers; living with partner; born in the UK; and, younger age, were associated with the risk of acquiring a key STI, and are likely associated with a higher risk of HIV.

2.8.2 Findings in relation to other literature

The most powerful individual predictor of HIV infection in PROUD was the diagnosis of syphilis or a bacterial rectal infection (chlamydia or gonorrhoea) in the previous twelve months; HIV incidence was 17.2 per 100 PY in this subpopulation. A recent analysis (2017) of MSM who were repeat attenders at sexual health clinics in England identified similar factors but the strength of the association was weaker and the proportion of infections associated with STI diagnosis was much smaller [63]. A secondary analysis of the iPrEx trial examined predictors of HIV infection in the placebo arm [76]. The only STI variable reported was whether an infection had been reported in the previous 6 months, irrespective of the type or site of infection. This lack of specificity may explain the small difference in HIV

infection incidence between participants with (4.9 per 100 PY) and without (3.6 per 100 PY) an STI report. Conversely, the strong effect in PROUD may be partly due to the regularity of STI screening in sexual health clinics in the UK, with participants receiving a median of 3 screens in the year prior to enrolment. Of note, oral and urethral STIs were not associated with an increased HIV risk, suggesting that the selection of variables to include in risk algorithms should focus on rectal infections and early syphilis.

The number of sexual partners in the previous three months was also an important predictive variable, particularly the number of ncRAI partners. Participants with fewer than two ncRAI partners were at a comparatively low risk of HIV infection (2.9 per 100 PY), although still above the WHO threshold of "substantial" risk [39]. This risk fell further below this threshold when combined with the absence of a key STI diagnosis, suggesting that this subgroup should be a lower priority for PrEP (i.e. one or fewer ncRAI partners in previous three months *and* no key STI diagnosed in previous 12 months). Assuming 100% PrEP efficacy, by providing PrEP only to those individuals reporting either a key STI or ncRAI with two or more partners (63% of the person-years), 95% of incident HIV infections could have been prevented. Of interest was the low risk identified in men who engage exclusively in insertive anal intercourse when not using a condom, consistent with findings in the iPrEx study [76]. Current guidelines focus solely on condomless sex, and do not differentiate between the risk of receptive and insertive intercourse [40-42]. However, individual clinical decisions should take into account current risk behaviours as well as historical and anticipated ones. The definition of "historical" is also not standardised across guidelines, one referring to the previous six months, one referring to 12 months, and another not specifying a time frame at all [40-42].

Analyses of risk factors for the acquisition of HIV infection among MSM have been conducted in multiple studies [59-76]. More recent analyses have been motivated by a desire to inform eligibility criteria for PrEP or to identify individuals at particularly high risk

who could potentially be targeted with other HIV prevention strategies [76]. Predictors of HIV and key STI (as a proxy for HIV) presented in this chapter were demographic (age, employment status, relationship status), clinical (STIs), and behavioural (number of sexual partners, chemsex associated drugs and popper-use). These findings were consistent with the predictors identified in the literature (Section 2.4).

2.8.3 Strengths and limitations

A number of studies have aimed to identify the risk factors of HIV acquisition (Section 2.4), but only one of these, a blinded placebo-controlled trial, has considered the risk factors among MSM willing to take PrEP [76]. The unique feature of the secondary analysis of PROUD presented in this chapter was the known PrEP status among MSM who were either actively seeking PrEP or had accepted a clinical recommendation from their clinician. This is both a strength and a limitation. The strength being that conclusions reached in this analysis are directly applicable to MSM willing to take PrEP. A limitation, however, is that caution is needed when using these conclusions to identify MSM for which PrEP should be offered in the first place (a step prior to that observed in PROUD).

HIV incidence among PROUD participants with no access to PrEP was four-fold higher than that of MSM repeatedly attending sexual health clinics in the UK [13, 63]. This is likely to represent an enrichment phenomenon whereby self-awareness of a high risk of acquiring HIV infection motivates individuals to seek PrEP. While the very high HIV incidence in PROUD raises the question of generalisability to other lower-risk settings, this concern applies more to the quantitative estimates than to the findings in general, which should be broadly applicable. However, this raises concerns about whether the results of population-based prediction models of HIV incidence can be validly applied in the context of PrEP eligibility [53, 54].

Data collected from PROUD participants at baseline, especially the anatomical site of STIs or position of anal intercourse, enabled the estimation of HIV risk associated with these characteristics. Given that the current PrEP initiation guidelines (2018) do not focus on the position of condomless sex (receptive or insertive) or the anatomical site of STIs, this was particularly advantageous in determining the MSM most in need of PrEP [42]. If STI diagnoses in the UK continue to increase, and HIV incidence continues to decrease, bacterial STIs will become less of a marker of those at the highest risk of HIV [80]. Therefore, future guidelines may need to be refined to target PrEP at MSM with a rectal STI or syphilis, rather than a bacterial STI at any anatomical site.

Matching to the national database of HIV diagnoses provided extra information on the HIV status of the participants. This provided an additional five infections which were unknown to PROUD. Given the high success rate in identifying the HIV diagnoses in those known to the trial team, we can be confident in the matching process to identify diagnoses which occurred in the UK. However, there is a potential to miss infections which have been diagnosed outside of the country. The matching exercise has further benefits for assessing the long-term effectiveness of PrEP (not included in PhD thesis).

Several publications conducted time-updated analyses accounting for change in sexual behaviour in addition to other risk factors [72, 81, 82], it was decided that was not necessarily the best approach to take here. The objective in this chapter was to identify high-risk characteristics of HIV at the time PrEP could have been initiated. By including time-updated variables, the focus shifts towards how the current risk factors affects current HIV risk rather than how the risk factors observed at the initial visit predicts future HIV risk. This is not to negate the value of time-updated analyses, however, which could usefully inform decisions on whether to stop or discontinue PrEP.

The main limitation of this analysis is the low number of incident HIV infections, but this was unavoidable due to the size of the trial. The consequences are two-fold: imprecise

estimates of HIV incidence; and an inability to undertake multivariable analyses to develop a risk algorithm, such as the one developed by Smith et al. [74]. The lack of a multivariable analysis precluded a formal analysis to identify subgroups at low risk of HIV infection, which was one of the objectives of this chapter. A non-parametric method proposed by Poynton et al. described a useful method which allowed characteristics to be ranked according to HIV risk; I consider this approach in Section 3.4.5 [82]. Although PrEP was not available through the NHS during the study period, some participants in the deferred arm may have accessed it through other means. PEP use was also common with 174 courses prescribed to 85 participants during the study period, which could have further reduced the estimated incidence [13].

I attempted to rectify the low number of HIV outcomes by using the diagnosis of a key STI (rectal STIs or syphilis) as a proxy for HIV risk. This had the benefit of a much greater statistical power than the direct analysis of HIV itself. This approach was useful because it could be used to identify risk factors of engaging in risky sex or in a high-risk sexual network. However, the binary approach did not discriminate between those with a single or multiple key STIs, and therefore it does not necessarily identify those characteristics at the highest risk. Appropriate methods for this type of analysis are explored further in Section 4.6.5.

2.8.4 Conclusion

In conclusion, the high HIV incidence in PROUD suggests that participants appropriately judged their risk of acquiring HIV and the benefits of PrEP. Eligibility criteria for a PrEP programme following PROUD can therefore be broad for MSM, as in the current guidelines. In this analysis, a recent history of syphilis, rectal chlamydia/gonorrhoea or two or more ncRAI partners indicated a high imminent risk of HIV infection, and HIV-negative MSM with any of these characteristics should be offered PrEP as a matter of urgency.

However, the risk of acquiring HIV is declining in some settings due to increased PrEP coverage, an increase in HIV testing, and rapid treatment after an HIV diagnosis [50, 52]. This complicates this judgement and may change the predictive value of individual risk factors. In particular, there could be a possible further reduction in the already low risk for those reporting only one ncRAI partner. It will be important to continue to review the need for PrEP in this and other groups.

3 Critique of epidemiological measures used in PrEP research

3.1 Introduction

PrEP trials and HIV prevention studies commonly report the number needed to treat (NNT) and the population attributable fraction (PAF). For instance, PROUD reported NNT to estimate the number of individuals who would need to access PrEP in order to avert one additional HIV infection [13]. A secondary analysis of the iPrEX trial used NNT and PAF to identify characteristics of individuals who would most benefit from PrEP [76]. In this chapter, I discuss whether NNT and PAF are relevant measures in the field of PrEP research.

3.2 Aims

The aims of this chapter are:

1. Make suggestions on the calculation, presentation and interpretation of NNT for PrEP trials (Section 3.3)
2. Critique the use of PAF in the context of determining eligibility criteria for PrEP and propose an alternative approach (Section 3.4)
3. Explore the use of a stepwise procedure to identify a subgroup at high risk of HIV based on multiple risk factors (Section 3.4.5. proposed by Poynten et al. [82])

3.3 Number needed to treat (NNT) in PrEP trials

3.3.1 Background

In 1988, Laupacis introduced the NNT, the average number of people that need to be treated with a particular treatment in order to prevent one additional outcome of interest [83]. Laupacis calculated NNT as the reciprocal of the absolute risk difference between two groups (or trial arms). Cook stated that NNT combines the statistical and clinical significance to the care provider [84]. Whilst Cook and Sackett have advocated the use of NNT, Hutton has been strongly critical of this measure, stating that due to its more favourable statistical properties, the absolute risk difference is a better measure [84-86]. Hutton's critique focused on the disjoint nature of confidence intervals for NNT when a treatment was ineffective. This is less of a concern for PrEP, which has shown to be highly effective.

In 2001, despite these concerns, the Consolidated Standards of Reporting Trials (CONSORT) guidelines recommended NNT for both binary and time-to-event outcomes [87]. NNT was primarily developed for trials with a binary outcome. However, NNT calculations are not as simple in the context of time-to-event (survival) outcomes (unless all patients are followed for the same amount of time) and requires careful consideration [88]. The literature provides conflicting recommendations for calculating NNT when follow-up time varies [89-92]. In a literature review by Hildebrandt et al., of the 34 studies reporting time-to-event outcomes, only 17 (50%) used an "appropriate" method to calculate the NNT [88], although others have argued that this is dependent on the disease area (i.e. chronic vs. acute) and treatment length (i.e. continuous vs. short fixed duration) [91, 92].

A number of PrEP studies have reported NNT [13, 44, 76, 93], i.e. how many individuals need to be provided with PrEP to avert one additional HIV infection (compared to

prevention standard of care)? The iPrEx trial reported an NNT value of 62 (95% CI: 44-147) [76]. The later PROUD and IPERGAY studies reported a much lower NNT: 13 (90% CI: 9-23) and 18 (95% CI: 15-38) respectively [13, 44].

In the drafting of the main PROUD manuscript there was considerable discussion around the wording to describe the NNT. The final paper stated that it "derived the number-needed-to-treat to directly avert (prevent or delay)" and "13 men (90% CI: 9–23) in a similar population would need access to 1 year of PrEP to avert one HIV infection" [13]. An initial idea to use the term "prevent" was questioned since some participants could acquire HIV later in time, and "avert" was considered to be a reasonable compromise. Also, the PROUD cohort had a much higher HIV risk than the general population, calling the generalisability of NNT into question. Hence, the addition of the term "in a similar population".

In the remainder of this section, I present different methods which have been used to calculate NNT in time-to-event outcomes (Section 3.3.2). I then discuss the interpretation of these methods and the relevance for PrEP (Section 3.3.3). I describe how NNT estimated in a PrEP trial can be applied to the general population at different risk to the trial population (Section 3.3.5). Finally, I discuss the indirect effect of PrEP on onward HIV transmissions (Section 3.3.6).

3.3.2 Calculation of NNT in time-to-event analyses

Several methods have been described to calculate NNT from individual patient data (IPD) or aggregate measures reported in published articles [88-91, 94-97]. In addition to these, I propose a method to incorporate the adherence/use of PrEP into the calculation of NNT. Methods are illustrated using a simple two-armed PrEP trial where participants are randomised to a PrEP or no-PrEP arm and where the outcome is acquiring HIV. Subscripts 0 and 1 denote the no-PrEP and PrEP groups, respectively.

Binary approach

One naïve approach considers the proportion of participants who acquire HIV by time t (regardless of the amount of follow-up participants have, and ignores loss-to-follow-up):

$$NNT_{RD}(\mathrm{t}) = \frac{1}{\pi_0 - \pi_1} \quad (1)$$

where π is the proportion of HIV infections acquired by time t .

The valid use of a binary approach for time-to-event outcomes is limited to acute conditions which are treated for a pre-determined duration [91]. However, this does not apply to PrEP, and therefore this approach will not be considered further.

Survival function

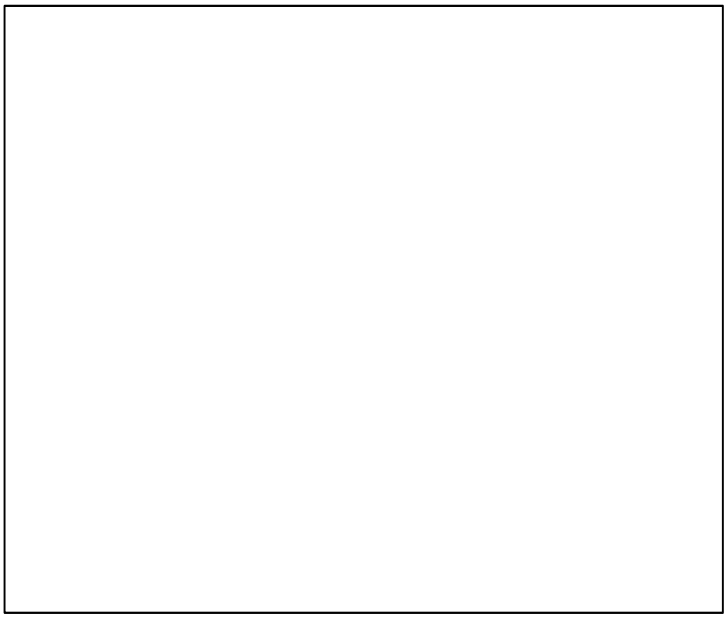
Altman et al. proposed the survival difference approach [96]:

$$NNT_S(t) = \frac{1}{S_1(t) - S_0(t)} \quad (2)$$

where S(t) is the estimated survival function for the proportion remaining HIV-negative by time t.

In contrast to the previous method, this approach takes account of the amount of follow-up per individual and censors at the end of the follow-up [89, 90, 94, 98]. This measure is time dependent and should be reported with a measure of time, for instance, $NNT_{6\ months}$ or $NNT_{1\ year}$. Altman suggested that NNT_S should be plotted as a continuous function of time rather than calculated at one arbitrary time point (Figure 3.1) [96]. The survival functions are generally estimated using the Kaplan-Meier method, which avoids the need for any parametric assumptions [99].

Figure 3.1: Altman et al. demonstrating the use of a figure to present NNT over time (image redacted due to copyright)



$NNT_S(t)$ can be calculated from a published article if the survival functions for each trial arm are presented. In the unlikely event that the article presents the hazard ratio (HR) and survival function for the control arm (but not the experimental arm), the following formula can be used [96]:

$$NNT_{S\mathrm{H}}(t) = \frac{1}{S_0(t)^{HR} - S_0(t)} \quad (3)$$

The iPrEx study estimated $NNT_S(t)$ by using the relationship between the Poisson and exponential distribution to relate the incidence rate and cumulative incidence [76]:

$$NNT_{S\mathrm{I}}(t) = \frac{1}{exp(-\lambda_1 t) - exp(-\lambda_0 t)} \quad (4)$$

where λ is the incidence rate of HIV. This approach was also advocated by Suissa et al. [90].

Direct comparison of incidence rates

Lubsen et al. and Mayne et al. proposed the use of incidence rates, rather than the survival function, to calculate NNT [91, 92]:

$$NNT_I = \frac{1}{\lambda_0 - \lambda_1} \quad (5)$$

The approach was used to calculate the NNT presented in the main PROUD analysis [13]. The use of incidence rates means that NNT_I is not time dependent and is interpreted in terms of person-years rather than a number of individuals (Section 3.3.3). However, it requires the assumption of constant hazard rates in both study arms.

Lubsen et al. suggested that if the incidence rates are not presented in a published paper, but the total mean survival follow-up (μ) and proportion of events (π) are, NNT_I can be approximated by [92]:

$$NNT_{IP} = \mu . \frac{1}{\pi_0 - \pi_1} \quad (6)$$

However, this method is not considered further due to the inappropriate assumption that μ was equal in each trial arm.

Scaling by use of study drug

Incidence rates (from which NNT_I is derived) are normally calculated according to the intention to treat approach, which ignores the amount of drug prescribed or taken. Lubsen et al. suggested that the NNT should be scaled by the proportion of follow-up time when patients were taking the treatment, giving an "on treatment" version of NNT [92]. Another possibility is to scale by the amount of drug prescribed rather than drug taken, particularly as the latter is difficult to estimate accurately.

The medication possession ratio (MPR) is a recognised adherence measure and is calculated by [100]:

$$MPR = \frac{Total\ number\ of\ pills\ prescribed}{Total\ number\ of\ days\ in\ follow-up} \quad (7)$$

Scaling the equation for NNT_I by the MPR gives the measure:

$$NNT_{MPR} = MPR.NNT_I \quad (8)$$

3.3.3 Confidence intervals for NNT

As with any other estimate, it is important to illustrate the uncertainty surrounding NNT by presenting confidence intervals. In Table 3.1 I present methods to calculate CIs for NNT_S, NNT_{SI}, NNT_I and NNT_{MPR} (described in Section 3.3.2). Altman et al. described that CIs for NNT_S could be derived simply by transforming the absolute risk reduction (ARR) CIs (estimated via the Kaplan Meier method) [96]. A similar approach can be used for NNT_I. These CIs can then be scaled by the MPR to obtain CIs for NNT_{MPR}. CI calculation for NNT_{SI} requires more derivation, but can be calculated using non-linear combinations of estimates derived from a Poisson model. This can be implemented using the Stata's *nlcom* command, which uses the Delta method (Appendix 8).

Table 3.1: Confidence interval calculation for NNT

NNT estimate	Method to calculate CIs for NNT
$NNT_S(t) = \frac{1}{S_1(t) - S_0(t)}$	CIs calculated on the absolute risk reduction (ARR) scale and inverted to NNT scale. 95% CI for ARR: ARR ± 1.96 SE(ARR), where SE(ARR)= $\sqrt{SE(S_1)^2 + SE(S_0)^2}$
$NNT_{SI}(t) = \frac{1}{exp(-\lambda_1 t) - exp(-\lambda_0 t)}$	CIs derived from the Poisson model using the delta method (using the *nlcom* command in Stata), where: $exp(-\lambda_1 t) - exp(-\lambda_0 t) = exp(-\exp(\alpha + b)) - exp(-exp(\alpha))$
$NNT_I = \frac{1}{\lambda_0 - \lambda_1}$	Same approach as NNT_S
$NNT_{MPR} = MPR.\frac{1}{\lambda_0 - \lambda_1}$	CIs derived by scaling CI for NNT_I by the constant MPR

An example of *nlcom* for NNT_I can be found in Appendix 8.
α, constant estimated from Poisson model; b, trial arm effect estimated from Poisson model.

3.3.4 Calculating and interpreting NNT for PrEP studies

Table 3.2 shows estimates of NNT_S, NNT_{SI}, NNT_I, and NNT_{MPR} based on the deferred phase of the PROUD trial [13]. Although the NNT estimates are quantitatively similar, they are conceptually different, and it is important to choose the method that is most relevant to the question being addressed. There are subtle differences in the interpretation of these measures. "Provide PrEP care" means to attend a clinic with access to PrEP, irrespective of whether drug is prescribed. This reflects the burden of clinic time and costs, including HIV/STI testing, risk reduction counselling, and the visits themselves. However, an important (although diminishing) cost of a PrEP programme is the direct drug cost, so that NNT in terms of "provide PrEP drug" is also useful. Whilst some participants may not have taken all the drug prescribed, this does not affect the PrEP budget.

Despite having the same interpretation, the values of NNT_S and NNT_{SI} at one year differed slightly: 12.5 men (95% CI: 8.5-24.9) and 13.5 men (95% CI: 6.5-20.6), respectively. One year is the natural time point for calculation as this was the planned duration of the deferred phase. However, not all visits took place at one year and the NNT_S estimate is strongly influenced by whether an infection was diagnosed just before or just after one year; for this reason the NNT_{SI} estimate is more stable. Both NNT_S and NNT_{SI} have a key conceptual weakness. Although the deferred phase in PROUD was one year, in practice PrEP should be prescribed indefinitely while the individual is at significant risk of HIV infection. A generalisable NNT measure for PrEP should therefore avoid arbitrary treatment durations, and calculating NNT in terms of person-years of follow-up (NNT_I) is most logical. The main Lancet paper reported that "13 men (90% CI: 9–23) in a similar population would need access to 1 year of PrEP to avert one HIV infection" [13]. Arguably, this language is too loose and should have referred to the person-years required.

The MPR in the deferred phase of PROUD (in the immediate PrEP arm) was 0.88, giving an NNT_{MPR} value of 11.3 (95% CI: 5.2-17.4) [13]. This is interpreted as the person-years of drug that needs to be prescribed to avert one additional HIV infection. At the time PROUD was conducted, the cost of Truvada was the dominant cost within a PrEP programme, and NNT_{MPR} therefore probably the most useful measure. However, the price of Truvada has fallen dramatically and NNT_I is now arguably the most useful single measure [101]. A comprehensive cost-effectiveness analysis would include separate components for the price of drug and the clinical care required to safely deliver the drug.

Table 3.2: Estimates and interpretation for different NNT measures

Acronym	**Calculation method** **Reciprocal of the difference in:**	**Interpretation** **On average, provide PrEP…**	**NNT for PROUD (95% CI)**
NNT_S	Survival functions at 1 year estimated from Kaplan-Meier curves	…care to X individuals to avert 1 additional HIV infection by 1 year	12.5 men (8.4-24.9)
NNT_{SI}	Survival functions at 1 year assuming exponential distributions	…care to X individuals to avert 1 additional HIV infection by 1 year	13.5 men (6.5-20.6)
NNT_I	Incidence rates	…care to X person-years to avert 1 additional HIV infection	12.9 PY (8.4-27.9)
NNT_{MPR}	Incidence rates adjusted for medicine possession ratio	…drug to X person-years to avert 1 additional HIV infection	11.3 PY (7.4-24.5)

PrEP, pre-exposure prophylaxis; NNT, number needed to treat; CI, confidence interval

NNT is usually presented as a whole number due to the interpretation relating to number of people, as in the main PROUD paper [13]. There is no good reason for this, as NNT refers to an average number. There is even less reason to so when reporting person-years of PrEP, and therefore, NNT should be reported with a higher degree of accuracy [95].

It is also possible to calculate the NNT for active-controlled trials, although interpretation is different. For example, the DISCOVER trial evaluated the effectiveness of TAF/FTC, using TDF/FTC as an active control group [102]. The incidence rates in the TAF/FTC and TDF/FTC groups were 0.16 and 0.34 per 100 PY, respectively, giving an NNT equal to 550.0. The

interpretation here is the person-years of TAF/FTC required to avert one infection compared to TDF/FTC (rather than no PrEP or placebo).

3.3.5 Generalising from trials to PrEP rollout programmes

NNT is a function of the effectiveness of the intervention and the baseline risk of the outcome. But what if the general population is inherently different to the trial population? In PROUD, the HIV incidence in the DEF arm during the deferred phase was seven times that of the general MSM UK sexual health clinic attenders [13, 103]. Even if PrEP effectiveness is the same, the NNT estimated in the trial will seriously under-estimate the NNT among sexual health clinic attenders, the main target group for a wider PrEP programme.

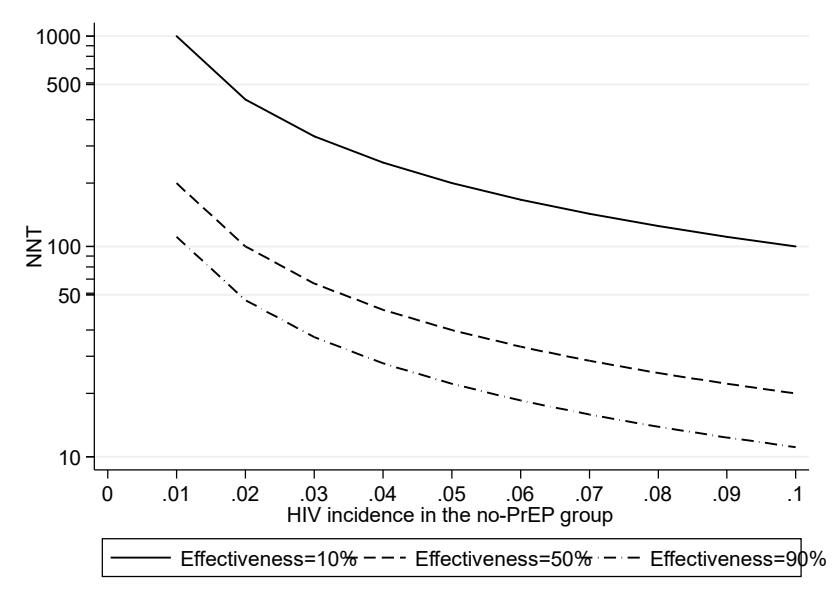
There are two ways the NNT estimated in a trial could be applied to the wider population. Firstly, Cook et al. proposed scaling NNT by the ratio (α) in HIV incidence between the trial population (subscript T) and the wider population (subscript P) [84]:

$$NNT_P = \frac{1}{\lambda_{0\mathrm{P}} - \lambda_{1P}} = \frac{1}{{}^{1}/_{\alpha}\lambda_{0\mathrm{T}} - {}^{1}/_{\alpha}\lambda_{1T}} = \frac{\alpha}{\lambda_{0\mathrm{T}} - \lambda_{1T}} = \alpha NNT_T \qquad (9)$$

For example, PROUD estimated a NNT of 12.9 and multiplying this by a factor of seven gives a NNT of 90.3 PY for the population of sexual health clinic attenders [13].

Another approach involves plotting the NNT for a range of effectiveness and HIV incidence values (Figure 3.2). For instance, if the HIV incidence was 3.0 per 100 PY and the PrEP effectiveness was 90%, then the NNT is estimated at 37.0.

Figure 3.2: NNT by HIV incidence in the no-PrEP group, stratified by PrEP effectiveness



3.3.6 Indirect effect of PrEP

Individuals taking PrEP are protecting themselves from HIV. However, infections prevented in these index cases also prevents onward transmission to their future sexual partners [104]. Therefore, PrEP has an indirect effect at the population level, which is important to consider in an epidemiological context.

MSM form a relatively small proportion of the population in the UK (3%) [105], and therefore, more closely connected to their sexual partners than the heterosexual population and more prone to epidemics of STIs [106]. In 2015-2016 a dramatic reduction in HIV incidence (up to 50%) was observed in some London clinics [50], re-iterating that the network of MSM is tightly connected. Although, the number of PrEP-users in the UK is unknown [27].

Between 2008 and 2015, the number of HIV diagnoses amongst MSM in the UK was relatively stable (with a small steady increase) at around 3000 per year [4]. This suggests (assuming no major changes in the interval between infection and diagnosis) that, on

average, each infected individual was transmitting HIV to one other individual (basic reproductive number [107]). This suggests that the NNT could be approximately halved, even without considering onward transmission of onward transmission.

Accurately quantifying NNT to account for prevention of onward transmission is challenging and beyond the scope of this thesis. In a US cost-effectiveness analysis, Chen et al. stated that they did not take secondary transmission into account because the interest lies with the individual taking PrEP [93]. This argument may apply in a clinical context and in conveying risks and benefits to individuals, but is demonstrably incorrect from a cost-effectiveness perspective. Simulation models are required to estimate the combined direct and indirect effects of PrEP. A cost-effectiveness analysis of a 80 year PrEP programme in the UK estimated that 25% of HIV infections could be averted by introducing PrEP (assuming 4000 MSM take PrEP by one year and 40,000 MSM take PrEP by 15 years) [53]. 42% of the averted infections were directly averted by those using PrEP, and the remaining 58% were avoided because of onward transmission.

3.4 Population attributable fraction (PAF) and related measures

3.4.1 Background

Chapter 2 identified baseline risk factors that were associated with the acquisition of HIV, but did not consider the impact of a PrEP programme on the incidence of HIV. To do this, in addition to the rate ratio (RR), it is also important to incorporate the prevalence of the risk factors. One such measure is the population attributable fraction (PAF), which has been used in PrEP and other HIV prevention studies to identify population subgroups which should be targeted to maximise the effect of an intervention [62, 63, 70, 76, 108, 109]. In this section, I review these studies and discuss the relevance of PAF (Section 3.4.3). I then

propose an alternative to PAF (Section 3.4.4) and consider a stepwise approach to identify individuals at high risk of HIV based on multiple characteristics (Section 3.4.5).

3.4.2 Definition of PAF

The definition of PAF is [110]:

> *"…the proportional reduction in average disease risk over a specified time interval that would be achieved by eliminating the exposure(s) of interest from the population while distributions of other risk factors in the population remain unchanged. This also can be interpreted as the proportion of disease cases over a specified time that would be prevented following elimination of the exposures, assuming the exposures are causal."*

PAF is calculated by [111]:

$$\mathrm{PAF} = \frac{\lambda_T - \lambda_u}{\lambda_T} \qquad (10)$$

$$= \frac{\mathrm{P(R-1)}}{\mathrm{P(R-1)+1}}$$

where λ_T and λ_u are the incidence rates in the total population and in the unexposed group, respectively, P is the proportion of the population with the risk factor, and R is the relative risk comparing the outcome between the exposed and the unexposed groups.

Zapata-Diomedi et al. reported that it was a relatively common mistake for PAF to be referred to as the population attributable risk (PAR) [111]. However, PAR is defined as the absolute risk difference between the incidence rate in the population and the incidence rate in the unexposed group, i.e. the numerator in equation (10).

3.4.3 Use of PAF in HIV prevention literature

I searched PubMed to identify studies which used PAF to inform HIV prevention strategies in the era of PrEP [("preexposure prophylaxis"[ti] OR "pre-exposure prophylaxis" [ti] OR PrEP[ti] OR "human immunodeficiency virus" [ti] OR HIV[ti]) AND (PAF[tiab] OR "population attributable fraction"[tiab] OR "population attributable risk"[tiab] OR PAR[tiab])]. I also considered papers identified in the literature review I identified in Section 2.4 [59-76]. Papers were subsequently excluded if they did not mention PrEP in the body of the text and did not include MSM populations. Of the 103 papers identified, I found six relevant papers (Table 3.3) [62, 63, 70, 76, 108, 109].

Table 3.3: Example of the use of Population Attributable Fraction (PAF) in HIV prevention literature

Author, year	Aim of study	Rationale for PAF
Barbee, 2017 [108]	"we sought to determine whether the association between rectal gonococcal and chlamydial infections and HIV diagnosis is independent of receptive anal sexual behavior and to estimate the population attributable risk percent (PAR%) of rectal bacterial STI on HIV diagnoses."	Not specified
Buchbinder, 2014 [76]	"To estimate the PAF and NNT of participants in the iPrEx study to identify subpopulations of people for whom pre-exposure prophylaxis may have the largest effect."	"Determining which subgroups of MSM/TGW have high PAF could help identify those subgroups most important for PrEP to reduce HIV infections at a population level."
Cheung, 2016 [62]	"The aim of this study was to determine the risk factors for HIV infections and the incidence in MSM. It is important to identify subgroups of MSM in which preventive interventions such as PrEP offered at the time of their last negative test would be considered cost-effective"	Not specified
Desai, 2017 [63]	To identify "predictors for HIV acquisition to help identify subgroups to which HIV prevention services can be directed for the greatest impact on HIV transmission."	"The relative contribution of each predictive factor was determined by calculating PAR, which combines the adjusted HR and the prevelance"
Kelley, 2015 [70]	"This longitudinal study of HIV-negative MSM undergoing routine screening for STIs and HIV provides the unique opportunity to define STI incidence and examine the cooccuring STI/HIV epidemics while controlling for behavioural risk factors to better understand drivers of the Atlanta MSM epidemic."	Not specified
Mitchell, 2016 [109]	"we used mathematical modelling to estimate the contribution made by these key populations to the HIV epidemic in Bangalore, the impact of offering PrEP to FSWs and/or MSM in Bangalore, and the population-level impact and efficiency of different PrEP prioritization strategies."	"The PAF quantifies the contribution of a particular risk factor to cases of disease. We used PAF to understand the factors driving HIV transmission, which is crucial for designing effective prevention interventions."

PAF, population attributable fraction; PAR, population attributable risk; NNT, number needed to treat; PrEP, pre-exposure prophylaxis; HIV, human immunodeficiency virus; MSM, men who have sex with men; TGW, transgender women; STI, sexually transmitted infection.

Cohort studies

Buchbinder et al. presented a secondary analysis of participants randomised to the placebo arm in the iPrEx trial, which aimed to identify participant characteristics that should be targeted in order for a PrEP programme to have the greatest impact on the HIV epidemic [76]. Adjusted RRs (from a Poisson model) were used in the standard PAF formula, however this is not appropriate and should have used an adapted formula incorporating adjusted relative risks and the proportion of cases exposed to the risk factors to account for confounding, and therefore this error could have affected the measures presented in their paper [110]. Buchbinder et al. plotted NNT against the PAF for a number of baseline characteristics (Figure 3.3). They argued that directing PrEP to those characteristics with the largest PAF and the lowest NNT would lead to the greatest reduction in new HIV infections.

Figure 3.3: Use of PAF and NNT by Buchbinder et al. (image redacted due to copyright)

Barbee et al. performed a case-control study of MSM attending a sexual health clinic in Seattle to determine whether there was a relationship between rectal STIs and HIV diagnosis, independent of receptive anal intercourse [108]. They calculated the proportion

of HIV infections attributed to rectal STIs by incorporating ORs into the adjusted PAF formula. Barbee et al. described that the use of the OR instead of risk ratio was acceptable given the low HIV event rate, and therefore the OR approximates the risk ratio. They identified a significant association between rectal STIs and HIV, with a PAF of 13.9%, concluding that a prior history of rectal STIs indicates those most need of HIV prevention services, including PrEP.

Cheung et al. analysed a retrospective cohort study of MSM attending a sexual health clinic in Melbourne with at least two HIV tests within the previous 12 months [62]. They examined the predictive value of demographic, sexual, and clinical factors reported in the first visit on HIV status at the subsequent visit. PAF was calculated for factors with an incidence greater than 2.0 per 100 PY, describing that this threshold had been widely reported as a cost-effective limit for PrEP. PAF was also calculated according to the number of different risk factors (e.g. STI diagnosis, injection drug use or PEP use) an individual reported. Cheung et al. concluded that HIV prevention efforts (including PrEP prioritisation) should be targeted towards MSM with a bacterial STI, inconsistent condom-use and PEP, given the high HIV incidence and commonality of these risk factors.

Desai at al. described a study of MSM who had attended a sexual health clinic in England at least twice in one year, using demographic and STI data from the initial visit [63]. Similarly to Buchbinder et al., they did not use the adapted PAF formula for adjusted HRs [110]. Desai et al. summed together the PAF from five risk factors (London resident, bacterial STI, rectal STI, syphilis and gonorrhoea) to conclude that these risk factors accounted for 37% of HIV infections. Although this is likely to be an over-estimate since individual PAFs should not be added together given the over-lap in risk factors [111, 112]. They suggested that MSM diagnosed with a bacterial STI in the previous year could be enrolled into a PrEP programme.

Kelley et al. presented an analysis of HIV-negative MSM undergoing routine screening for STIs and HIV [70]. They aimed to estimate the effect of bacterial STIs on HIV incidence to inform HIV prevention strategies, including PrEP. Kelley et al. used adjusted HRs from propensity-score-weighted Cox models to estimate the proportion of HIV infections attributable to rectal STIs. They concluded that, whilst the PAF for rectal STIs may have been modest (14.6%), prevention of rectal STIs is important for the control of STIs an HIV in the MSM population. The paper also highlights the importance in other HIV prevention strategies, such as PrEP, in order to reduce HIV incidence.

Simulation study

Mitchell et al. conducted a mathematical modelling study for the HIV epidemic amongst female sex workers and MSM in Bangalore, India [109]. Their first aim was to estimate the proportion of HIV infections attributable to commercial sex work and MSM. They then aimed to estimate the impact of PrEP on these populations under a number of scenarios. PAF was calculated for each ten-year period (between 1986 and 2025) for commercial sex workers and MSM by assuming that transmission risk within each group was set to 0 during each period. In contrast to the epidemiological papers above, PAF was calculated by assuming that the infection risk was zero in the exposed groups (rather than equivalent to the unexposed). Although, Mitchell et al.'s focus was more towards population level risk factors (e.g. MSM or female sex workers), rather than individual risk factors (e.g. chemsex, STI). They then estimated the proportion of averted infections by modelling a number of scenarios for a PrEP programme (e.g. adherence and coverage) over five and ten years, assuming a 93% effectiveness. I argue below that it is more relevant than PAF (Summary).

Summary

PAF is the proportionate reduction in number of HIV infections that would be achieved by reducing incidence in the exposed group to the level in the unexposed group. PAF is relevant

when the intervention corresponds to the exposure of interest. For example, the difference in HIV incidence between uncircumcised and circumcised men is a paramount consideration when considering the impact of a circumcision programme. However, in the context of PrEP the question of interest is the effect of providing PrEP to those with a given risk factor, rather than modifying the risk factor themselves. Emerson et al. also pointed out this fundamental problem in the application of PAF to PrEP [113]. In addition, whether or not a risk factor is modifiable, a necessary condition for PAF to be meaningful, does not matter for PrEP. Rather than the difference in HIV risk between exposed and unexposed groups, estimation of the population impact of a PrEP programme must also consider PrEP effectiveness. The modelling approach taken by Mitchell et al. was more appropriate in estimating the effect of PrEP by incorporating a number of a factors, including efficacy and adherence [109].

3.4.4 Proportion of potential averted infections (PPAI): an alternative to PAF

Here, I propose an alternative measure to PAF that represents the relative reduction in the number of HIV infections for a given PrEP strategy. The proportion of potential averted infections (PPAI) is calculated by:

$$\text{PPAI} = \frac{\lambda_T - \lambda_P}{\lambda_T} \quad (11)$$

where λ_P is the overall HIV rate after the proposed PrEP strategy and λ_T is the overall HIV rate in the population without PrEP.

At first glance this is similar to the formula for PAF:

$$\text{PAF} = \frac{\lambda_T - \lambda_U}{\lambda_T} \quad (12)$$

where λ_T is the incidence rate in the total population and λ_U in the unexposed group, respectively. However, PPAI is inherently different to PAF – rather than comparing overall incidence to that of the unexposed group, the expected overall incidence is compared before and after a theoretical PrEP programme has been implemented. PPAI is a function of PrEP effectiveness, PrEP uptake, the prevalence of risk factor, and rate ratio of incidence between the exposed and unexposed groups (in the absence of PrEP), as shown in Table 3.4.

Table 3.4: Incidence pre- and post-PrEP programme, by exposure to risk factor and accounting for PrEP effectiveness and PrEP uptake

Exposure to risk factor X	**PrEP uptake**	**Proportion in group**	**Rate in population (pre-PrEP)**	**Rate post-PrEP focussed towards exposed**
Unexposed (U)	NA	1-P	λ_U	λ_U
Exposed (E)	No uptake	P(1-γ)	λ_E	λ_E
	Uptake	Pγ	λ_E	$\lambda_E(1-\vartheta)$
Overall		1	λ_T =(1-P)λ_U + Pλ_E	λ_P =(1-P)λ_U+P(1-γ)λ_E +P$\gamma\lambda_E(1-\vartheta)$

U, unexposed to risk factor; E, exposed to risk factor; P, proportion of follow-up exposed to risk factor; λ_E, rate in the exposed group; λ_U, rate in the unexposed group; γ, proportion of PrEP uptake; ϑ, effectiveness of PrEP

$$\text{PPAI} = \frac{\lambda_T - \lambda_P}{\lambda_T} \qquad (13)$$

$$= \frac{[(1-\text{P})\lambda_U + \text{P}\lambda_E] - [(1-\text{P})\lambda_U + \text{P}(1-\gamma)\lambda_E + \text{P}\gamma\lambda_E(1-\vartheta)]}{(1-\text{P})\lambda_U + \text{P}\lambda_E}$$

$$= \frac{\text{P}\gamma\lambda_E\vartheta}{(1-\text{P})\lambda_U + \text{P}\lambda_E}$$

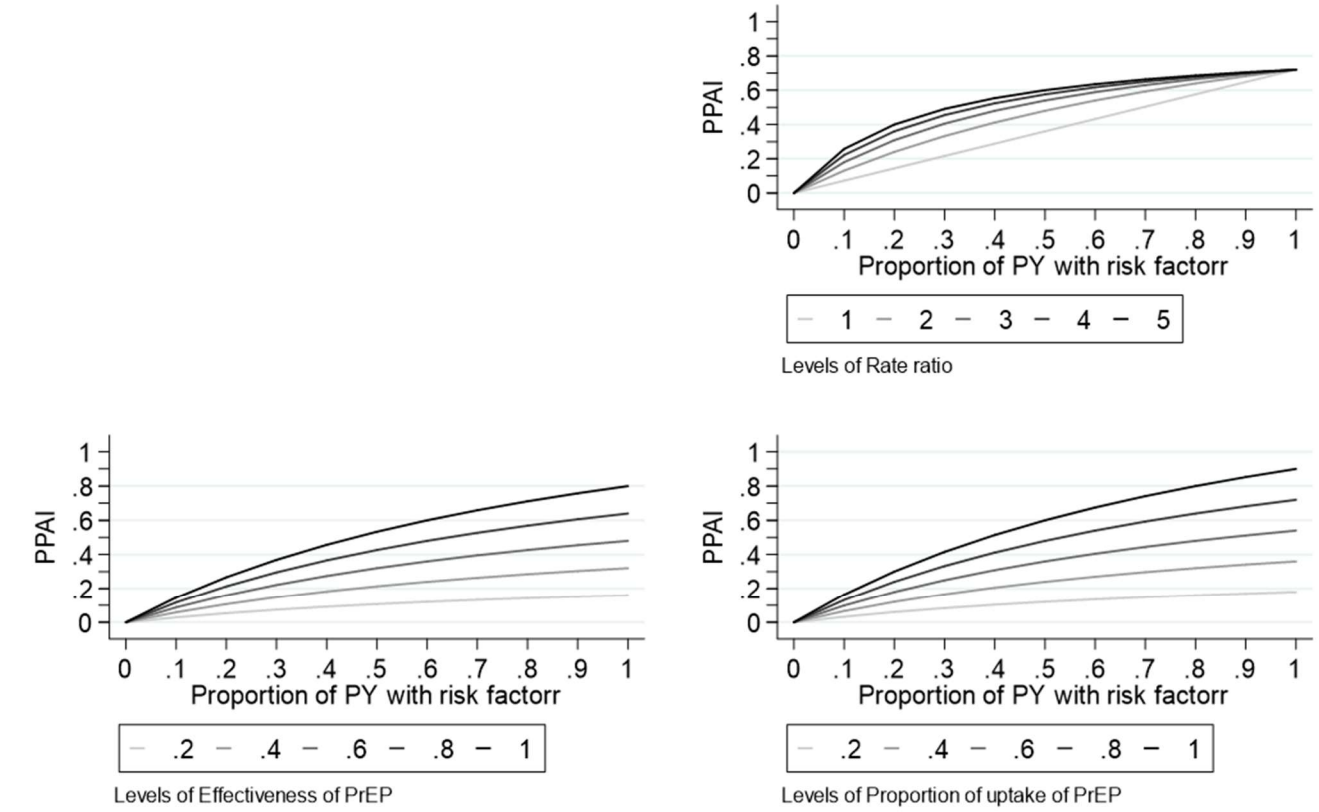
$$= \frac{P\gamma R\vartheta}{(1-P)+PR}$$

where P is proportion of follow-up time under exposure to the risk factor, λ_U is the incidence rate in the unexposed group, λ_E is the rate in the exposed group, ϑ is the effectiveness of PrEP, R is the rate ratio of the pre-PrEP HIV incidence between the exposed and unexposed groups, γ is the proportion of PrEP uptake in the exposed group (accepting the offer of PrEP).

Figure 3.4-Figure 3.7 show that PPAI increases as: (a) proportion of follow-up exposed to risk factor increases (i.e. the prevalence of the risk factor); (b) rate ratio between exposed and unexposed groups increases; (c) effectiveness of PrEP increases – linear relationship as value only appears in numerator; and (d) uptake of PrEP increases – linear relationship as value only appears in numerator.

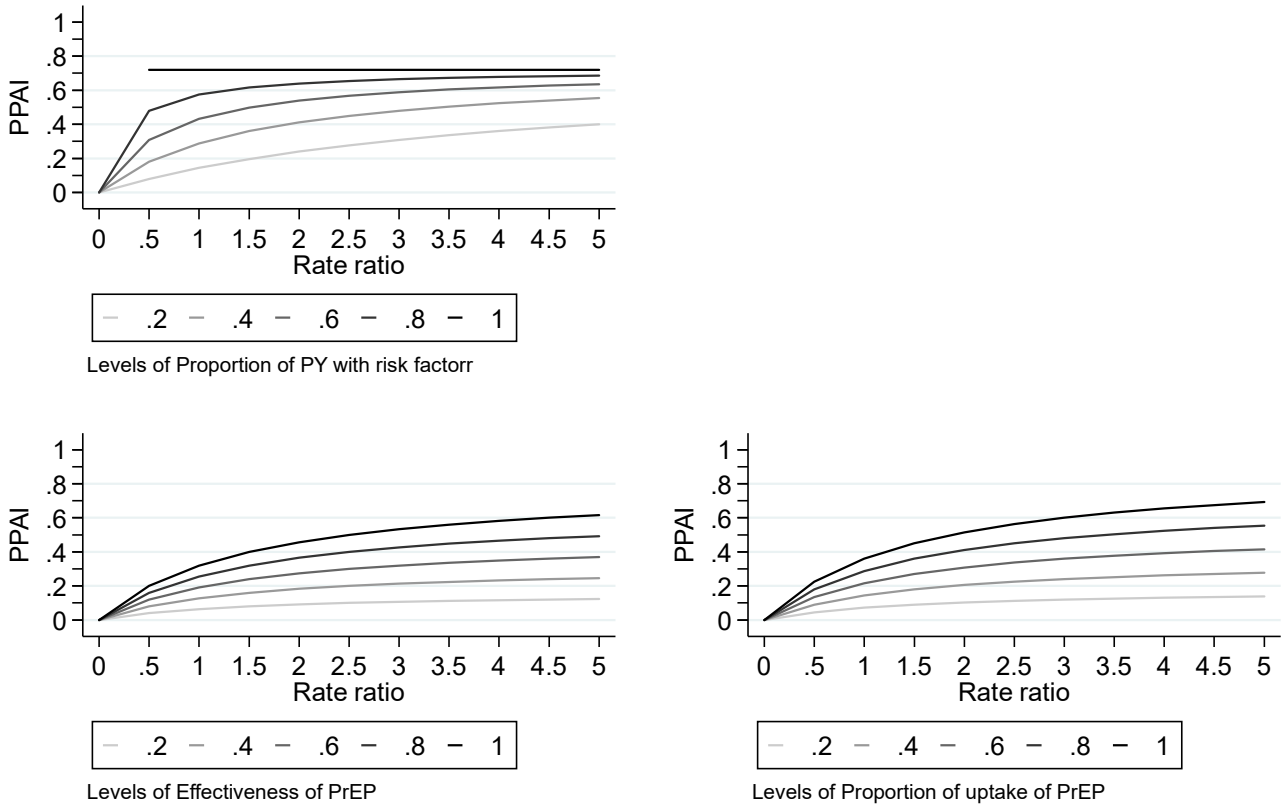
Unlike NNT, PPAI is not a function of HIV incidence and would therefore generalise to populations with a different background HIV incidence, assuming that the other parameters remain the same.

Figure 3.4: Relationship between PPAI and proportion of follow-up exposed to risk factor



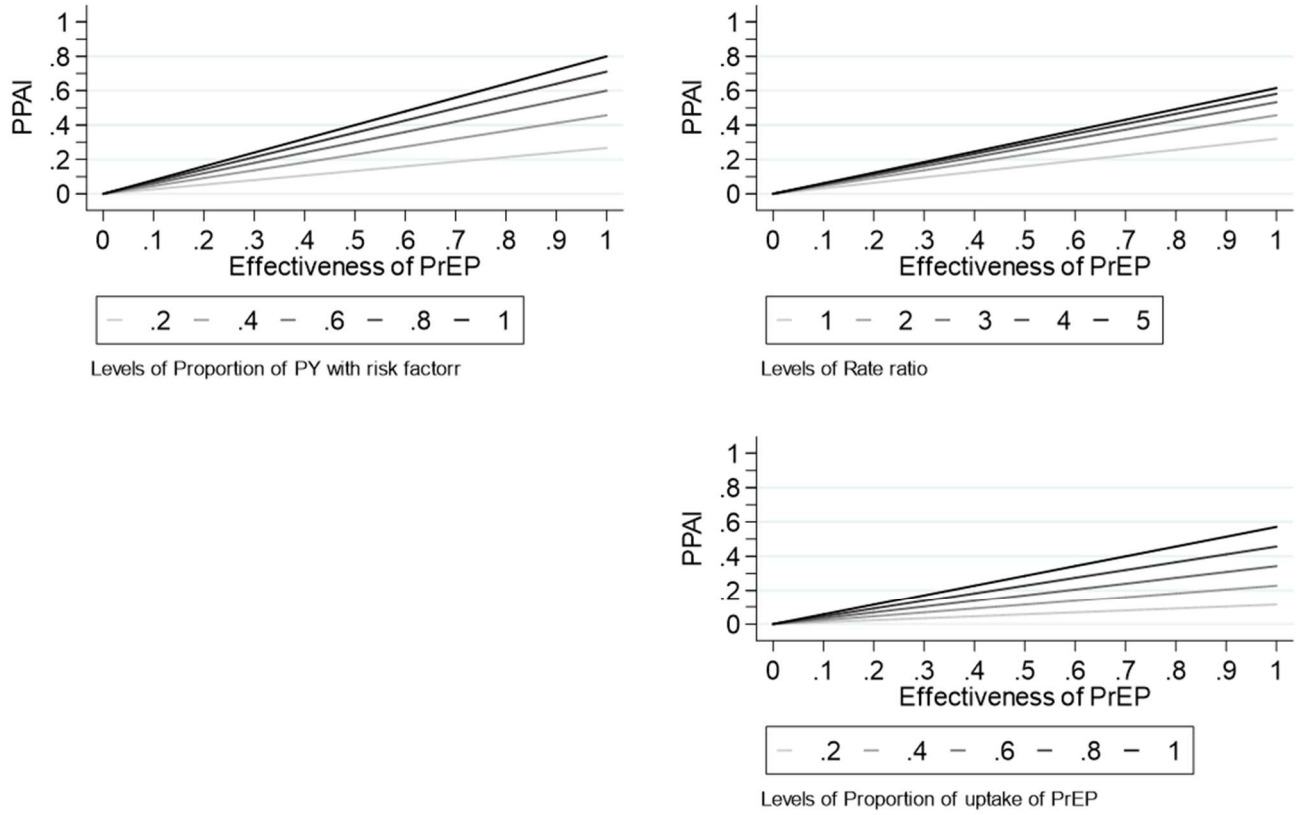
Baseline scenario: rate ratio=2, effectiveness=90%, uptake=80%

Figure 3.5: Relationship between PPAI and rate ratio



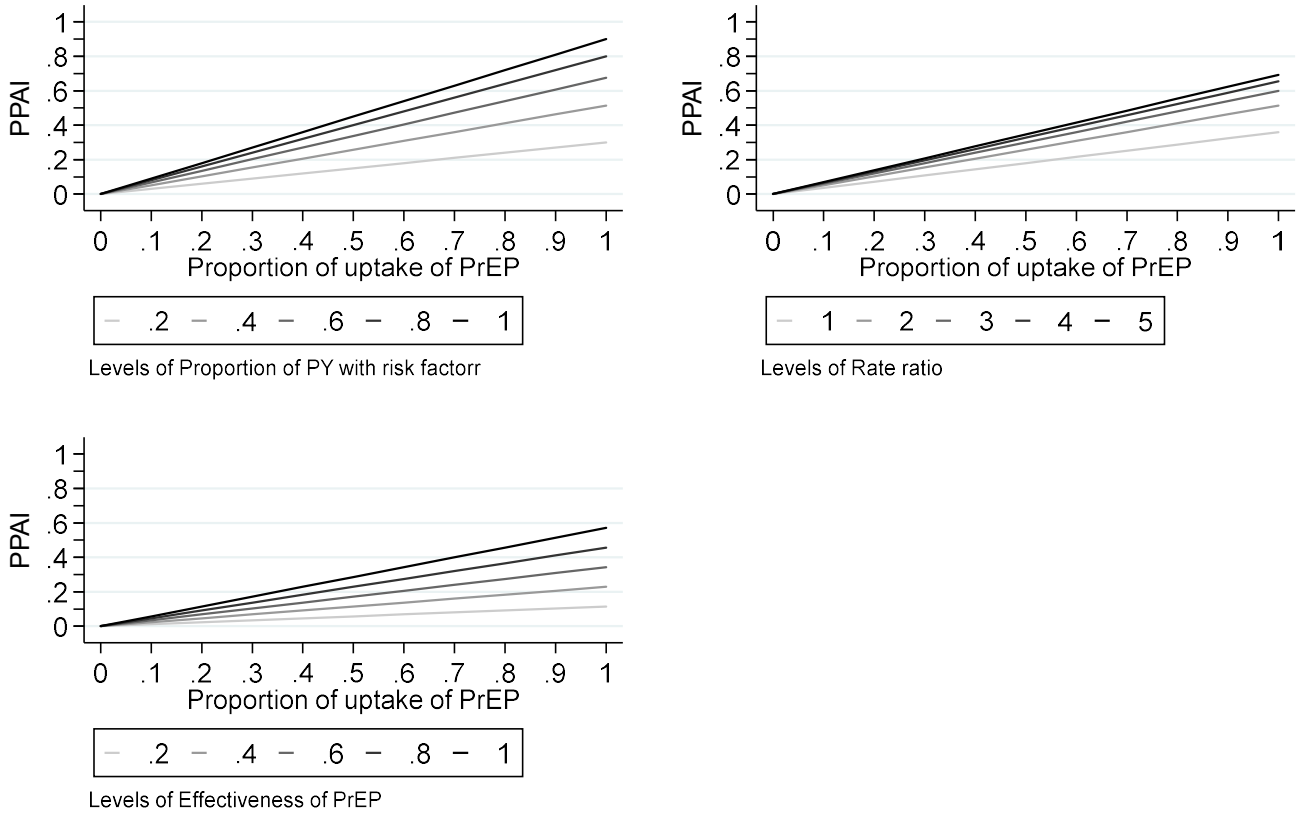
Baseline scenario: proportion of PY with risk factor=0.4, effectiveness=90%, uptake=80%

Figure 3.6: Relationship between PPAI and PrEP effectiveness



Baseline scenario: proportion of PY with risk factor=0.4, rate ratio=2, uptake=80%

Figure 3.7: Relationship between PPAI and PrEP-uptake



Baseline scenario: proportion of PY with risk factor=0.4, rate ratio=2, effectiveness=90%

Application of PPAI to PROUD

I calculated PPAI for selected baseline characteristics in the PROUD trial, assuming 90% efficacy and 100% PrEP uptake (Table 3.5). PPAI varied widely, from 27.0% for five or more HIV screens (in the year prior to enrolment) to 85.5% for low depression score.

PPAI is plotted against the PAF calculation for these risk factors (Figure 3.8). Whilst correlated, PPAI is consistently higher than PAF due to the high assumed effectiveness of PrEP, which is incorporated in the PPAI calculation.

Table 3.5: Proportion of Potential Averted Infections (PPAI) for selected baseline characteristics in PROUD

Characteristic	Infections, *n*	Total PY	Rate per 100PY	% of follow-up time	RR	PAF	PPAI	NNT
Key STI[a]	15	87.0	17.2	38.2	4.8	59.5	67.5	6.4
Five or more HIV screens[a]	6	38.1	15.7	16.8	2.1	15.8	27.0	7.1
Two or more ncRAI partners[b]	17	125.3	13.6	55.0	4.6	66.6	76.5	8.2
PEP use[a]	9	80.3	11.2	36.1	1.4	14.0	40.5	9.9
Chemsex[b]	12	108.1	11.1	47.0	1.9	30.5	56.8	10.0
Full-time employment	18	173.0	10.4	73.3	2.2	46.6	77.1	10.7
Not circumcised	17	166.2	10.2	69.5	1.8	35.6	72.9	10.9
University degree	15	146.7	10.2	61.8	1.5	25.2	64.3	10.9
Single	13	127.3	10.2	53.9	1.4	17.4	55.7	10.9
Age<35	12	119.1	10.1	49.8	1.3	14.7	51.4	11.0
White ethnicity	19	192.3	9.9	81.4	2.1	47.7	81.4	11.2
Born outside UK	9	96.6	9.3	40.7	1.1	3.6	38.6	11.9
Low depression score	19	205.1	9.3	91.7	1.7	39.5	85.5	12.0
London site	15	167.4	9.0	70.0	1.1	4.8	64.3	12.4
No poppers[b]	10	117.9	8.5	51.2	1.1	2.8	47.4	13.1

[a]In the previous year
[b]In the previous 3 months
n, number of participants; PY, person-years; RR, rate ratio; PAF, population attributable fraction; PPAI, proportion of potential averted infections; R_{PP}, ratio of PPAI and the proportion of follow-up; STI, sexually transmitted infections; HIV, human immunodeficiency virus; ncRAI, receptive anal intercourse without a condom; PEP, post-exposure prophylaxis; UK, United Kingdom
*Assuming PrEP has 90% effectiveness, 100% uptake

Figure 3.8: Relationship between PPAI and PAF for baseline characteristics in PROUD

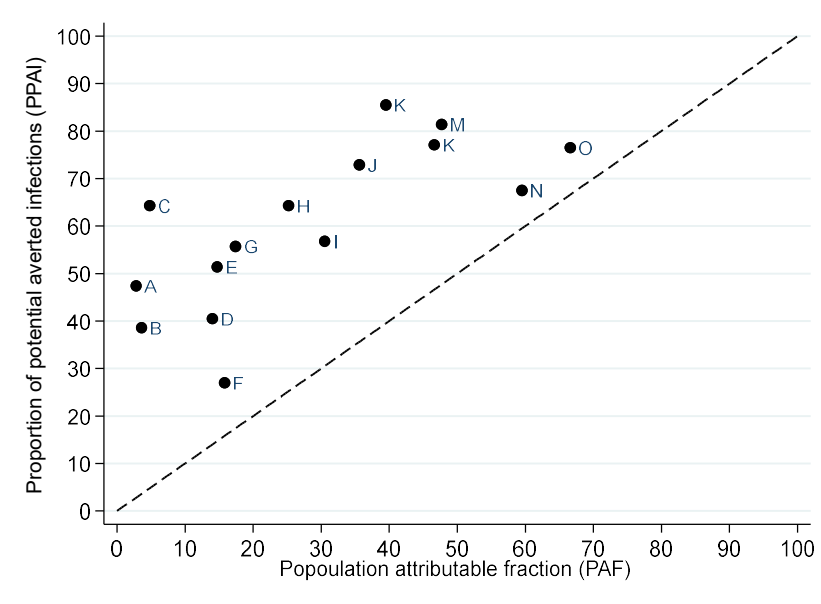


Figure legend: *dashed line represents PPAI=PAF. A, no poppers; B, born outside UK; C, London site; D, PEP use; E, age<35; F, five or more HIV screens; G, single relationship status; H, University degree; I, chemsex; J, not circumcised; K, low depression score; L, full-time employment; M, white ethnicity; N key STI; O, two or more ncRAI partners.*

Targeting PrEP at high risk groups

Whilst PPAI reflects the population impact of a targeted PrEP programme, it does not necessarily inform the subgroups that should be targeted. Clearly, providing PrEP to individuals who share a common risk factor prevents many HIV infections, regardless of whether it is predictive of HIV. For example, if the prevalence of the risk factor (P) is 80%, but that factor was not predictive of HIV (R=1), offering PrEP to this group would prevent 72% of the infections (assuming 100% uptake and 90% effectiveness). However, the same proportion of infections would be prevented if a risk factor was highly predictive (R=4) but the prevalence of the risk factor was only 50%.

It makes sense to prioritise risk factors which results in preventing the most infections for the least amount of PrEP. In a similar way to Buchbinder et al., I plotted PPAI against NNT to assess this (Figure 3.9)[76]. Two factors were an obvious choice for PrEP prioritisation: two or more ncRAI partners (NNT=8.2 and PPAI=66.6%); and a key STI (NNT= 6.5 and

PPAI=67.5%). This is in line with the conclusions from Chapter 2, which identified high risk factors according to high HIV incidence alone.

Figure 3.9: Proportion of potential averted infections by number needed to treat in PROUD

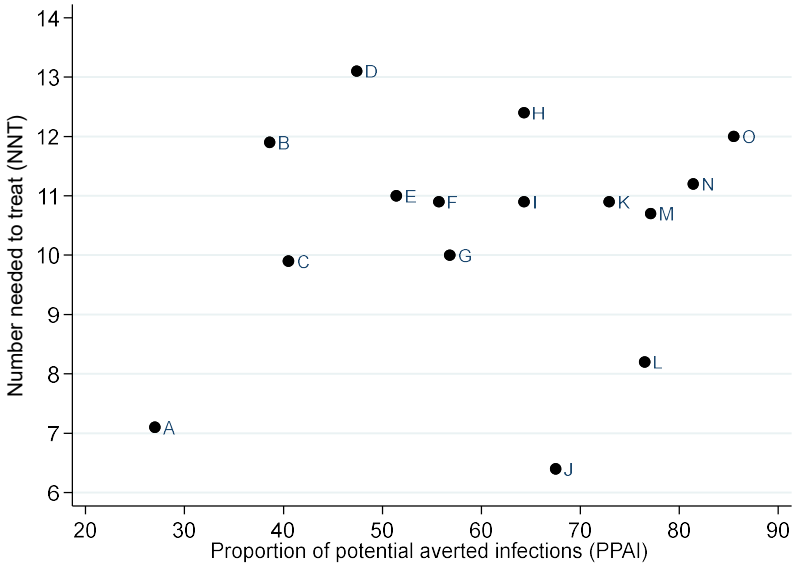


Figure legend: *A, five or more HIV screens; B, born outside UK; C, PEP use; D, no poppers; E, age<35; F, single relationship status; G, chemsex; H, London site; I, university degree; J, key STI; K, not circumcised; L, two or more ncRAI partners; M, full-time employment; N, white ethnicity; O, low depression score.*

Both PAF and PPAI are univariable measures and do not account for associations between risk factors. Rockhill et al. suggested that a 'summary PAF' could be calculated, whereby the exposed group is defined to be those with at least one of the risk factors [110]. In the next section, I apply a related stepwise approach described by Poynten at al. to identify combinations of multiple factors in PROUD that predict a high risk of HIV [82].

3.4.5 A stepwise procedure to identify multiple variables at high risk of HIV

The natural approach for identifying combinations of several variables that identify individuals at highest HIV risk is to fit a multivariable predictive model. The VAXGEN study in the USA, which observed ~300 HIV infections, used logistic regression analysis to identify

significant predictors and then weighted the regression coefficients to create an index score [74]. However, the small number of HIV endpoints in PROUD (*n*=21) precludes such an approach as the number of covariates that can be examined is constrained by the number of endpoints. A similar problem was faced by investigators of an Australian cohort study, who aimed to identify characteristics of an MSM population which had a high enough HIV incidence to be eligible for a theoretical prevention trial [82]. I adapted a non-parametric, stepwise approach developed by Poynten et al. to identify groups of individuals who were at an increased risk of HIV:

> ***STEP ONE*** – Rank characteristics in terms of highest to lowest HIV incidence
>
> ***STEP TWO*** – Individuals with the characteristic with the highest incidence are selected as eligible for the prevention intervention. Exclude participants with this characteristic from the dataset.
>
> ***STEP THREE*** – Return to ***STEP ONE*** until highest incidence is below 3.0 per 100 PY[7]
>
> **STEP FOUR** – Individuals are eligible for the prevention intervention if they have <u>any</u> of the characteristics selected at step two. Calculate incidence and PPAI at each iteration for individuals with any of the characteristics selected up to that point.

Applying approach to PROUD

In the application of Poynten's approach to PROUD, I first grouped categorical variables into binary variables, as performed in their paper. However, this method could easily incorporate categorical variables. In the first iteration, key STI ranked highest with an incidence of 17.2 per 100 PY, and accounted for 15 of the 21 HIV infections. After excluding

[7] For this analysis, the threshold was set at a HIV incidence of 3.0% to reflect the WHO guidelines of PrEP initiation. Poynten et al. set this at 2.0% to reflect adequate power and achievable sample size in a PrEP trial.

individuals with this characteristic, the process next identified high depression score (9.8 per 100 PY), followed by two or more ncRAI partners in the previous three months (6.5 per 100PY), and finally five or more HIV tests in the previous 12 months (11.7 per 100 PY) (Table 3.6). It is noted that these four characteristics capture all 21 HIV infections.

Table 3.6 also shows the HIV incidence at each iteration among all individuals with any of the characteristics selected up to that point in the iterative process. Individuals reporting at least one of the criteria listed in Table 3.6 had an estimated HIV incidence of 12.6 per 100 PY (95% CI: 7.8-19.2). The combined PPAI was calculated at each iteration, assuming a 90% effectiveness and a 100% uptake. This suggests that 90% of infections could be averted by providing PrEP to any of the four identified characteristics, although this is likely an over-estimate due to variable selection bias. It is useful to note the trade-off between PPAI and the required person-years of PrEP to achieve this reduction (Figure 3.10 and Table 3.6). This estimates that 64% of infections could be averted by providing PrEP to 36% of the total person-years of follow-up, if targeting PrEP towards those with a key STI. Similarly, 90% could be averted by providing PrEP to 70% of person-years (any one of the four characteristics).

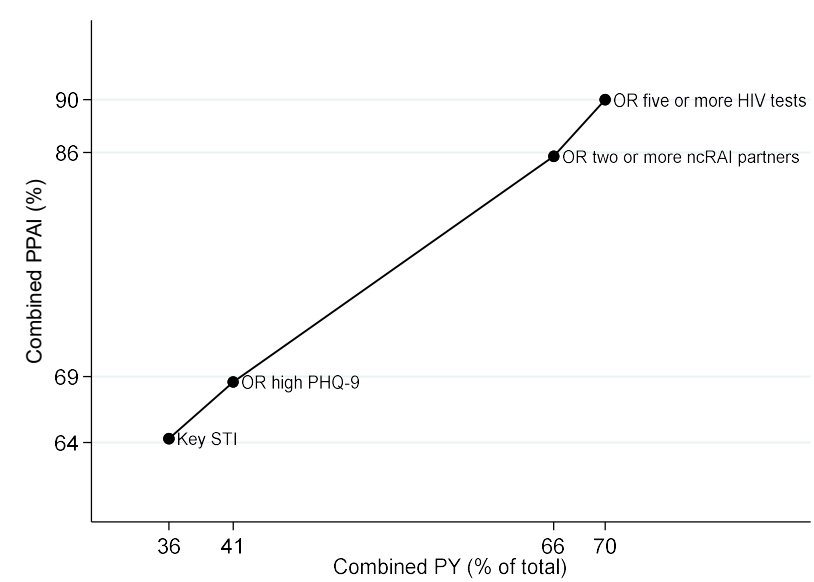
The small number of HIV infections in PROUD means that the results of this analysis are highly unstable, and is presented more as a demonstration of the method rather than a realistic application. Some of the characteristics, especially rare characteristics, could have been selected by the play of chance. For example, depression emerged in the second iteration because a single infection occurred in this group with only 10 person-years of follow-up.

Table 3.6: HIV incidence and PPAI by characteristics identified by a stepwise procedure

Risk factors (iteration)	Combined PY (% of total)	Combined HIV infections	Combined incidence (95% CI)	Combined PPAI
Key STI	87.0 (36%)	15	17.2 (9.7-28.5)	64.3%
OR high PHQ-9	97.2 (41%)	16	16.5 (9.4-26.7)	68.6%
OR two or more ncRAI partners	158.2 (66%)	20	12.6 (7.7-19.5)	85.7%
OR five or more HIV tests in previous year	166.8 (70%)	21	12.6 (7.8-19.2)	90.0%

PY, person-years; HIV, human immunodeficiency virus; CI, confidence interval; key STI, rectal chlamydia/gonorrhoea or syphilis; STI, sexually transmitted infection; PHQ-9, patients health questionnaire (depression score).

Figure 3.10: Person-years of PrEP plotted against PPAI at each iteration



3.5 Discussion

3.5.1 Key findings

- In the context of PrEP research, NNT calculations should be based on estimates of HIV incidence rather than cumulative incidence. It may be helpful to present two different values, one based on total person-years of follow-up and a second scaled by the MPR to reflect the amount of drug prescribed

- NNT is not generalisable to a population with a different HIV incidence but can be scaled up or down if the incidence in the wider population is known
- The use of PAF to the measure the impact of PrEP on population HIV incidence is misleading and should be avoided. PPAI is an appropriate alternative measure.
- PPAI and NNT can be used in conjunction to identify individual characteristics defining population subgroups that would most benefit from PrEP prioritisation
- A step-wise approach can be used to identify a set of characteristics when multivariable analysis is not feasible

The NNT is a potentially useful measure for counselling patients who are thinking about starting PrEP and for assessing the cost-effectiveness of PrEP in light of the very high lifetime costs in the care of a HIV-positive patient. However, several studies have described that patients and caregivers do not always fully understand the interpretation of NNT and that other effectiveness measures may be more readily understood [114-116]. Also, there is some evidence that the magnitude of NNT has a smaller than expected effect on treatment decisions [114, 116]. There are two main limitations in using NNT for cost-effectiveness decision making. First, the trial population from which the NNT is derived may be highly unrepresentative of the population to which it is being extrapolated. The larger concern is around a different underlying HIV incidence, with PrEP trials tending to attract individuals at particularly high risk of infection. PPAI does not suffer from this limitation but whether effectiveness estimates from trials (with relatively short follow-up) can be extrapolated to the wider population is also debateable. Second, the NNT fails to account for the onward transmissions prevented as a result of PrEP, as well as infections in the individuals taking PrEP. This is also a limitation of PPAI. Thus the use of comprehensive cost-effectiveness or sexual network models, cannot be avoided [104].

A limitation of NNT and PPAI is that they are univariable measures. Poynten et al. described an alternative approach to define a set of characteristics that identify individuals with high

HIV incidence. Individuals with any one of these characteristics is deemed to be at high risk. This is more easily applied in a clinical setting compared to a complex risk score and is in line with eligibility criteria in PrEP guidelines, which are also based on "or" logic [42]. However, the small number of infections in PROUD meant that this method was highly unstable, with a strong possibility of variable selection bias (as occurs in regression modelling). The effect of this could be reduced by adding a step to the procedure, where the threshold for inclusion could also incorporate the person-years of follow-up for that risk factor.

The ideas developed in this chapter are not likely to be directly relevant to future PrEP trials as it is now generally considered to be unethical to include a placebo (or no PrEP) group given that Truvada has been shown to be highly effective. However, there may be applications in other areas of HIV prevention, including vaccine trials, or in other infections.

4 Assessing whether access to PrEP increases STI incidence

4.1 Introduction

Risk compensation is a phenomenon seen in individuals using preventative interventions, whereby the perceived lower risk results in higher risk behaviour; this behaviour could negate the benefits of the intervention [117]. Risk compensation is a particular concern for PrEP, where recipients may increase the number of sexual partners with whom they do not use a condom due to their belief in the efficacy of PrEP in protecting against HIV [118]. This could lead to an increase in the number of STIs. A PrEP programme, therefore, could result in increased costs for STI screening and treatment for the individuals receiving PrEP, as well as enhancing the spread of STIs in the wider population. This is clearly an important public health concern and many previous studies have attempted to assess risk compensation through self-reported sexual behaviour [13, 119]. However, these data are often unreliable and, in PROUD, were incomplete with a high likelihood of selective completion bias. As risky sexual behaviour is not negative *per se*, this chapter will focus on the adverse clinical outcome, STIs, rather than sexual behaviour data.

Specifically, I will consider the three major bacterial STIs: gonorrhoea; chlamydia; and syphilis. HCV is reported separately (Chapter 5) due to the extra data collected on this infection. This chapter will emphasise methodological considerations and the challenge these present when drawing conclusions on whether PrEP really does impact on STI incidence. This includes a critique of open-label PrEP studies and three analyses of PROUD STI data: a re-analysis of the deferred phase; a new analysis of the deferred and post-deferred phase comparison; and STI incidence over calendar time.

4.2 Background

Several placebo-controlled PrEP trials, including iPrEX and IPERGAY, have compared STI diagnoses between the active-treatment and placebo arms [12, 14]. However, given that participants were unaware of their PrEP status (assuming blinding was successful), such trials provide no information on risk compensation. Only open-label studies, such as PROUD, are informative in this respect. A systematic literature review was conducted by Traegar et al. of such studies, considering both sexual risk behaviour and STIs as outcomes [120]. PROUD was the only randomised study that they identified. In Section 4.4, I present a critique of the individual studies reporting STI outcomes included in the Treagar et al. review.

STI analyses for PROUD have been presented previously in the main Lancet publication [13]. The paper presented the probability of detecting an STI during the deferred phase, with a higher risk found in the IMM group. However, this was biased by the higher number of STI screens within this group and, after adjustment for this, there was no significant difference between the groups, both for individual STIs and overall. This analysis has several limitations, which are discussed in Section 4.6. This section also includes alternative analyses of the deferred phase.

The long-term follow-up STI data in PROUD have not been analysed and reported in detail previously. Although less robust than the randomised comparison of the deferred phase, a pre-PrEP vs. post-PrEP comparison of the DEF arm is presented. Calendar time trends for PROUD in both the IMM and DEF arms are considered when examining the evidence of a long-term effect of PrEP on STI risk in Section 4.8.

4.3 Aims

The aims of this chapter are:

1. Critique the methods used by individual studies included in the Traegar et al. systematic review (Section 4.4)
2. Describe STI data collected during PROUD and discuss methodological considerations when conducting STI analyses of PrEP studies (Section 4.4-4.6)
3. Re-analyse the STI data collected during the deferred phase of PROUD, and compare results and interpretations using different approaches (Sections 4.6.5 and 4.6.7)
4. Analyse STI data collected during the long-term follow-up of PROUD (Sections 4.7-4.8).

4.4 Systematic review of open-label studies

4.4.1 Rationale

As discussed in the Background of this chapter, only open-label PrEP studies can provide insight into risk compensation. Recognising this, Traeger et al. conducted a systematic review and meta-analysis of open-label studies, excluding blinded trials [120]. Their search included studies published before August 2017 that reported either sexual risk or STI outcomes for MSM taking daily PrEP. They aimed to estimate the effect of PrEP on STI status by combining the odds-ratios (ORs) derived from each study in a random-effects meta-analysis. Here I discuss the methods and findings from: (a) the meta-analysis, which is based on selected studies from the systematic review; and (b) the individual papers identified by the systematic review. As well as a stand-alone review, my critique informed approaches for analysing the STI data collected in PROUD.

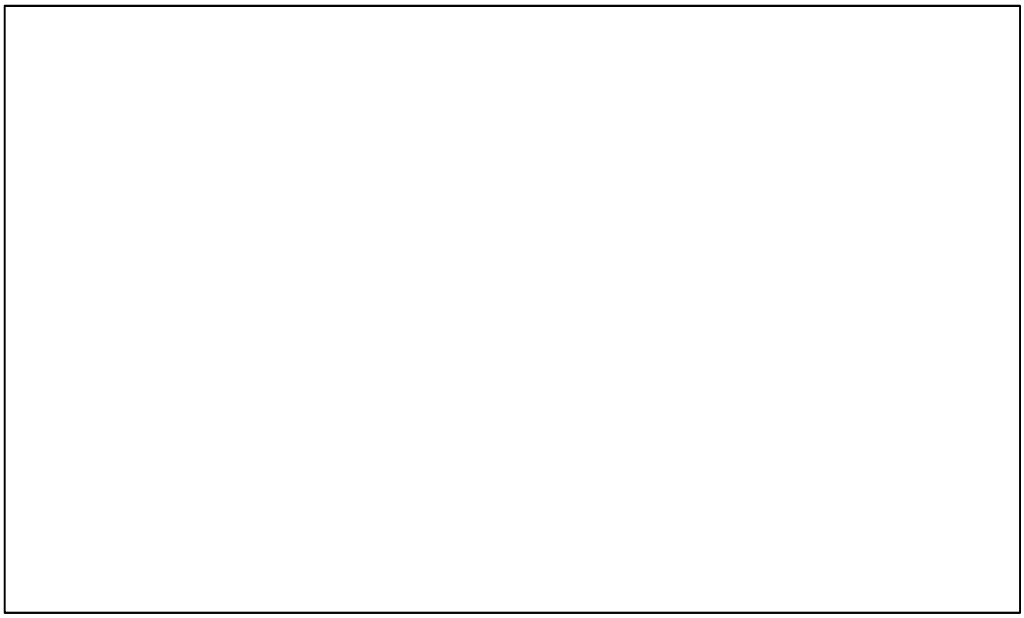
4.4.2 Critique of meta-analysis

Traegar et al. identified seventeen studies that fitted the inclusion criteria for their systematic review. However, the meta-analysis was limited to eight studies that reported

STI status at both baseline and one or more follow-up visits [13, 119, 121-126]. The outcome was defined as the number of participants diagnosed during follow-up. For inclusion into the meta-analysis, Traegar et al. mandated that studies had screened for STIs at baseline. Despite this, not all comparisons were made between follow-up and baseline status, e.g. PROUD compared IMM to DEF and Corales et al. compared STI prevalence pre- and post-PrEP [13, 121]. The PrEP effect was measured in two ways: (a) comparing STI prevalence in PrEP and non-PrEP-users; and (b) comparing STI prevalence over time in PrEP-users. Paired data for pre- and post-PrEP comparisons did not appear to be accounted for, possibly due to the lack of individual patient data (IPD). If ORs were not presented in the paper, these were calculated from reported prevalence data. If neither was available, Traegar et al. contacted the authors of the original paper.

The pooled OR for any STI diagnosis was 1.24 (95% CI: 0.99–1.54, p=0.59), and there was moderate heterogeneity between studies (I^2=50%, p=0.052) (Figure 4.1). PrEP-use was associated with a significant increase in rectal chlamydia alone (OR=1.59 [95% CI: 1.19–2.13], p=0.002), and in combination with gonorrhoea (any rectal) (OR=1.39 [95% CI: 1.03-1.87], p=0.03). An increase in chlamydia at any anatomical site (OR=1.23 [95% CI: 1.00-1.51], p=0.051) appeared to be driven by the increase in rectal infections. There was no evidence of a significant increase in gonorrhoea at any anatomical site (OR=1.13 [95% CI: 0.78], p=0.515), or for syphilis (OR=1.12 [95% CI: 0.86-1.47], p=0.41). Heterogeneity between studies was identified for any gonorrhoea (I^2=74%, p=0.004), urethral gonorrhoea (I^2=72%, p=0.030) and any rectal infections (I^2=66%, p=0.012).

Figure 4.1: Random-effects meta-analysis of effects of PrEP on STI diagnosis, presented by Traegar et al. (image redacted due to copyright)



This meta-analysis has several limitations. First, there was a stringent requirement that a screen for STIs had to take place on the initiation date of PrEP. PROUD should not therefore have been included in the meta-analysis given that STI screening was not mandated at baseline [13]. This requirement meant that some clearly relevant studies were excluded, such as Beymer et al., which compared STI incidence (rather than prevalence) pre- and post-PrEP [127]. Second, the stated use of binary outcomes was to maximise the number of studies in the meta-analysis. However, the follow-up periods differed between studies, ranging from six months to twelve months. Third, the studies collected data on different STIs and the analysis of "any STI" therefore means different things in different studies. For example, one study collected information only on syphilis infections [119], whereas others collected data on all bacterial STIs [13, 124, 125]. Finally, different types of ORs – unadjusted and adjusted – reported by the individual studies were combined. For instance, PROUD adjusted for the number of STI screens, whereas the others did not [13]. The question of adjusting for the number of screens, to control for so-called detection bias, is discussed in Section 4.6.3.

4.4.3 Critique of selected individual studies

The Traegar et al. systematic review lacked detail on the methods and results reported in the original studies. Therefore, I reviewed all 17 original papers, regardless of whether they were included in the meta-analysis, assessing the STI data collected, the use of controls, the associated statistical methods, and their findings. I then focussed on studies that: (a) presented STI data whilst the participants were receiving PrEP; and (b) had a control group, i.e. a group of individuals who concomitantly did not receive PrEP, or a pre-PrEP period of observation before PrEP was initiated. Of the 17 papers, I excluded six papers because they presented solely sexual behavioural data, and two were excluded because they lacked a control group for STI data.

I searched for additional papers published after the original search conducted by Traegar et al. Using the search criteria ["STI"[ti] OR "sexually transmitted infection"[ti] OR "STD"[ti] OR "sexually transmitted disease"[ti]] AND ["pre-exposure prophylaxis"[ti] OR "PrEP"[ti] OR "preexposure prophylaxis"[ti]], I identified 254 papers were published between 15/08/2017 and 01/09/2018. Five were considered relevant based on title, but four were subsequently excluded upon reading the full paper. The remaining retrospective cohort study was included in my review [128]. Thus a total of ten papers were scrutinised (Table 4.1) [13, 119, 121-128].

STI data collection

One study did not specify the screening frequency, nor the infections screened for [121]. Seven studies reported that STI screening was conducted on a quarterly basis [122-128]. PROUD and iPrEX-OLE reported that screening occurred approximately every six months [13, 119]. In addition to these pre-planned time points, three studies, including PROUD, reported that screening could be conducted on indication, i.e. when a participant reported symptoms or through contact tracing [13, 119, 122].

Five studies collected diagnoses of syphilis and chlamydia and gonorrhoea at all three anatomical sites (rectal, urethral and oral) [13, 124, 125, 127, 128]. Three studies collected data on chlamydia and gonorrhoea infections but not by all anatomical sites [122, 124, 126]. Nine studies collected information on syphilis diagnoses [13, 119, 122-128]. iPrEX-OLE collected information on chlamydia, gonorrhoea and syphilis but only reported syphilis [119].

Control groups

The studies used different types of control groups, some using two or more different techniques. Eight studies used the pre-PrEP experience of the PrEP initiators as an internal control. Three studies compared STI prevalence at baseline with prevalence at later time points, after participants had started PrEP [123-125]. Five studies collected data pre- and post-PrEP [121, 122, 126-128]. Two of these five compared STI incidence in the twelve month period before and after PrEP initiation [127, 128]. The other three of these five studies compared the STI prevalence instead (one at twelve months and two at six months) [121, 122, 126]. In addition to the pre- and post-PrEP comparison, two studies used control groups of individuals who did not receive PrEP [126, 128]. One control group was comprised of patients after a post-exposure prophylaxis (PEP) prescription within the same clinic [128]; another group was comprised of HIV-negative MSM in the same region (presumably with an unknown PrEP status) [126]. These control groups are not ideal due to underlying differences in individuals that do and do not take PrEP. Although, Nguyen et al. adjusted for confounding factors in the analysis to account for these differences [128].

Of the remaining two studies, one was a cohort study composed of participants who had been previously enrolled in PrEP trials (iPrEX-OLE), and compared individuals who accepted the offer of PrEP against those who declined the offer [119]. The other study was PROUD, which was the only study with a randomised control group, thus providing the most robust comparison [13].

Statistical methods

The three studies which used STI prevalence at baseline as a reference used different analysis techniques [123-125]. Liu et al. did not report the statistical methods used, but described assessing the significance of time trends in STI prevalence and calculating overall incidence (but with no PrEP/no-PrEP comparison) [124]. Inappropriately, Lal et al. and Marcus et al. used chi-squared tests to compare STI prevalence at different time points. Marcus et al. compared trends in STI prevalence at three-monthly time-points from PrEP initiation [123, 125]. Lal et al. compared the proportion (cumulative incidence) with an STI between baseline and month three with that of the proportion between month three and twelve. However, in this study, participants had already initiated PrEP in the baseline to three-month comparison, and the time-periods differed in length, which is particularly problematic for cumulative incidence [123]. Therefore, I chose to compare STI prevalence reported at baseline with that at month twelve for this study (Section 4.4.4).

Of the five studies that compared STI rates pre- and post-PrEP, Beymer et al. was the only study to account for the dependency within individuals by using a Generalised Linear Mixed Model [127]. Corales et al., Golub et al. and Montano et al. compared the proportion of subjects with one or more STIs between the two periods, but none reported statistical tests [121, 122, 126]. Golub et al. used different time-scales pre- and post-PrEP (six months and three months, respectively), and the comparison is therefore uninterpretable [122]. Better inference is obtained via incidence rates and Poisson models which can accommodate different follow-up periods [127, 128]. Unfortunately, Montano et al. only compared STI prevalence between pre- and post-PrEP periods, despite comparing STI incidence between PrEP-users and HIV-negative controls [126].

iPrEX-OLE compared the incidence of syphilis between the PrEP initiators and the non-initiators. Although the statistical model was not reported, the presentation of hazard ratios suggests the Cox model was used [119]. PROUD used logistic regression models to analyse

the probability of an infection during the deferred phase, and adjusted for the number of screens received [13]. However, this approach fails to distinguish between those with a single infection and multiple infections, and does not fully capture the clinical burden of STIs (described further in Section 4.6.5).

Detection bias

Detection bias is a phenomenon whereby the more STI testing that is conducted the more infections that are diagnosed [129]. In general, more STI screens are performed during the receipt of PrEP, likely related to increased visits to sexual health clinics to collect the PrEP prescription. The issue of detection bias was considered by four studies [13, 126-128]. Montano et al. considered symptomatic infections (urethral gonorrhoea and syphilis) and asymptomatic infections separately, since the former are likely to self-refer and therefore less affected by the testing schedule [126]. However, this is an over-simplification of why individuals receive an STI screen, e.g. does not consider contact tracing or tests of cure. Beymer et al. surprisingly reported a 7% decrease in the average number of STI screenings between the pre-PrEP period to the post-PrEP period (p<0.0001), but they did not appear to account for this in their analysis [127]. Nguyen et al. adjusted for the number of screens pre- and post-PrEP in a Poisson model but acknowledged that they may not have accounted for detection bias sufficiently due to the systematic screening in the PrEP-users [128]. The fourth study was PROUD, which is discussed in Section 4.6.3 [13].

4.4.4 Main STI findings from the individual studies

The three studies comparing STI prevalence to baseline observed some differences over time [123-125]. Lal et al. reported a significant increase in the proportion with an STI between baseline and month 12 (12.3% vs 29.5%, p=0.002) [123]. Liu et al. found that the proportion with a rectal and pharyngeal STI reduced between baseline and week 24 (15% to 9% and 11% to 7%, respectively [estimated from figure in paper]), and then increased at

week 48 (14% and 9%, $p<0.05$) [124]. Marcus et al. found no significant change in STI prevalence between baseline and month 12, except for an increase in urethral gonorrhoea (0.9% to 2.5%, $p=0.012$) and rectal chlamydia (7.7% to 14.1%, $p<0.001$) [125].

All four studies comparing pre- and post-PrEP periods found differences in STI rates [121, 126-128]. Nguyen et al. reported an increase in overall STI incidence rate (incidence rate ratio (IRR) =1.72 [95% CI: 1.22-2.40]). After adjusting for the number of screens, this difference was attenuated and was not formally statistically significant (adjusted incidence rate-ratio (aIRR): 1.39 [95% CI: 0.98-1.96]) [128]. This study also compared STI incidence between PrEP-users and PEP-users, and incidence was higher among PrEP-users for all STIs (IRR=1.76 [95% CI: 1.14-2.71]), with the exception of oral gonorrhoea (IRR=0.53 [95% CI: 0.23-1.25]). Beymer et al. observed a significant increase in the incidence of rectal chlamydia (IRR=1.83 [95% CI: 1.13-2.98], $p=0.01$) and syphilis (IRR=2.97 [95% CI: 1.23-7.18], $p=0.02$) comparing the pre- and post-PrEP periods [127]. In contrast, Corales et al. reported a reduction in the proportion of subjects with at least one STI diagnosis between the six months pre- and post-PrEP (7.4% vs. 3.0%, $p=0.17$) [121]. In a similar analysis over 12 month periods, Montano et al. showed an increase in the prevalence of chlamydia (6.5% to 22.2%, $p=0.001$) and gonorrhoea (10.2% to 19.4%, $p=0.06$), but a (non-significant) decrease in syphilis (10.2% to 6.5%, $p=0.33$) [126]. For this cohort, STI incidence in the PrEP-users was substantially higher than that of the HIV-negative population, e.g. chlamydia incidence: 53.9 per 100 PY for PrEP-users vs. 2.3 per 100 PY for HIV-negative population (*p*-values or denominators not reported).

In the iPrEx-OLE cohort, there was no significant difference in syphilis incidence between PrEP-recipients and non-recipients (7.2 per 100 PY vs. 5.4 per 100 PY, HR=1.35 [95% CI: 0.83-2.19]) [119]. In PROUD, after adjustment for the number of screens, there was no evidence of a difference between the trial arms for individual STIs or overall (OR=1.33 to aOR=1.07 [95% CI: 0.78-1.46], $p=0.74$) [13].

4.4.5 Summary

Several open-label PrEP studies have attempted to address the impact of PrEP on STI incidence. Most identified an increased risk of STIs among PrEP-users but findings were not consistent; this was supported by the heterogeneity identified in the Traegar et al. meta-analysis [120]. Also, the studies suffered from serious methodological limitations, for example, using control groups which were particularly susceptible to temporal (e.g. background changes in STI rates over time for pre- and post-PrEP comparisons) [121, 122, 127, 128] or selection bias (e.g. comparison with participants not continuing with PrEP in iPrEX) [119]. The statistical approaches used were not the most appropriate for making pre- and post-PrEP comparisons or for analysing repeated outcome data. Furthermore, in most studies follow-up was limited to one year after PrEP initiation. The most fundamental limitation, however, was that none of the studies, apart from PROUD had a randomised comparison, and therefore, the control group may differ substantially from the group who initiated PrEP. PROUD is the only study that was both randomised and open-label, and provides the most robust evidence on the impact of PrEP on STI incidence. It also has a relatively long period of follow-up (up to four years). In the rest of this chapter, I present new analyses of PROUD, along with a detailed discussion of the methodological issues underlying these analyses. This is preceded by a description of the STI data collected in PROUD.

Table 4.1: Review of methods used to assess effect of PrEP on STIs in the literature

Study	STI data collected	Screening frequency	Control group	Statistical methods	Findings
Beymer [127]	r/u CT and r/u/o GC, syphilis	Quarterly STI screening (when on PrEP)	Historical control group of pre-PrEP	Generalised linear mixed model (GLMM) to determine the difference in STI incidence 365 days pre- and the 365 days post-PrEP. All STIs were included in the same model and the interest was with the interaction between the STI (and location) and the pre-/post-PrEP variable. The GLMM was a log-link random intercept Poisson model with the log of time since last screen as an offset.	There were no significant changes in r/u/o GC or uCT. Significant changes were observed in rCT (IRR=1.83, *p*=0.01) and syphilis (IRR=2.97, *p*=0.02).
Corales* [121]	Not specified	Not specified	Historical control of group pre-PrEP	Compared the proportion of those with infection in the six months prior to the proportion in the six months after PrEP. No statistical test reported). I compared using chi-squared tests.	7.4% self-reported STI in six months prior. After initiating PrEP, 3.0% reported an STI (*p*=0.17).
Grant* [119]	CT, GC and syphilis (only present syphilis)	Every 24 weeks or where symptoms present	Participants of the iPrEX trial that did not uptake PrEP in the open label extension (not randomised)	Reported incidence of syphilis comparing those that were on PrEP to those that did not take up PrEP use generalised estimating equations.	There was no significant difference in rates of syphilis between PrEP and non-recipients (7.2 vs. 5.4 per 100 PY, HR=1.35 [95% CI: 0.83-2.19]).
Golub* [122]	r/u CT and GC and syphilis	Quarterly or where symptoms present	Historical control of group pre-PrEP	Presented proportions positive at each quarter. Also presented the proportion with an STI in the 6 months prior but did not directly compare the rates. No statistical test reported.	13% of participants were diagnosed with an STI in the six months pre-PrEP. At three months, 13% were diagnosed with an STI but these cannot be compared due to the different time-frames.
Lal* [123]	r/u CT and r/o GC and syphilis	Quarterly	None (but collected STI data at start of PrEP)	Compared incidence between the 0-m3 and the m3-m12 using negative-binomial model. Proportion of participants with at least 1 STI in 0-m3 and m3-m12 were compared by using a chi-square test. I compared cumulative at baseline with m9-m12 using chi-squared tests.	There was a significant increase in the proportion with an STI between baseline (12.3%) and m9-m12 (29.5%)(*p*=0.005).

Table continued on following page

Liu* [124]	r/u/o CT and GC and syphilis	Quarterly	None (but collected STI data at start of PrEP)	STI incidence was calculated from enrolment until the last STI test. Presented proportion of individuals with infection (by anatomical site) at each time interval in a figure	Proportion with a rectal and pharyngeal STI reduced between baseline and week 24 (15% to 9% and 11% to 7%, respectively [estimated from figure in paper]), and then increased at week 48 (14% and 9%, $p<0.05$). Syphilis and pharyngeal infections remains relatively stable during follow-up.
Marcus* [125]	r/u/o CT and GC and syphilis	Quarterly	None (but collected STI data at start of PrEP)	Calculated cumulative incidence of STIs by time point using the Kaplan Meier method and the proportion of positivity at each quarter was analysed using chi-squared tests.	STI positivity by quarter remained stable from baseline to month 12, except uGC (0.9%-2.5%, $p=0.012$) and rCT (7.7%-14.1%, $p<0.001$).
McCormack* [13]	r/u/o CT and GC and syphilis	Six monthly or on indication	Randomised control group of deferred PrEP	Proportions and logistic regression analysis adjusting for number of screens to account for detection bias.	After adjustment for the number of screens, there was no difference in STI positivity between the trial arms (OR=1.33 to aOR=1.07 [95% CI: 0.78-1.46], $p=0.74$). More detailed analysis presented in remainder of chapter.
Montano* [126]	rCT, r/u GC and syphilis	Quarterly	Pre- and post-PrEP and HIV-negative population	Compared proportions of infections before and after PrEP. Compared STI incidence between PrEP-users and HIV-negative population. No statistical test reported. I used chi-squared tests to compare pre- and post-PrEP proportions. Incidence could not be formally compared due to no presentation of denominator.	There was an increase in the prevalence of chlamydia (6.5% to 22.2%, $p=0.001$) and gonorrhoea (10.2% to 19.4%, $p=0.06$), but a decrease in syphilis (10.2% to 6.5%, $p=0.33$). STI incidence in the PrEP-users was substantially higher than that of the HIV-negative population: CT, 53.9 vs. 2.3 per 100 PY; GC, 46.3 vs. 2.1 per 100 PY.
Nguyen [128]	r/u/o CT and GC and syphilis	Screen at patients' discretion in year prior and then quarterly when on PrEP	Historical control of group pre-PrEP and a post-PEP control group	Incidence analysis with multivariate Poisson analysis, adjusting for the number of screening visits during the 12 months pre-PrEP and 12 months post-PrEP periods.	Increase in overall STI rates between the pre- and post-PrEP phase (IRR=1.72, 95% CI: 1.22-2.40). After adjusting for number of screens, this difference remained but was inconclusive (aIRR: 1.39 [95% CI: 0.98-1.96]). STI risk was among PrEP-users was higher than that observed in the PEP group (aIRR: 1.76 [95% CI: 1.14-2.71]).

Table continued on following page

STI, sexually transmitted infection; r, rectal; u, urethral; o, oral; CT, chlamydia; GC, gonorrhoea; PrEP, pre-exposure prophylaxis; *p*, p-value; CI, confidence interval; HR, hazard ratio; PY, person-years; GEE, Generalised estimating equations; PEP, post-exposure prophylaxis; IRR, incidence rate ratio; aIRR, adjusted incidence rate ratio;
*Included in Traegar et al. meta-analysis

4.5 STI data collection in PROUD

4.5.1 STI history prior to enrolment

Participants self-completed a questionnaire at enrolment and were asked to specify which, if any, bacterial STIs they had been diagnosed with in the prior twelve months. 95.0% (517/544) completed these questions, and 60.5% (313/517) reported at least one STI diagnosis.

At enrolment, clinicians were asked to report historical information on whether the participant had ever been screened for, or diagnosed with, each of the STIs (not presented in this thesis).

4.5.2 STI screening at enrolment and follow-up

PROUD visits were scheduled to occur quarterly to obtain PrEP and perform HIV screens, with an additional visit one month after the initiation of PrEP primarily to check adherence. At the start of the trial, clinics were asked to perform pharyngeal swabs, rectal swabs, and urine/urethral swabs for gonorrhoea and chlamydia, and collect blood for syphilis every six months. At other visits, including enrolment and one month after PrEP initiation, clinics were advised to screen for STIs if indicated, and according to routine clinic practice. 49.6% (270/544) participants had an STI screen at baseline. The protocol amendment in October 2014 required that STI screens be conducted every three months, rather than every six months, in line with changes in national guidelines [130]. However, more frequent STI screening pre-dated this change due to screening by indication or clinic practice.

For each infection, the number of screens carried out and the number of infections identified since the participant's last visit was recorded, by anatomical site when relevant (Lab CRF,

Appendix 6). The analytical implications of combining different STIs and/or different sites of infection are discussed in Section 4.6.4. One screen was reported for each infection at the majority of visits (87%), which was likely to have occurred at that current visit. Data were also collected on viral infections, such as: hepatitis B, genital warts, and genital herpes, but these are not analysed in this thesis.

4.5.3 STI screening by phase of trial

The deferred phase was defined according to that described in Section 2.5.3. The date of the participant's final STI screen was used if this was prior to their assigned deferred phase. The post-deferred phase was defined as the time from the end of the participant's deferred phase to the date of their last STI screen (if screened during this period). STIs diagnosed on the last date of their deferred phase were attributed to the deferred phase.

During the deferred phase, 509 participants (IMM 265 vs. DEF 244) contributed at least one of 1969 screens (IMM 1093 vs. DEF 876) over a total follow-up of 462.7 PY. Of the 35 participants who were not screened, 3 were diagnosed with HIV at baseline (IMM 2 vs. DEF 1), 13 (IMM 2 vs. DEF 11) were last seen at baseline, 11 (IMM 5 vs. DEF 6) were seen after randomisation but did not receive a screen, and 8 (IMM 1 vs. DEF 7) acquired HIV before receiving an STI screen.

453 (IMM 245 vs. DEF 208) participants contributed 3458 screens (IMM 1832 vs. 1626) during the post-deferred phase over 779.1 PY. Of those not screened during this period, 21 (IMM 5 vs. DEF 16) were censored due to diagnosis of HIV infection (either during the deferred phase or early during the post-deferred phase), 37 (IMM 17 vs. DEF 20) never attended clinic during this period, and 1 (IMM 0 vs. DEF 1) participant attended clinic but was not screened.

4.6 Methodological considerations and PROUD results

This section of the chapter discusses methodological challenges in analysing STI data, both generally and in assessing whether STI incidence is affected by the provision of PrEP. A re-analysis of the deferred phase of PROUD is presented in this section to demonstrate specific methodological points.

4.6.1 Control group

The principal methodological consideration is defining an appropriate control group. There are two main possible approaches. First, one can compare the IMM and DEF groups during the deferred phase in terms of STI outcomes, as was reported in the main trial publication [13]. This comparison is unbiased (randomisation ensures the comparability of the two groups) and the groups are compared during the same period of calendar time, an important consideration given that STI incidence can show strong temporal variation (Section 4.8). A limitation of this approach is that the very high efficacy of Truvada was not generally appreciated until the publication of the results from PROUD and IPERGAY [12, 13]. Thus risk behaviour during the deferred phase may not reflect current behaviours.

The second approach is to compare the two periods when the DEF group did and did not have access to PrEP in a before-and-after analysis (pre- and post-PrEP). This can be done either by (a) a direct comparison of STI incidence in the deferred and post-deferred phases, or (b) estimating STI incidence by calendar time and observing whether there was a detectable shift when knowledge of Truvada efficacy became widely known. The IMM group could also be informative for (b). However, a before-and-after analysis is less robust than the first approach described above. There are likely to be temporal changes in STI incidence and sexual risk behaviour is not static over time, likely towards lower risk as seeking enrolment in the trial suggests a self-perception of high risk at the point of enrolment [131].

However, the indication of an increase in HIV incidence during the deferred phase may suggest this is not the case in PROUD (Chapter 2).

4.6.2 Inclusion of baseline infections

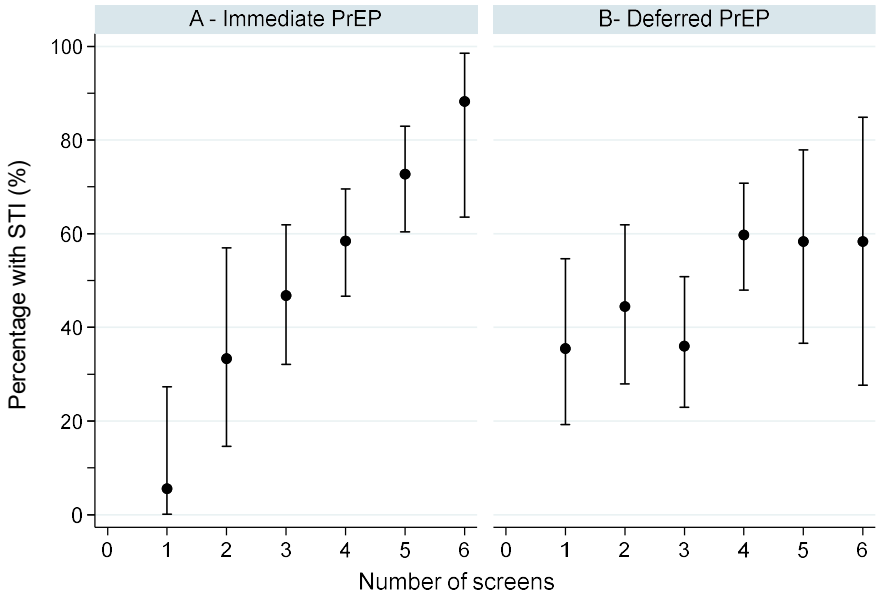
STI screens were not conducted on all participants at baseline as this was not a protocol requirement. This raises two analytical considerations: (a) how to account for the unknown STI status of participants at baseline; and (b) the inclusion/exclusion of infections diagnosed at baseline. A number of participants who were not screened at baseline, were subsequently diagnosed with an infection at their first screen, e.g. 6% of participants were diagnosed with oral gonorrhoea at their first screen after baseline (data not shown). As the infections could have genuinely been acquired during follow-up, they were included and therefore analyses presented in this chapter may over-estimate the number of infections acquired during follow-up. Infections at baseline were not counted in the majority of analyses as they could dilute differences between trial arms seen during follow-up. However, they were included in the analyses over calendar time (Section 4.8).

4.6.3 Detection bias

Detection bias, defined in Section 4.4.3, is a highly pertinent issue in PROUD. First, during the deferred phase there was a highly significant difference in the number of STI screens between IMM and DEF groups (mean 4.1 vs. 3.6, p=0.0008). This was probably due to IMM participants attending clinic more frequently in order to obtain PrEP [13]. Second, the protocol STI screening schedule changed from every six months to every three months in October 2014, complicating interpretation of temporal trends in general, and comparisons of the deferred phase and post-deferred phases in particular.

Figure 4.2 shows the relationship between the number of screens and the probability of detecting an STI during the deferred phase, by trial arm. In the IMM arm, a strong linear relationship was seen: a 92% increase in the odds of STI positivity for each additional STI screen (OR=1.9 [95% CI: 1.5-2.4], p<0.001). The trend was not as clear in the DEF arm but remained statistically significant (OR=1.3 [95% CI: 1.1-1.5], p=0.001).

Figure 4.2: Relationship between number of screens and probability of STI in deferred phase, by trial arm



Adjustment for number of screens

In the main Lancet publication, a logistic regression analysis was performed adjusting for the number of screens (fitted as a linear term) [13]. Figure 4.2 casts doubt on the validity of the analysis since it suggests that the effect of the number of screens should be modelled differently in the IMM and DEF arms. On the other hand, there is no obvious explanation why the relationship should be dependent on arm. Possible reasons other than chance could be the loss of the highest risk participants in the DEF arm due to HIV infection, or the loss of low risk participants in the DEF arm due to lack of need for PrEP.

Table 4.2 shows unadjusted and adjusted estimates repeating the analysis presented in The Lancet. After adjusting for the number of screens, the trial arm effect shifted towards the null for all outcomes. After adjustment, there remained an indication of an increased risk of chlamydia in the IMM arm; however, this was not formally significant.

Table 4.2: Logistic regression analysis of STI diagnosis during deferred phase. Comparison of trial arms, with and without adjustment for the number of screens

STI	OR (95% CI)	*p*-value	aOR (95% CI)	*p*-value
Any	1.4 (1.0-2.0)	0.068	1.1 (0.8-1.6)	0.548
Key	1.3 (0.9-1.8)	0.173	1.1 (0.8-1.7)	0.458
Chlamydia	1.6 (1.1-2.4)	0.024	1.4 (0.9-2.1)	0.110
Gonorrhoea	1.2 (0.8-1.7)	0.366	0.9 (0.6-1.4)	0.664
Syphilis	1.4 (0.8-2.4)	0.310	1.3 (0.7-2.4)	0.327

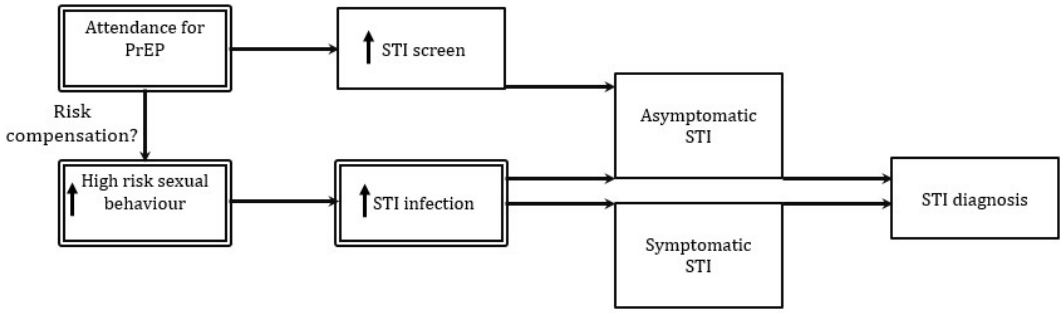
STI, sexually transmitted infection; OR, odds ratio (IMM vs DEF); CI, confidence interval; aOR, adjusted OR (adjusting for number of screens as a linear term); key, rectal chlamydia, rectal gonorrhoea or syphilis.

Appropriateness of adjusting for number of screens

Figure 4.3 illustrates the complexity in ascertaining whether PrEP leads to a greater risk of STI infection (via risk compensation). In a real-life setting, we can only know the number of STI diagnoses and the number of screens an individual has received, rather than their true STI status. To account for the relationship between STI screens and STI diagnoses, several studies have adjusted for the number of STI screens in their analysis [13, 128]. However, whilst this is appropriate for an external confounder (e.g. additional screening driven by clinic attendance for PrEP - which we want to adjust for), it is not appropriate for a variable that lies on the causal pathway (e.g. clinic attendance driven by symptoms - which we do not want to adjust for) (Figure 4.3) [132, 133]. Other reasons for attending for a screen include a perceived high risk of acquiring STIs and partner notification by a sexual contact who has an STI. Therefore adjusting for the number of screens in the analysis may be an *over-adjustment*, defined as introducing bias or reducing precision [132]. In reality, the number of STI screens (and their timing) is likely both a confounder *and* an instrumental variable and it is neither completely correct to apply adjusted or unadjusted models. Causal

models, which require information on the reasons for screening, would be a possible approach to resolve this dilemma [134]. In summary, caution is needed when using STI diagnoses as an indicator of risk compensation. Nonetheless, it remains the most relevant indicator and presenting results with and without adjustment for the number of screens is a pragmatic compromise.

Figure 4.3: The mediating role of STI screening between PrEP and STI infection



Assessing the impact of a different screening schedule

To gain some insights into the impact of screening frequency on measured STI incidence I conducted an analysis of PROUD data after January 2015, by which time the protocol schedule changed from STI screening every six months to every three months (plus testing on indication). The analysis was restricted to participants with at least three consecutive three-monthly screens after this protocol change, and if multiple screens were conducted within the same quarter, then results were combined. STI incidence was first calculated using this "complete" dataset based on a three-monthly screening schedule. Next, incidence was calculated under hypothetical six-monthly screening by not directly counting the results of screens conducted at months 3, 9, 15, etc. Instead, any STIs diagnosed at these visits were projected forwarded to the next visit under the assumption that they would not have naturally cleared in an interval of less than three months. This is equivalent to counting STIs diagnosed at consecutive screens as one infection rather than two infections.

Follow-up time was defined from the first screen after January 2015 until their last screen included in the dataset. 306 participants were included in the analysis, with a median of 6 (IQR: 5-7) quarterly screens. Total follow-up time was 360.9 person-years; the median follow-up was 1.3 years (IQR: 1.0-1.5 years). During this period, 132 participants were diagnosed with chlamydia, 137 participants diagnosed with gonorrhoea and 82 with syphilis.

There was an increase in STI incidence assuming a three-monthly screening pattern compared to six-monthly (Table 4.3): a relative increase of 9.3% for chlamydia (p=0.39); 9.2% for gonorrhoea (p=0.37); and 23.0% for syphilis (p=0.07). The more pronounced effect observed for syphilis was driven by a higher rate of consecutive diagnoses compared to chlamydia and gonorrhoea. This could be partly due to a reporting bias whereby the STI is recorded as a new infection prior to clearance. Syphilis is particularly susceptible to this given the longer recuperation period [135-137]. This is an indication that the STI data captured in PROUD would have benefitted from detail on the time of diagnosis, time of treatment, test of cure, and reason for each screen.

Table 4.3: STI incidence by hypothetical three- and six-monthly STI screens

			Six-monthly screening		**Three-monthly screening**		
STI	***n***	**PY**	**Total diagnoses**	**Incidence (per 100 PY)**	**Total diagnoses**	**Incidence (per 100 PY)**	**Relative increase in incidence**
Chlamydia	300	356.7	183	51.3	200	56.1	9.3
Gonorrhoea	300	356.7	195	54.7	213	59.7	9.2
Syphilis	306	360.9	135	37.4	166	46.0	23.0

STI, sexually transmitted infection; *n*, number of participants; PY, person-years.

The increase in STI incidence between six- and three-monthly screening highlights the importance of considering screening frequency when comparing trial arms, different studies or different phases within a study when screening frequency differs. However, as

discussed in the previous subsection, the best approach for dealing with this is unclear. For simplicity, subsequent analyses in this chapter will present unadjusted analyses.

4.6.4 Multiplicity: concurrent STIs and site of infection

STI screening is conducted according to anatomical site and infection. A swab is taken from the rectum and pharynx (oral) and occasionally the urethra, although this site is more typically assessed using a urine specimen. Nucleic acid amplification tests (NAATs) are run for both chlamydia and gonorrhoea using the same specimen. Syphilis requires a blood test to be conducted and tested using rapid plasma regain (RPR), enzyme-linked immunosorbent assay (ELISA) or Treponema pallidum haemagglutination (TPHA), depending on syphilis history. STI treatment is infection specific, although the duration of treatment may vary according to the anatomical site. Given the multiplicity of different STIs and different sites of infections, one needs to consider how to combine this complex information, according to the question of interest. In this subsection, I illustrate these considerations using data from the entirety of PROUD.

Concurrent STIs

Table 4.4 shows the permutations of concurrent diagnoses of chlamydia (any site), gonorrhoea (any site), and syphilis. Infections were mostly detected in isolation (82.9%), although concurrent chlamydia and gonorrhoea was not uncommon (12.5%). As each infection is clinically and epidemiologically distinct (including infectivity) it is logical to analyse them separately.

Table 4.4: Permutations of concurrent STIs, by infection

Chlamydia	Gonorrhoea	Syphilis	*n*	%
	■		453	39.1
■			295	25.4
		■	214	18.4
■	■		126	10.9
■		■	32	2.8
	■	■	21	1.8
■	■	■	19	1.6

n, number of concurrent diagnoses

Site of infection

Table 4.5 shows the permutations of the different sites where chlamydia and gonorrhoea were detected. Chlamydia was generally detected in the rectum alone (62.9%), although urethral chlamydia was also relatively common (27.9% overall). The frequencies of rectal and oral gonorrhoea were similarly high, with infection at these sites commonly observed (60.3% and 55.3% overall, respectively). The low frequencies of oral chlamydia alone (6.4%) and urethral gonorrhoea alone (8.2%) raise questions about the cost-effectiveness of these screens.

Table 4.5: Permutations of concurrent STIs, by site of infection

Chlamydia				
Rectal	**Oral**	**Urethral**	***n***	**%**
■			297	62.9
		■	85	18.0
■		■	34	7.2
	■		30	6.4
■	■		13	2.8
■	■	■	10	2.1
	■	■	3	0.6
Gonorrhoea				
Rectal	**Oral**	**Urethral**	***n***	**%**
■			186	30.0
	■		173	27.9
■	■		119	19.2
		■	51	8.2
■		■	39	6.3
■	■	■	30	4.8
	■	■	21	3.4

n, number of concurrent diagnoses

As the treatment of chlamydia and gonorrhoea does not depend on the site of infection (although the duration of treatment may) it makes sense to create composite variables for the detection of infection at any site, separately for chlamydia or gonorrhoea. A number studies reporting STI data, including those reviewed in Section 4.4, do not distinguish by

site of infection in their analysis. Although composite variables are the most relevant from a clinical and public health perspective, analyses by site of infection may provide insights into the mechanisms of risk compensation and shifts in population sexual risk behaviour. For example, if PrEP largely impacted the use of condoms for anal sex, one would anticipate changes in the frequency of urethral and anal infections rather than the frequency of oral infections.

Composite variables

The analysis of baseline predictors of HIV (Chapter 2) introduced the concept of a "key STI", defined as rectal chlamydia, rectal gonorrhoea, or syphilis. The rationale for this was that these infections were most likely contracted through receptive anal sex without a condom, and this variable may therefore be a useful surrogate for being at high risk of acquiring HIV infection. Table 4.6 shows the different components of this composite variable and demonstrates that each infection makes an important numerical contribution.

Table 4.6: Permutations of concurrent key STIs, by infection

Rectal chlamydia	Rectal gonorrhoea	Syphilis	*n*	%
	■		259	30.3
■			229	26.8
		■	222	26.0
■	■		80	9.4
■		■	29	3.4
	■	■	19	2.2
■	■	■	16	1.9

n, number of concurrent diagnoses

In addition, an analysis of the total number of STI diagnoses (regardless of site) gives an overall picture of STI risk and a measure of clinical burden. It is also of interest to describe the proportion of participants who do not experience any STIs; given their high endemicity and the long follow-up in PROUD, this is an indication (although not proof) that an

individual participant is at low risk of HIV infection and thus possibly taking PrEP needlessly. Variability between individuals is discussed further in Section 4.6.5.

Analyses in this section and Section 4.7 will consider concurrent diagnoses of the same pathogen at different anatomical sites (e.g. rectal chlamydia and urethral chlamydia) as one infection due to the need for only one form of treatment. Concurrent pathogens will be counted as multiple infections even when present at the same anatomical site since they require different treatments, and, therefore, provide information on the clinical burden of these diagnoses. Analyses in this section and the next therefore use composite STI outcomes: any; key; and infection specific (chlamydia, gonorrhoea and syphilis).

4.6.5 Repeat infections

The standard approach for analysing disease incidence data is Poisson models. These models assume that all individuals have the same underlying rate of experiencing the event of interest. It is important to examine this assumption given that individuals can experience several episodes of each STI. When this assumption is violated it is referred to as over-dispersion, frailty, or heterogeneity [138]. An important consequence of ignoring over-dispersion and incorrectly fitting Poisson models is that standard errors for incidence rates and for incidence rate ratios (when comparing two or more groups) are under-estimated.

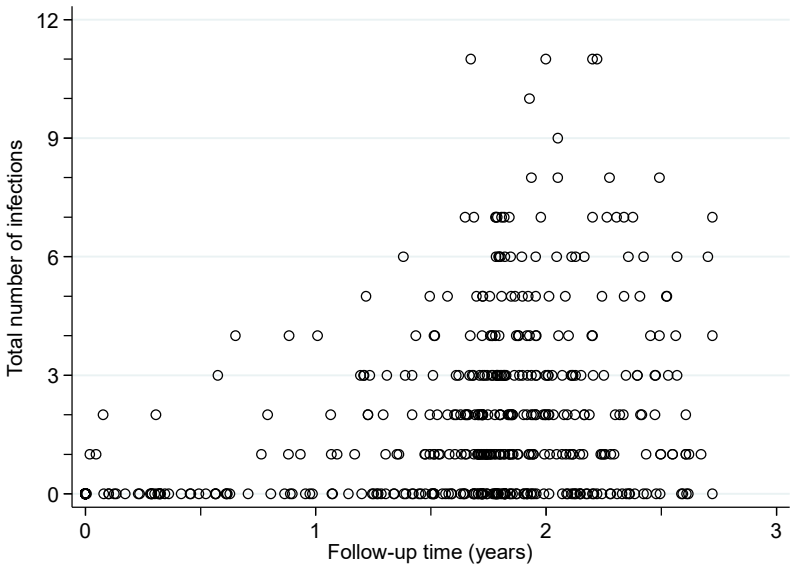
There are a number of possible alternative models when heterogeneity is present in count data, including negative-binomial, zero-inflated Poisson, and zero-inflated negative-binomial [139]. Negative-binomial models account for heterogeneity by incorporating a dispersion parameter (α). The Poisson model is a special case of the negative-binomial model, where $\alpha=0$ [138, 140]. Zero-inflated models employ two components that correspond to two zero generating processes. The first process is governed by a binary distribution that generates “structural” zeros [138]. The second process is governed by the

Poisson or negative-binomial distribution that generates counts, some of which may also be zero.

Comparison of models using post-deferred phase in PROUD

I illustrate the problem using data from the post-deferred phase in PROUD (combining IMM and DEF groups) since the longer follow-up gives more information on the degree of heterogeneity. Of the 453 participants with a screen during the post-deferred phase, follow-up time ranged from 2 days to 2.7 years (total follow-up 779.1 PY). The number of STIs diagnosed per individual ranged widely (range: 0-11, median 1 [IQR: 0-3]). Many participants (156/453, 34.4%) had no STI diagnoses during this period, even those with a long follow-up (Figure 4.4).

Figure 4.4: Association between total follow-up time and number of STI diagnoses in the post-deferred phase



Each model was fitted with an offset for the follow-up time, defined from the start of the post-deferred phase until the last STI screen in the trial. From the parameter estimates and each individual's follow-up time, the expected number of participants diagnosed with 0, 1 ,2, 3, … infections was calculated for each model (Table 4.7). This clearly indicates an excess of individuals with no infections and individuals with a large number of infections compared

to predictions by the Poisson model. The zero-inflated Poisson model, whilst accounting appropriately for the excess zeros, did not adequately predict the number of participants with a large number of infections. The number of predicted infections from the zero-inflated negative-binomial model was similar to that from the negative-binomial.

Table 4.7: Observed and predicted number of STI diagnoses per individual during the post-deferred phase

		Predicted, by statistical model			
Number of infections	**Observed**	**Poisson**	**NBREG**	**ZIP**	**ZINB**
0	156	81.7	147.1	152.4	153.1
1	88	114.0	102.8	63.3	90.4
2	63	108.9	69.5	74.2	69.4
3	56	76.1	46.2	65.8	49.1
4	28	41.9	30.4	46.4	33.0
5	20	19.1	19.9	27.2	21.6
6	17	7.5	13.0	13.7	13.8
7	15	2.6	8.4	6.1	8.7
8	4	0.8	5.5	2.4	5.4
9	1	0.2	3.6	0.9	3.3
10	1	0.1	2.3	0.3	2.0
11+	4	0.0	4.4	0.1	3.2
BIC	---	1872.3	1682.2	1739.0	1684.9

NBREG, negative-binomial regression; ZIP, zero-inflated Poisson; ZINB, zero-inflated negative-binomial, BIC, Bayesian information criterion

To identify the "best" fitting model it is important to account for the additional parameters in the more complex models (one extra parameter for zero-inflated Poisson and negative-binomial models, relative to Poisson; two extra parameters for zero-inflated negative-binomial). One way of doing this is via the Bayesian information criterion (BIC), which is a function of log-likelihood, the number of observations, and the number of parameters in model. Lower values of BIC are indicative of a better model fit [141]. Table 4.8 compares the BIC between the different models for different STI outcomes. In general, the negative-binomial model gives the best fit using this criterion, although the zero-inflated Poisson

model performed better for chlamydia. For consistency, negative-binomial models are used in this section and Section 4.7.

Table 4.9 presents the parameter estimates from the negative-binomial model for each STI outcome: the constant (or the logarithm of the average incidence rate) and the shape parameter, α. Heterogeneity was highly significant for all infections (p<0.001), although syphilis had the highest estimate of α (3.1 [95% CI: 2.2-4.4]).

Table 4.8: Comparison of model fit for models of STI diagnoses in post-deferred phase

	Poisson		NBREG		ZIP		ZINB	
STI	**Estimated incidence (95% CI)**	**BIC**	**Estimated incidence (95% CI)**	**BIC**	**Estimated incidence (95% CI)**	**BIC**	**Estimated incidence (95% CI)**	**BIC**
Any	115.0 (107.7-122.8)	1872.3	114.8 (103.4-127.5)	1682.2*	114.0 (104.3-123.7)	1739.0	114.6 (103.0-126.3)	1684.9
Key	90.0 (83.6-96.9)	1739.7	89.8 (79.4-101.6)	1511.6*	89.4 (80.4-98.4)	1569.0	89.8 (79.1-100.5)	1515.1
Chlamydia	40.6 (36.4-45.4)	1016.7	40.5 (35.6-46.1)	1006.0	40.5 (35.3-45.7)	996.7*	40.5 (35.3-45.7)	1002.8
Gonorrhoea	46.7 (42.2-51.8)	1097.0	46.5 (41.2-52.6)	1079.4*	46.5 (41.1-51.9)	1086.3	46.5 (41.2-52.6)	1085.5
Syphilis	28.7 (25.2-32.8)	983.3	29.1 (23.5-36.1)	822.7*	28.7 (23.4-34.0)	859.5	29.1 (23.5-36.1)	828.8

NBREG, negative binomial regression; ZIP, zero-inflated negative binomial regression; ZINB, zero-inflated negative-binomial; STI, sexually transmitted infection; CI, confidence interval; BIC, Bayesian-information criteria; key, rectal chlamydia, rectal gonorrhoea or syphilis.
*Indicates best fitting model according to BIC

Table 4.9: Negative-binomial model parameter estimates for models of STI diagnoses in post-deferred phase

	Constant (95% CI)	**Estimated incidence, per 100 PY (95% CI)**	**Shape parameter, α (95% CI)**	***p*-value**
Any	0.1 (0.03, 0.2)	114.8 (103.4, 127.5)	0.7 (0.6, 1.0)	<0.001
Key	-0.1 (-0.2, 0.02)	89.8 (79.4, 101.6)	1.1 (0.8, 1.4)	<0.001
Chlamydia	-0.9 (-1.0, -0.8)	40.5 (35.6, 46.1)	0.5 (0.3, 0.9)	<0.001
Gonorrhoea	-0.8 (-0.9, -0.6)	46.5 (41.2, 52.6)	0.5 (0.3, 0.8)	<0.001
Syphilis	-1.2 (-1.4, -1.0)	29.1 (23.5, 36.1)	3.1 (2.2, 4.4)	<0.001

STI, sexually transmitted infection; CI, confidence interval; PY, person-years; key, rectal chlamydia, rectal gonorrhoea or syphilis
p-value for likelihood ratio test of shape parameter=0

4.6.6 Incidence vs. cumulative incidence

This main PROUD trial publication compared selected STI outcomes (any STI, chlamydia, gonorrhoea, syphilis, and rectal [chlamydia or gonorrhoea]) between the IMM and DEF arms during the deferred phase [13]. It did this using a binary approach by defining the endpoint of at least one occurrence of each outcome (or "cumulative incidence"), using standard methods for proportions and logistic regression analysis. Two analyses were performed: an unadjusted analysis and a second analysis adjusting for the number of screens. The rationale for adjustment was discussed in Section 4.6.3. A binary approach for the deferred phase was considered to be acceptable for two reasons: (a) duration of follow-up was approximately the same (12 months) for most participants, although clinic non-attendance and early closure of the DEF arm meant that some participants had less follow-up (minimum 5.5 months); (b) the relatively short follow-up meant there should be relatively little loss of information by ignoring multiple episodes.

The more natural metric for measuring STI risk is incidence, the number of episodes divided by the duration of follow-up. This has several advantages: (a) it accounts for variation in duration of follow-up between individuals; (b) because data are not collapsed it should be statistically more powerful; and, (c) it is a better measure of the clinical burden of STIs than summarising whether or not individuals experienced any diagnoses. These advantages are more compelling the longer the duration of follow-up. The maximum follow-up in PROUD was 3.7 years and a binary analysis on this time-scale is highly inefficient.

Table 4.10 shows a re-analysis of the deferred phase of PROUD, comparing estimates of cumulative incidence (updated from the main trial publication) and incidence. Using negative-binomial models, confidence intervals for incidence estimates and IRRs (i.e. PrEP effect) account for between patient heterogeneity (see Section 4.6.5). Of note, the cumulative incidence analysis can ignore this complication due to masking of repeat

infections. Negative-binomial models included follow-up time as an offset to account for differential follow-up between participants.

For both the binary and incidence analyses, the proportions and incidences were consistently higher in the IMM arm, compared with the DEF arm, for each STI outcome (Table 4.10). ORs and IRRs were comparable for each STI outcome. The PrEP effect was not particularly strong, with the exception of chlamydia, which was significantly higher in the IMM arm for both analyses (OR=1.6 [95% CI: 1.1-2.4], p=0.024 and IRR=1.4 [95% CI: 1.0-2.0], p=0.027); this difference was driven by differences in rectal (IRR=1.6 [95% CI: 1.1-2.4], p=0.024) and oral diagnoses (IRR=2.7 [95% CI: 0.8-8.7], p=0.094)[8]. Despite the additional power for the incidence approach, the width of the confidence intervals for relative risks were comparable between the two approaches.

Whilst the two approaches produced similar estimates of relative STI risk between the IMM and DEF groups, their interpretation is different. The incidence estimates are arguably the easier to interpret and this metric is used for the remaining analyses in this chapter.

[8] Rectal chlamydia incidence: IMM 29.9 per 100 PY vs. DEF 18.6 per 100 PY. Oral chlamydia incidence: IMM 6.2 per 100 PY vs. DEF 2.4 per 100 PY.

Table 4.10: Randomised comparison of STI risk between IMM and DEF group in deferred phase, by STI: comparison of binary approach and incidence approach

STI	Trial arm	Binary approach				Incidence approach			
		Participants with infection/screen	Proportion with infection (95% CI)	OR (95% CI)	*p*-value	Total infections/PY	Incidence per 100 PY (95% CI)	IRR (95% CI)	*p*-value
Any	IMM	155/265	58.5 (52.3 - 64.5)	1.4 (1.0-2.0)	0.068	280/246.9	114.7 (99.4-132.3)	1.2 (1.0-1.5)	0.076
	DEF	123/244	50.4 (44.0 - 56.8)	1.0		201/215.8	94.3 (80.1-110.9)	1.0	
Key	IMM	109/265	41.1 (35.1 - 47.3)	1.3 (0.9-1.8)	0.173	186/246.9	76.5 (63.6-92.0)	1.3 (1.0-1.7)	0.094
	DEF	86/244	35.2 (29.3 - 41.6)	1.0		127/215.8	60.1 (48.6-74.4)	1.0	
Chlamydia	IMM	81/260	31.2 (25.6 - 37.2)	1.6 (1.1-2.4)	0.024	99/243.5	40.7 (33.3-49.8)	1.4 (1.0-2.0)	0.027
	DEF	53/239	22.2 (17.1 - 28.0)	1.0		60/212.7	28.2 (21.9-36.5)	1.0	
Gonorrhoea	IMM	106/260	40.8 (34.7 - 47.0)	1.2 (0.8-1.7)	0.366	143/243.5	58.9 (49.6-69.9)	1.1 (0.8-1.4)	0.573
	DEF	88/239	36.8 (30.7 - 43.3)	1.0		116/212.7	54.7 (45.2-66.1)	1.0	
Syphilis	IMM	30/264	11.4 (7.8 - 15.8)	1.4 (0.8-2.4)	0.310	38/246.3	15.9 (10.8-23.4)	1.3 (0.7-2.4)	0.389
	DEF	21/243	8.6 (5.4 - 12.9)	1.0		25/214.5	12.2 (7.7-19.3)	1.0	

STI, sexually transmitted infection; CI, confidence interval; OR, odds ratio; PY person-years; IRR, incidence rate ratio; IMM, immediate; DEF, deferred; key, rectal chlamydia, rectal gonorrhoea or syphilis.

4.6.7 STI incidence in deferred phase stratified by pre-trial STIs

The previous analysis found no clear effect of PrEP on STI incidence. However, there may have been an effect that was masked because the population was already at a very high level of risk for STIs. In this section, I repeat the comparisons of the IMM and DEF groups stratified by whether that specific STI had been reported in the twelve months prior to enrolment. Analytical methods were the same as used in Section 4.6.5. In addition, interactions between the trial arm effect and STI diagnoses in twelve months prior to enrolment were considered.

The number of screens in the year prior to enrolment was significantly higher in those with a prior diagnosis compared to those with no diagnosis in the twelve months prior to baseline (3.4 vs. 2.4, $p<0.001$). During follow-up, the number of screens in each trial arm was similar in those without a prior diagnosis (IMM 3.9 vs. DEF 3.6, $p=0.26$) but differed in those with a prior diagnosis (IMM 4.3 vs. DEF 3.6, $p<0.001$).

This analysis showed intriguing differences for participants reporting no STI diagnosis in the year prior. There was an indication of higher incidence in the IMM arm for: any STI (IRR=1.5 [95% CI: 1.0-2.1], $p=0.043$); key STI (IRR=1.4 [95% CI: 1.0-2.1], $p=0.069$)[9]; chlamydia (IRR=1.6 [95% CI: 1.0-2.5], $p=0.040$)[10]; and syphilis (IRR=2.0 [95% CI: 1.0-3.9], $p=0.048$) (Table 4.11 and Figure 4.5). These differences were not as marked in those who did have a prior STI diagnosis, although tests for interaction were not statistically significant, possibly due to lack of power.

[9] Rectal chlamydia IRR=2.0 [95% CI: 1.2-3.4, $p=0.005$], rectal gonorrhoea IRR=0.9 [95% CI: 0.6-1.4, $p=0.763$], syphilis IRR=2.0 [95% CI: 1.0-3.9, $p=0.048$]

[10] Rectal chlamydia IRR=2.0 [95% CI: 1.2-3.4, $p=0.005$], urethral chlamydia IRR=1.4 [95% CI: 0.7-2.7, $p=0.325$], oral chlamydia IRR=4.4 [95% CI: 0.8-22.7, $p=0.081$]

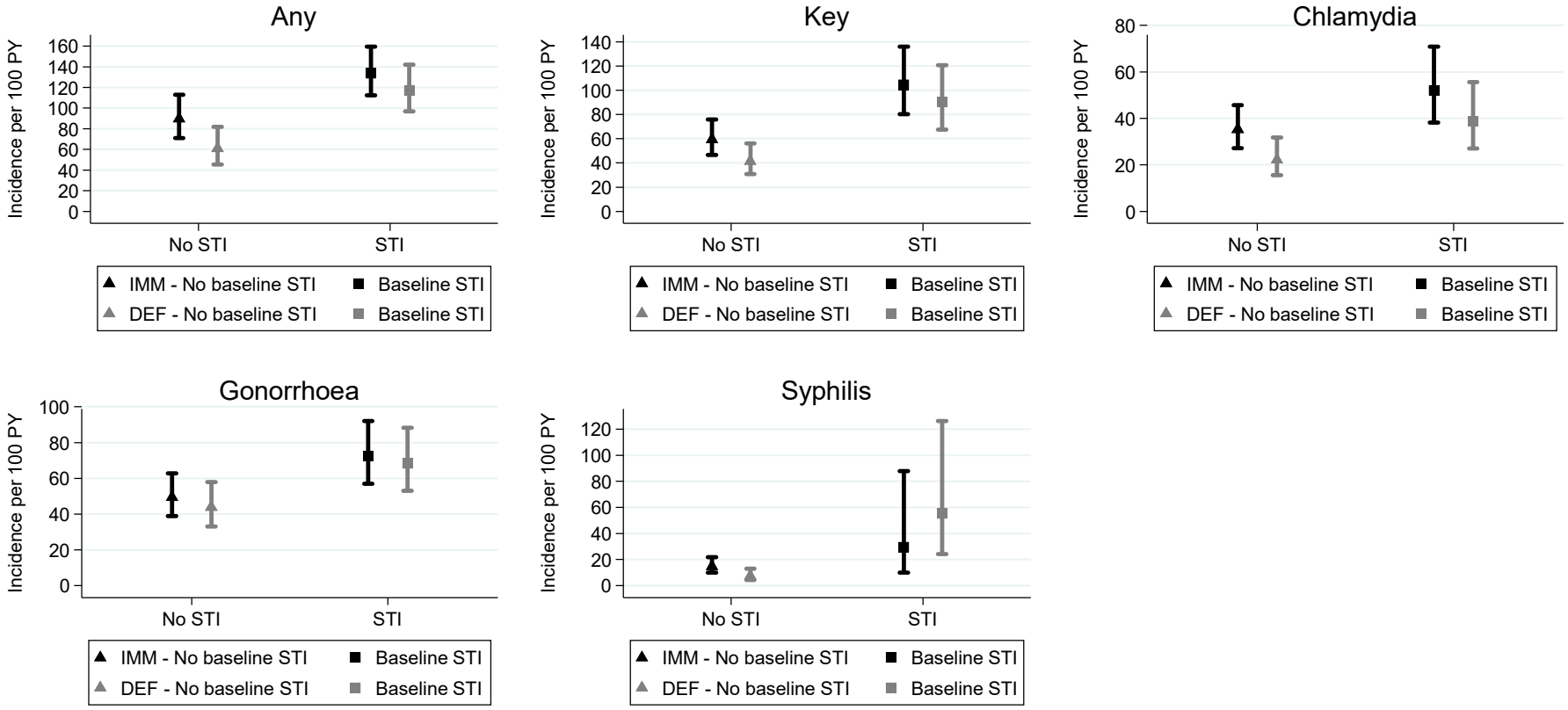
Given the difference in the number of screens pre- and post-PrEP in those reporting a prior infection, participants may also be more susceptible to detection bias. However, my analysis in Section 4.6.3 demonstrated that doubling the frequency of screening increased the incidence by a relatively small amount (23% increase in syphilis), and, therefore, detection bias does not explain the much larger effects seen in this analysis. This differential effect could be as a result of risk compensation in a group that was previously at lower risk of STIs.

Table 4.11: STI incidence in deferred phase stratified by trial arm and STI status in twelve months prior to enrolment

STI	**Base-line STI status**	**Trial arm**	**Total infections /PY**	**Incidence per 100 PY (95% CI)**	**IRR (95% CI)**	***p*-valu e**	***p*-value (interac tion)**
Any	**No**	IMM	96/108.2	89.6 (71.1-112.9)	1.5 (1.0-2.1)	0.043	0.274
		DEF	54/89.1	61.0 (45.4-81.8)	1.0		
	Yes	IMM	184/138.7	133.8 (112.3-159.4)	1.1 (0.9-1.5)	0.322	
		DEF	147/126.8	117.3 (96.9-142.0)	1.0		
Key	**No**	IMM	91/155.9	59.4 (46.5-75.9)	1.4 (1.0-2.1)	0.069	0.450
		DEF	55/134.0	41.5 (30.7-56.0)	1.0		
	Yes	IMM	95/91.0	104.5 (80.3-135.9)	1.2 (0.8-1.7)	0.463	
		DEF	72/81.9	90.2 (67.4-120.7)	1.0		
Chlamydia	**No**	IMM	58/164.6	35.3 (27.2-45.7)	1.6 (1.0-2.5)	0.040	0.608
		DEF	30/135.3	22.2 (15.5-31.8)	1.0		
	Yes	IMM	41/78.9	52.0 (38.2-70.8)	1.3 (0.8-2.2)	0.225	
		DEF	30/77.4	38.8 (27.1-55.6)	1.0		
Gonorrhoea	**No**	IMM	71/143.9	49.4 (38.9-62.8)	1.1 (0.8-1.6)	0.519	0.801
		DEF	52/118.7	43.8 (33.1-57.9)	1.0		
	Yes	IMM	72/99.7	72.4 (56.9-92.1)	1.1 (0.7-1.5)	0.756	
		DEF	64/94.0	68.4 (53.0-88.3)	1.0		
Syphilis	**No**	IMM	33/228.9	14.7 (10.0-21.7)	2.0 (1.0-3.9)	0.048	0.091
		DEF	14/193.4	7.4 (4.2-12.9)	1.0		
	Yes	IMM	5/17.5	29.5 (9.9-87.9)	0.5 (0.1-2.1)	0.368	
		DEF	11/21.1	55.3 (24.2-126.3)	1.0		

STI, sexually transmitted infection; PY, person-years; CI, confidence interval; IRR, incidence rate ratio; IMM, immediate; DEF, deferred; key, rectal chlamydia, rectal gonorrhoea or syphilis.
p-value for interaction was to test for a difference in the trial arm effect according to STI diagnoses in the twelve months prior to enrolment.

Figure 4.5: STI incidence stratified by trial arm and baseline STI diagnoses



Note: y-scale differs between figures

4.7 Comparison of deferred and post-deferred phases

Previous sections in this chapter have mainly focussed on the deferred phase of PROUD. The next two sections contain analyses of the STI data based on the entire PROUD follow-up. First, I compare STI incidence between the deferred and post-deferred phases, which is clearly of most interest in the DEF group. Second, I examine more detailed trends in STI incidence over calendar time using three-month time windows (Section 4.8).

To account for dependency within individuals between phases, negative binomial models included a random intercept by participant. Tests were performed to assess whether there was an interaction between the trial arm effect and trial phase.

In the DEF arm, an increase in STI incidence between the deferred and post-deferred phase was observed for all outcomes, with the exception of gonorrhoea (Table 4.12 and Figure 4.6). The increase was statistically significant for syphilis (IRR=2.2 [95% CI: 1.3-3.7], p=0.003), key STIs (IRR=1.4 [95% CI: 1.1-1.9], p=0.004)[11], and chlamydia (IRR=1.4 [95% CI: 1.1-1.9], p=0.023)[12]. A similar quantitative increase in syphilis incidence was observed in the IMM arm (IRR=2.0 [95% CI: 1.3-3.1], p=0.002), but the increase in key STI incidence was smaller (IRR=1.2 [95% CI: 1.0-1.5], p=0.095) and no increase was observed for chlamydia (IRR=1.0 [95% CI: 0.8-1.3], p=0.854).

The findings for syphilis are highly instructive in the interpretation of before-after comparisons of STI incidence in other studies. Without a control group (here the IMM arm) the large increase observed in the DEF group could have been misinterpreted as strong

[11] Rectal chlamydia IRR=1.6 [95% CI: 1.1-2.3, p=0.015], rectal gonorrhoea IRR=1.0 [95% CI: 0.7-1.4, p=0.993], syphilis IRR=2.2 [95% CI: 1.3-3.7, p=0.003]

[12] Rectal chlamydia IRR=1.6 [95% CI: 1.1-2.3, p=0.015], urethral chlamydia IRR=0.9 [95% CI: 0.5-1.5, p=0.660], oral chlamydia IRR=1.9 [95% CI: 0.6-5.9, p=0.290]

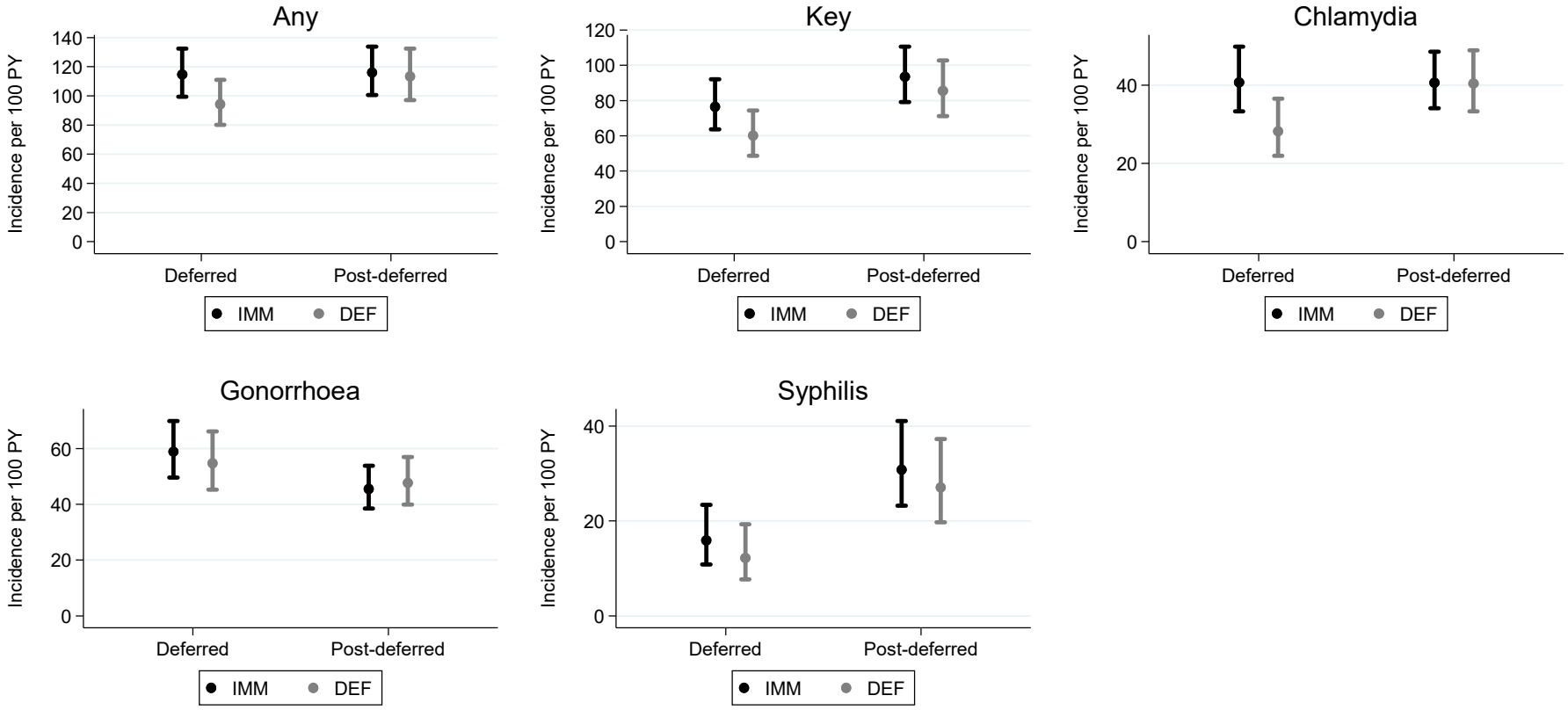
evidence for risk compensation. The similar change in the IMM group shows that this change was probably unrelated to the use of PrEP. Detection bias could be a factor here as the switch to the more intensive screening frequency occurred primarily during the post-deferred phase of the trial. On the other hand, gonorrhoea incidence, which would have been expected to have been similarly affected, showed a slight decrease between the deferred and post-deferred phases. The relative increase in chlamydia diagnoses in the DEF group was the same as that observed in the randomised comparison between IMM and DEF, and similarly driven primarily by rectal chlamydia (Section 4.6.5); this further supports that chlamydia diagnoses were higher among PrEP-users. However, it remains unclear whether this is a marker of higher sexual risk or a result of higher screening frequency when on PrEP.

Table 4.12: STI incidence by trial arm and phase

STI	Trial arm	Deferred phase		Post-deferred		IRR (95% CI)	*p*-value	*p*-value (interaction)
		Total infections/PY	Incidence per 100 PY (95% CI)	Total infections/PY	Incidence per 100 PY (95% CI)			
Any	**IMM**	280/246.9	114.9 (98.6-133.8)	488/423.7	115.9 (101.2-132.8)	1.0 (0.8-1.2)	0.857	0.136
	DEF	201/215.8	94.6 (79.7-112.4)	408/355.4	113.5 (97.9-131.6)	1.2 (1.0-1.5)	0.067	
Key	**IMM**	186/246.9	76.5 (63.3-92.6)	392/423.7	93.5 (79.3-110.2)	1.2 (1.0-1.5)	0.095	0.269
	DEF	127/215.8	60.2 (48.5-74.9)	309/355.4	85.6 (71.4-102.5)	1.4 (1.1-1.9)	0.004	
Chlamydia	**IMM**	99/243.5	40.9 (33.1-50.6)	169/416.8	40.6 (34.2-48.2)	1.0 (0.8-1.3)	0.854	0.061
	DEF	60/212.7	28.3 (21.7-36.9)	144/353.4	40.4 (33.6-48.7)	1.4 (1.0-1.9)	0.023	
Gonorrhoea	**IMM**	143/243.5	59.0 (49.2-70.6)	190/416.8	45.5 (38.7-53.5)	0.8 (0.6-1.0)	0.024	0.468
	DEF	116/212.7	54.8 (45.0-66.8)	170/353.4	47.8 (40.2-56.8)	0.9 (0.7-1.1)	0.280	
Syphilis	**IMM**	38/246.3	15.8 (10.8-23.3)	129/421.3	30.8 (23.1-41.1)	2.0 (1.3-3.1)	0.002	0.749
	DEF	25/214.5	12.2 (7.7-19.2)	94/354.4	27.1 (19.7-37.3)	2.2 (1.3-3.7)	0.003	

STI, sexually transmitted infection; PY, person-years; CI, confidence interval; IRR, incidence rate ratio; IMM, immediate; DEF, deferred; key, rectal chlamydia, rectal gonorrhea or syphilis.
p-value for interaction was to test for a difference in the trial arm effect according to trial phase

Figure 4.6: STI incidence by trial arm and phase



Note: y-scale differs between figures

4.8 STI incidence over calendar time

Analyses in the previous section point to the presence of calendar time changes in the incidence of some STIs. In this section I examine the effect of calendar time in more detail. STI incidence was calculated by calendar quarter and trial arm. Contributions of person-time for each quarter was calculated by splitting the follow-up from the date of randomisation until the last screen, regardless of whether the participant had a screen during that given period or not. Incidence was only presented for the time periods with more than 30 person-years follow-up. In contrast to comparative analyses of the randomised groups, the analysis over calendar time includes infections reported at baseline to reflect time trends.

Figure 4.7 shows the calendar trends in incidence for STIs by pathogen and anatomical site. Two time points when sexual behaviour among trial participants could have changed are marked on the graphs. The first was in October 2014, when the IDMC advised that all participants should be given access to PrEP, and the second was in February 2015, when the results of PROUD were presented at CROI and the high effectiveness of PrEP (86%) became widely known [34].

There was little difference between the incidence rates in the two arms. The only consistent difference was a higher rate of syphilis in the IMM arm, compared to DEF, until 2015-quarter (Q)2. Between October 2014 and February 2015, the DEF group had a lower incidence of rectal chlamydia compared to other time points and the IMM arm, possibly reflecting a change in screening or clinic attendance when coming forward for PrEP.

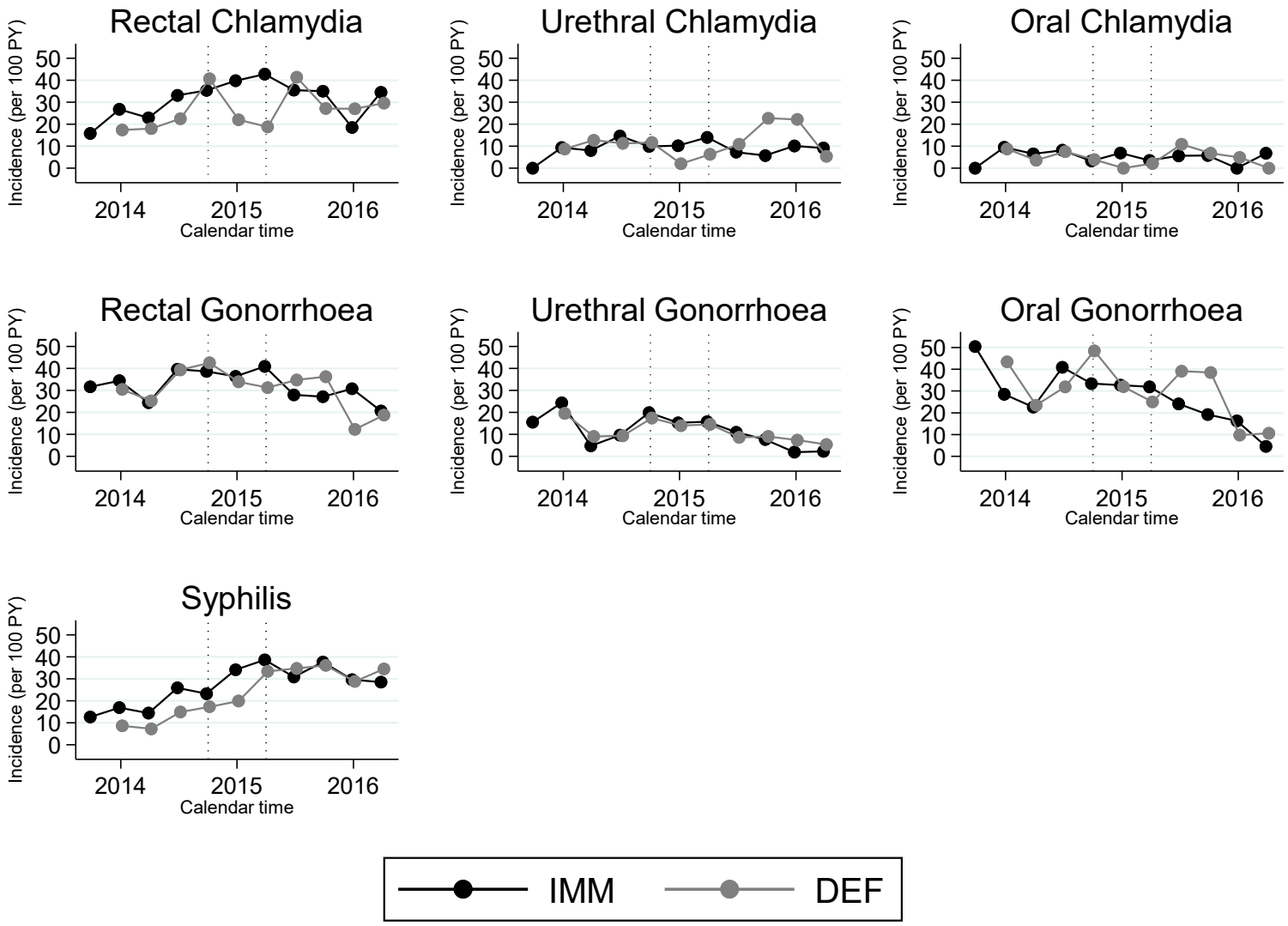
There were clear changes in STI incidence over calendar time for some individual STIs. Syphilis incidence increased until 2015-Q2 and then plateaued going from 12.6 per 100 PY (95% CI: 3.4-32.2) in 2013-Q4 to 38.6 per 100 PY (95% CI: 24.2-58.5) in 2015-Q2 in the DEF

arm. Rectal chlamydia, but not oral or urethral chlamydia, also increased until 2015-Q2. Gonorrhoea incidence reduced during the study, at all three anatomical sites. Despite these changes, none appeared to be associated with the closure of the DEF arm or announcement of PrEP effectiveness.

The reduction in gonorrhoea incidence at all three anatomical sites suggests that this was being driven by external factors (e.g. gonorrhoea in general MSM population), rather than solely behavioural changes. In contrast, the increase in rectal chlamydia diagnoses was not reflected in urethral and oral infections. Given that incidence of urethral and oral chlamydia remained constant, diagnoses of rectal chlamydia are likely to provide an indicator of penetrative anal intercourse.

In the context of national data, trends observed in PROUD were similar to those observed in MSM attending STI clinics in England [142]. Over the course of PROUD (2012-2016), the number of syphilis diagnoses in England increased over two-fold, which was similar to the relative increase observed between the deferred and post-deferred phase in the trial. Chlamydia diagnoses among MSM were consistently on the rise in England until 2015, and remained similar in 2016 (~13000). After a seven-fold increase in gonorrhoea diagnoses between 2007 and 2015, there was a 22% reduction between 2015 and 2016. This reduction coincided with an uptake in HIV prevention strategies, as part of this strategy, an increase in STI testing may have aided the diagnoses of asymptomatic infections and prevention of onward transmission [142]. These factors could have also contributed to the reduction in gonorrhoea seen in PROUD.

Figure 4.7: STI incidence over calendar time by trial arm



4.9 Discussion

4.9.1 Key findings

- Although there are several open-label studies in PrEP-users, PROUD is the only study with a randomised design to evaluate the impact of daily PrEP on STIs
- Reported studies and PROUD confirm that MSM seeking PrEP are at high risk of STIs and frequent screening is clinically justified
- Analyses need to pay careful attention to selection of the control group, risk of detection bias, choice of statistical model, managing concurrent diagnoses (more than one anatomical site, more than one pathogen) and repeat infections, and changes in background STI incidence over calendar time
- Estimating STI incidence is more appropriate than estimating that probability of ever being diagnosed, and the negative-binomial model was the best fit for the PROUD data due to the heterogeneity in risk between participants
- Using these methods, I conclude that the incidence of STIs, particularly rectal chlamydia, was higher among PROUD participants with access to PrEP
- Detection bias may have inflated the observed STI incidence in PrEP-users compared to non-users
- The fact that STI incidence was high in PROUD participants before they enrolled in the trial may limit the ability to assess whether PrEP increases STI incidence

In this chapter, I argued that STI acquisition is the appropriate objective outcome measure for risk compensation as it is of public health relevance. There was a high ongoing incidence of STIs, especially rectal and syphilis infections during PROUD, demonstrating that participants remained at high risk of HIV throughout the study. This highlights that participants continued to require PrEP, and is further evidence of the durability of PrEP for

preventing HIV. The high STI incidence supports the change to three-monthly STI screening in PROUD for the majority of participants, as well as the quarterly screening recommendation for PrEP-users by BHIVA/BASHH [42]. Although, a substantial proportion of PROUD participants never experienced an STI. Therefore, a lack of an STI diagnosis may raise the question around whether PrEP remains relevant for the individual (Chapter 2).

This chapter has discussed the use of an incidence approach over a binary approach. Incidence incorporates all infections acquired over follow-up reflecting the clinical burden and accounting for differences in follow-up time. Whilst the results did not substantially differ between the binary and incidence methods in PROUD, caution needs to be taken if using a binary approach for future STI analyses due to repeated events and differential follow-up. Another consideration, from a statistical perspective, is the high heterogeneity in STI risk between individuals, and this should be taken into account when selecting the analytic method. For the PROUD data, I identified that the negative-binomial model provided the best fit to the data.

There was an indication that STI risk was higher amongst PrEP-users, particularly chlamydia, although, this was not a particularly strong effect. Given the dense social networks of MSM populations, even small changes in sexual behaviour are likely to impact STI acquisition [106]. Therefore, it was surprising that the effect of PrEP on STI risk was not more pronounced. The PROUD cohort was already at high sexual risk upon entering the study and, therefore, it may be that there was little possibility of further change in behaviour as a result of PrEP. PrEP had a slightly more marked effect on the STI risk in those with no history of STIs in the twelve months prior to enrolment which may reflect a lower risk behaviour profile prior to joining the study. This was especially marked for rectal chlamydia and syphilis which could imply a greater likelihood of condomless anal intercourse and an increase in sexual partners who were HIV-positive (among whom STI incidence rates are

generally higher)[143]. However, this could be partly explained by a change in screening patterns.

This chapter has described the impact that the number of STI screens can have when using STI diagnoses as a marker of risk compensation ("detection bias"). It is difficult to establish whether this has driven the association between PrEP and the increase in STI rates observed in PrEP studies so far, given the complex nature of screening and sexual behaviour [13, 123-128]. An analysis presented in Section 4.6.3 demonstrated that a doubling in screening from six- to three-month would increase STI diagnoses rates by 9% in gonorrhoea and chlamydia and 23% in syphilis. These effects are relatively small and therefore it is unlikely that the observed differences in incidence were driven solely by differences in screening. Simple statistical adjustment that does not discriminate between reasons for screening is likely to over-adjust for factors related to STI risk. Therefore unadjusted analyses provide a more clinically relevant insight into the PrEP effect on STIs, but the 'truth' is likely to lie between adjusted and unadjusted results [132]. In order to answer whether STIs increase because of PrEP, complex causal modelling would be required to separate these effects. This would require detailed and complex datasets on the precise dates of STI diagnoses, the dates and outcome of STI treatment, and the reasons for screening. PROUD, and other studies reported in the literature, did not collect these details, and it is unlikely that another randomised PrEP study would be conducted to collect this. Even so, there is a possibility that however detailed and complex an analysis or dataset, residual bias would likely remain.

Strong trends in STI incidence over time have been observed in both PROUD and sexual health clinic attendees [142, 144]. Given that changes in the background STI incidence are likely to be reflected in a PrEP study population, caution needs to be taken when performing a pre- and post-PrEP comparison, as is common in the literature [121, 122, 126-128]. A key

strength of PROUD is the ability to make a randomised PrEP comparison on STI risk, and a control with access to PrEP for the entire study (IMM arm) for longer term analyses.

4.9.2 Conclusion

In conclusion, regardless of whether PrEP is driving the increase in STI incidence, MSM seeking PrEP are at risk of STI acquisition. For those using PrEP it should be made clear that they remain at risk of acquiring STIs despite being protected from HIV. Nevertheless, PrEP has been shown to be almost entirely effective at preventing HIV, and a PrEP programme is likely to play an important role in controlling the onward transmission of STIs in this high-risk population [145].

The extensive analyses I conducted using the PROUD data support the results of other studies that observed a small increase in STIs in PrEP-users, but the changes over calendar time were more impressive confirming the importance of national surveillance of STIs in the population regardless of PrEP use.

5 Hepatitis C risk and predictors in PrEP-users

5.1 Introduction

At the beginning of PROUD, in 2012, HCV incidence among HIV-negative MSM was considered low and was not part of routine screening [146, 147]. Early observations in PROUD suggested that participants were at a much higher than expected risk for HCV and quarterly HCV testing as part of the trial was introduced in March 2015 [148, 149]. In this chapter, I will summarise the literature on HCV amongst HIV-positive and HIV-negative MSM (including those accessing PrEP), describe the data collected in PROUD, estimate HCV seroprevalence and incidence, identify predictors of HCV acquisition and examine trends over time.

5.2 Background

PrEP may lead to any or all of: a decrease in condom-use during anal intercourse; an increase in the number of casual sexual partners; and an increase in the number of HIV-positive sexual partners [118]. Little is known about HCV incidence amongst HIV-negative MSM in the UK, especially those seeking PrEP. A systematic review concluded that HCV incidence was 19-fold higher in HIV-positive MSM compared to HIV-negative MSM (described further in Section 5.4) [150], and therefore sexual mixing could increase the chance of exposure to HCV amongst HIV-negative MSM taking PrEP [151].

In 2012, the National Institute for Health and Care Excellence (NICE) published guidelines on hepatitis B and C testing [147]. Testing in sexual health clinics was recommended in individuals at increased risk of HCV. The guidelines noted that this could be individuals who have injected drugs, were HIV-positive MSM, or had been in close proximity to someone with chronic HCV. The same year, the British Association for Sexual Health and HIV (BASHH)

produced a report on safer sex which described that high HCV risk was associated with anal intercourse without a condom (ncAI) among HIV-positive MSM or individuals reporting fisting, regardless of HIV status [46].

In spite of the guidelines released in 2012, HCV testing was not commissioned and therefore not part of routine screening in the sexual health clinics where PROUD took place. Risk was generally thought to be low amongst the HIV-negative MSM population, and the PROUD protocol initially recommended screening for HCV "on indication" [152]. In March 2015, additional funding was acquired to reimburse study sites for HCV screening at every PROUD visit (which occurred quarterly). The visit CRF was also expanded to capture HCV-associated risk factors including chemsex, group sex, injecting, fisting and use of sex toys.

5.3 Aims

The aims of this chapter are:

1. Summarise the current literature on: HCV risk in HIV-positive and HIV-negative MSM (Section 5.4); and HCV risk amongst MSM using PrEP (Section 5.5)
2. Describe HCV screening and risk factor data collected during PROUD (Section 5.6) and identify predictors of acquiring a HCV screen before it became routine (Section 5.7)
3. Estimate HCV seroprevalence and incidence in PROUD (Section 5.8)
4. Discuss methods for calculating HCV incidence over calendar time (Section 5.9)
5. Identify predictors of HCV acquisition and examine the trends of HCV risk factors over time (Section 5.10-5.11).

5.4 Literature review: HCV incidence among HIV-negative and HIV-positive MSM

A systematic literature review and meta-analysis estimating the HCV incidence amongst HIV-positive and HIV-negative MSM was published in 2017 by Ghisla et al. [150].

5.4.1 Study selection

Ghisla et al. searched medical databases for papers reporting HCV incidence in MSM between January 2000 and October 2016. In order to reduce bias from different transmission routes (i.e. infected blood products) in developing countries, study areas were restricted to Europe, North America, Australia, and Taiwan. Pooled estimates of HCV incidence were calculated by performing a DerSimonian and Laird random-effects meta-analysis. Ghisla et al. identified 28 relevant studies: 27 included HIV-positive populations, four of which also analysed HIV-negative individuals; and one study was solely HIV-negative participants. From the UK, five studies reported HCV incidence for HIV-positive MSM [153-157], of which one also presented data on HIV-negative MSM [157].

5.4.2 HCV incidence

Overall, the estimated incidence in HIV-positive MSM was 7.8 per 1000 person-years (PY) (95% confidence interval (CI): 6.0–9.7 per 1000 PY) (Figure 5.1). This was 19 times higher than that estimated amongst HIV-negative MSM (0.4 per 1000 PY [95% CI: 0.0-0.9]).

HCV incidence varied widely geographically but incidence in HIV-positive MSM was consistently higher than negative populations in the same location, with the exception of one Australian cohort (HIV-negative 1.1 per 1000 PY [95% CI: 0.3-2.6] and HIV-positive 0 per 1000 PY [95% CI: 0.0-15.4])[158]. Although, in this study, the HIV-positive group was much smaller than the HIV-negative group (238.1 vs. 4412.1 PY). There was variability

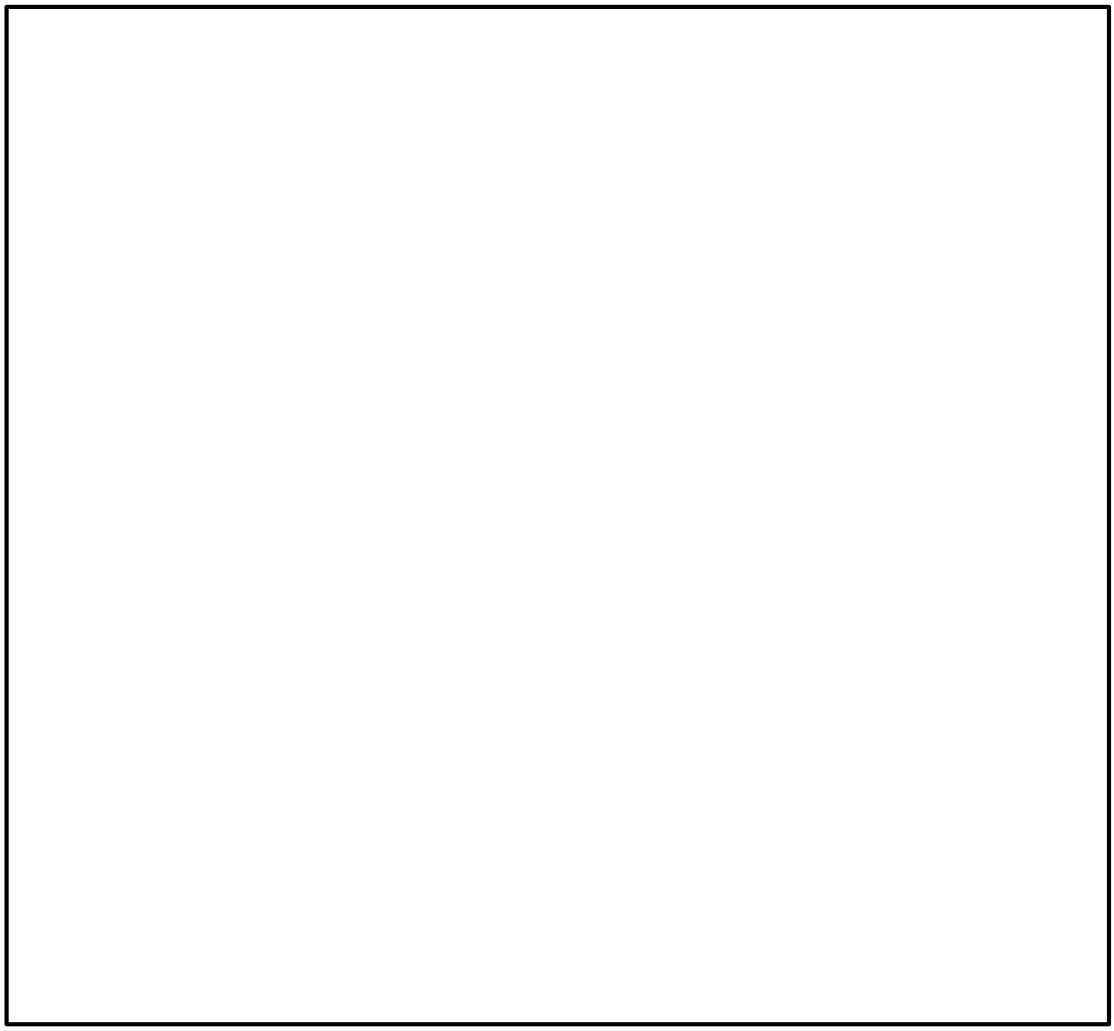
amongst the HIV-positive MSM, where HCV incidence ranged from 0 per 1000 PY (95% CI: 0–15.4 per 1000 PY) in a cohort in Sydney, up to 23.5 per 1000 PY (95% CI: 16.6–33.3 per 1000 PY) in an Amsterdam outpatient clinic [158, 159]. Interestingly, no HCV infections were observed in a cohort of HIV-negative MSM in Amsterdam during 7808 PY of follow-up (0 per 1000 PY, 95% CI: 0.0-0.5) [160].

UK studies of HIV-positive MSM, published between 2006 and 2016, reported similar HCV incidence to one another (8.5-11.8 per 1000 PY) [153-157], substantially higher than HIV-negative MSM in a 2008 Brighton study (1.5 per 1000 PY [95% CI: 0.5-3.5]) [157].

Ghisla et al. reported were also trends over time, with HCV incidence in HIV-positive MSM increasing up to 2010. Studies with follow-up before 2000 had a pooled incidence of 2.6 per 1000 PY (95% CI: 0-5.8 per 1000 PY), increasing to 6.8 per 1000 PY (95% CI: 3.0-10.6 per 1000 PY) between 2000 and 2005, and further to 10.1 per 1000 PY (95% CI: 5.8-14.3 per 1000 PY) in 2006-2010. After 2010, the incidence then stabilised (8.1 per 1000 PY, 95% CI: 2.7-13.5).

HCV incidence estimates varied widely between studies, even within participants of the same HIV status. There are three possible explanations for this. First, incidence estimates depend on HCV screening strategy, with a trend for this to have become less selective in recent years. Second, there is likely substantial variability by geographical location and the characteristics of the cohort being followed. Third, there is evidence that background HCV incidence may change over calendar time within a study population. This is observed, for example, in the comparison of HCV incidence reported by van de Laar et al. and Vanhommerig et al. in the Amsterdam cohort studies (1.8 per 1000 PY [follow-up: 1984-2003] vs. 4.5 per 1000 PY [follow-up: 1984-2012])[159, 161].

Figure 5.1: Forest plot of meta-analysis produced by Ghisla et al. of HCV incidence in HIV-negative and HIV-positive MSM (image redacted due to copyright)



5.4.3 HCV risk factors

Thirteen papers reported HCV risk factors, two of which included HIV-negative populations. They reported risk factors mentioned in at least three different studies. Although, they reported "other sexual risk factors", regardless of the number of reporting studies (Table 5.2).

Several predictive factors were identified: history of syphilis; acute syphilis; history of injection drug use; recreational drug use; sexual behaviour; fisting; and the use of sex toys. Eight studies estimated the effect of syphilis (history or acute) on HCV incidence, and all found a significant association. Given that both HCV and syphilis can be acquired sexually,

this not particularly surprising. However, it is unclear whether syphilis increases the risk of HCV acquisition or both are markers of high-risk behaviours (or "risky sex"). Two studies considered the effect of other STIs, but these were not presented in the Ghisla et al. review[13] [162, 163].

The association between injecting drugs and HCV acquisition is well established, and therefore it was unsurprising that injection drug use was found to be a predictor of HCV in two of the three studies which considered this. Two studies demonstrated an increased risk for other recreational drug-use (poppers and alcohol intake), which could be driven by sexual disinhibition whilst using such substances. Associations with other risk factors, such as rimming, fisting, and use of sex toys, were not as clear and require further investigation.

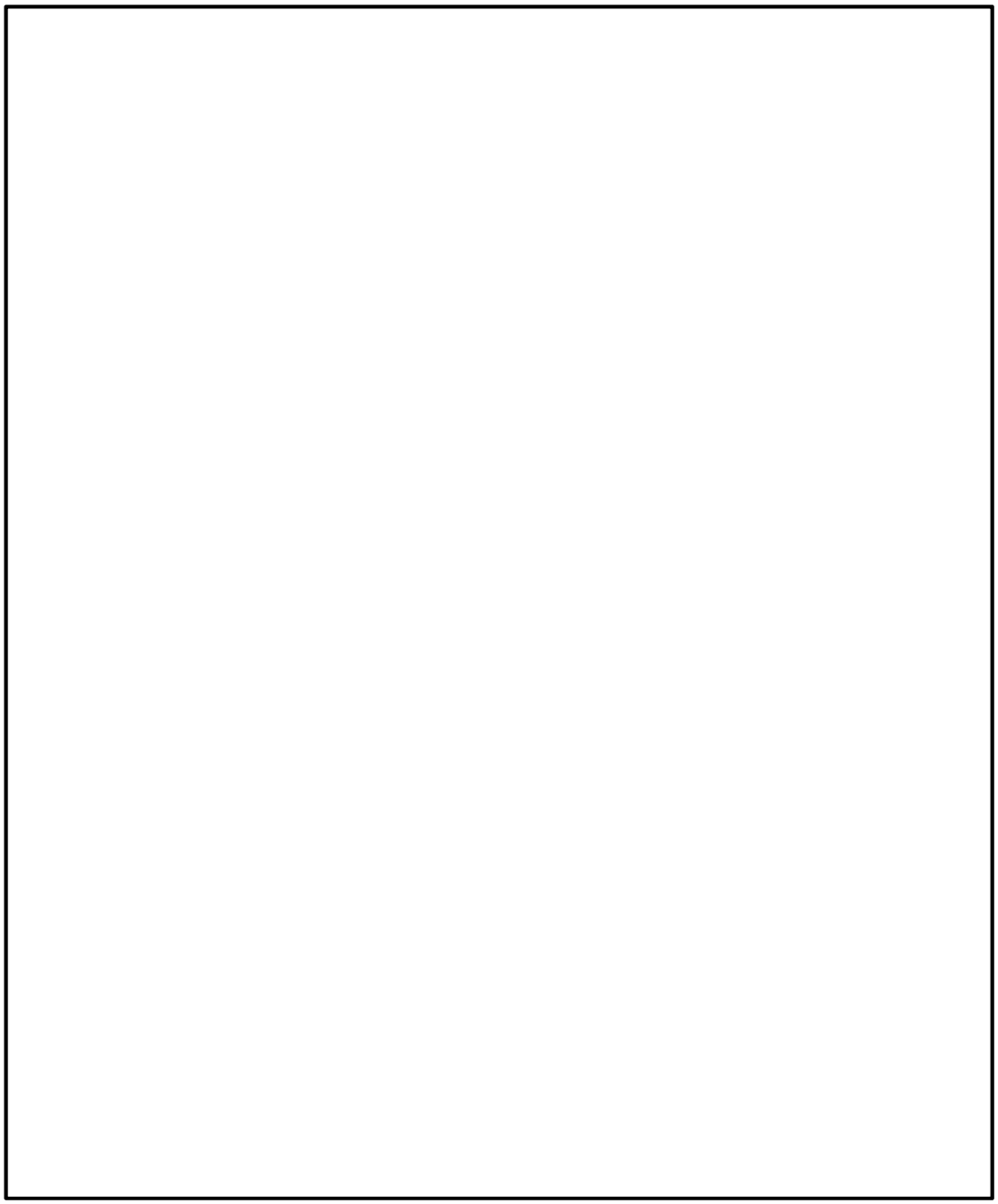
5.4.4 Summary

HCV risk amongst HIV-positive MSM was consistently higher than HIV-negative MSM in studies within similar locations. However, HCV incidence estimates were highly heterogeneous and few studies included an HIV-negative population (*n*=5). The strength of this systematic review was the thorough search of the literature. However, the estimates of HCV incidence may be unreliable since HCV testing during the period of follow-up (1984-2014) is likely to have been selective (only 41.5% screened in Brighton study) [157]. Findings in terms of factors associated with increased HCV risk were largely consistent. However, no attempt was made to derived a pooled estimate of the effects of the different HCV risk factors across studies.

[13] Apers et al.: chlamydia or gonorrhoea in past year: aOR=4.5 [95% CI: 1.1-18.3]
Breskin at al.: gonorrhoea aRR=1.0 [95% CI: 0.8-1.1]; chlamydia aRR=1.2 [95% CI: 1.0-1.4]

Given the sexual risk behaviours of individuals seeking PrEP, HCV risk is likely to be higher in PrEP-users compared to HIV-negative MSM who are not seeking PrEP. The next section describes a literature search I conducted on HCV risk amongst PrEP-users.

Figure 5.2: Effect sizes of risk factors for HCV (combined HIV-negative and HIV-positive MSM) produced by Ghisla et al. (image redacted due to copyright)



5.5 Literature review: HCV risk among PrEP-users

5.5.1 Study selection

In July 2018, I searched PubMed using the terms described in Table 5.1 to identify studies which estimated HCV prevalence or incidence amongst PrEP-users. For the papers identified in the search, the references were also checked to verify that no relevant papers had been missed. Abstracts for the International AIDS Conference (AIDS), International AIDS Society Conference (IAS), and CROI between 2016 and 2018[14] were also searched to identify relevant abstracts which may not have been published, as were papers reporting the results of PrEP trials in MSM (described in Section 1.3).

Table 5.1: PubMed search terms for HCV incidence among PrEP-users

	Topic of interest	Location in paper	Search term used
1	Hepatitis C	Title	(“HCV”[ti] OR "Hepatitis"[ti]))
2	Hepatitis C	Abstract	(“HCV”[ab] OR "Hepatitis"[ab])
3	PrEP	Title	(“preexposure prophylaxis”[ti] OR “pre-exposure prophylaxis”[ti] OR “PrEP”[ti])
4	Date of publication	Paper published since PrEP approved by FDA (2012)	("2012/01/01"[PDat]:"2018/07/09"[PDat])

FDA, Food and Drug Administration

Search used: (1 OR 2) AND 3 AND 4

The search in PubMed identified 39 papers which fit the criteria. 34 papers were excluded for a number of reasons, including: study was not focused on MSM; the participants were not on PrEP; the study reported hepatitis A or B, rather than HCV; or the article was an editorial discussing papers identified in the search. Five papers were deemed relevant for inclusion into the review [12, 128, 164-166]. No additional papers were found in the references of these papers. A further three studies reported HCV incidence in PrEP-users at CROI 2018 [167-169]. The eight relevant studies are discussed below and presented in

[14] AIDS 2016, IAS 2017, CROI 2016-2018

Table 5.2 [12, 128, 164-169]; two were from the AmPrEP study [164, 168] and two were from IPERGAY [12, 167]. If studies did not report confidence intervals for prevalence and incidence estimates, I calculated these using the *cii* command in Stata.

5.5.2 Summary of studies

IPERGAY (Molina et al. and Gras et al.)

IPERGAY was a randomised trial in France and Canada to assess the efficacy of an on-demand PrEP regimen, where participants were randomised to receive TDF-FTC (*n*=199) or placebo (*n*=201) [12]. Participants were included in the trial if they reported a history of unprotected anal sex with at least two partners in the past 6 months. An exclusion criterion of the trial was identifying chronic HCV at the enrolment visit. Screening for HCV occurred at enrolment, every six months, and on indication if high alanine transaminase (ALT) was detected at quarterly visits.

The main paper of the IPERGAY trial reported five incident HCV infections during the trial, but they did not report this by trial arm [12]. A secondary analysis aimed to assess the sensitivity of tests used to diagnose HCV infections in the blinded and open-label phases of the trial [167]. HCV incidence was estimated to be 1.4 per 100 PY (95% CI: 0.7-2.4).

AmPrEP (Hoornenborg et al., 2017 and Hoornenborg et al., 2018)

The AmPrEP study is a demonstration project in Amsterdam which was set up to assess the uptake and acceptability of daily vs. event-driven PrEP [164]. Inclusion was restricted to participants reporting a bacterial STI in the six months prior, ncAI with a casual partner, a course of PEP, or a HIV-positive partner with either an unknown or detectable viral load. 375 MSM were screened for HCV at baseline and quarterly study visits [164, 168]. AmPrEP reported a baseline HCV prevalence of 4.8% (18/375, 95% CI: 2.9-7.5%), which was much higher than previously reported in HIV-negative MSM.

HCV-positivity at PrEP initiation was associated with: lower age (p=0.019); bacterial STI (rectal, urethral, chlamydia, gonorrhoea and syphilis) in the six months prior to enrolment (p=0.041); higher number of ncRAI in the previous three months (p<0.001); injection drug use (p=0.003); and chemsex (p<0.001). Phylogenetic analyses demonstrated that the HCV isolates in PrEP-users were in clusters with both HIV-positive and HIV-negative MSM, suggesting an overlap in sexual networks.

HCV incidence during follow-up was 1.51 per 100 PY (95% CI: 0.72-3.17). Rates were not significantly different (p=0.69) between those taking daily PrEP group (1.16 per 100 PY) and those taking event-driven PrEP (1.68 per 100 PY) [168]. Because of the high HCV seroprevalence at baseline and incidence during follow-up, the AmPrEP investigators recommended that continued HCV screening should be offered to PrEP-users in order to prevent the spread to the wider HIV-negative MSM population.

Nguyen et al.

A retrospective cohort study in a Montreal sexual health clinic compared the incidence of STIs (including HCV) in MSM, prior to, and 12 months following, the prescription of PrEP (n=109) [128]. PrEP was prescribed to individuals reporting a HIV-positive sexual partner with a detectable viral load, or multiple ncRAI partners with unknown HIV status. Patients were considered in the analysis if they had at least 12 months follow-up pre- and post-PrEP initiation. STI incidence was also estimated for MSM in the twelve months following a PEP prescription in the same clinic (n=86). The frequency of recommended HCV screening differed between groups; this was at the patients' discretion prior to PrEP and post-PEP, but occurred quarterly for PrEP-users. No incident cases of HCV were observed for any of the participants, however two had been previously infected (one PrEP and one PEP user). Nguyen et al. concluded that the rates of HCV were lower amongst the MSM attending than the MSM participating in AmPrEP.

Volk et al.

Volk et al. wrote a letter to the editor of *Clinical Infectious Diseases* journal about HCV seroconversions occurring amongst PrEP-users in a San Francisco clinic [166]. The frequency of HCV screening was not reported. Over a total follow-up of 304 PY (*n*=485 participants), two HCV infections were observed, giving an incidence of 0.7 per 100 PY (95% CI: 0.08-2.4 per 100 PY). No HCV risk factors, other than ncRAI, were reported for the two individuals, highlighting the important of sexual transmission in MSM receiving PrEP. The authors concluded that it was important to monitor for HCV amongst individuals initiating PrEP and to counsel on the risk of acquiring HCV sexually.

Mikati et al.

A sexual health clinic in New York City (NYC) performed HCV Ab screening when individuals came to initiate PrEP (*n*=758) or PEP (*n*=381) [169]. 99.7% of patients received a screen at PrEP or PEP initiation. HCV seroprevalence was calculated for both groups and was found to be low, 0% (95% CI: 0-1.0) in PrEP-users, and 0.4% (95% CI: 0.08-1.2) in PEP-users. Mikati et al. reported that the seroprevalence within the HIV-negative MSM attending their sexual health clinic was lower than that estimated for the general population in NYC (2.4% [range: 1.5-4.9]) and the United States (1.3% [95% CI: 1.2-1.5) [170, 171]. Despite this, Mikati et al. concluded that a PrEP programme at an STI clinic provides a good opportunity to monitor trends for sexually acquired HCV.

Cotte at al.

Cotte et al. estimated HCV prevalence and incidence among HIV-positive MSM (*n*=10049) and MSM using PrEP (*n*=930) in a large French cohort [165]. HCV screening was carried out yearly for HIV-positive MSM and quarterly for PrEP-using MSM. HCV incidence was estimated to be the same in the HIV-positive (1.2 per 100 PY [95% CI: 0.6-2.2]) and PrEP–using MSM (1.2 per 100 PY [95% CI: 0.9-1.6]). Cotte et al. pointed out that this could be due

to HIV-positive individuals and MSM accessing PrEP sharing similar sexual practices, and therefore should receive the same prevention strategies for HCV.

5.5.3 Summary

To summarise, the studies that have estimated HCV seroprevalence and incidence in MSM that have initiated PrEP are also highly heterogenous, with a study in Montreal reporting no infections [128] and the AmPrEP study observing a 4.8% seroprevalence and incidence of 1.51 per 100 PY [164, 168]. European studies reported higher rates than North American studies, suggesting a strong geographical influence on the risk of HCV.

Table 5.2: Summary of PrEP studies reporting HCV risk

	Location	Period of study	Methods	Frequency of HCV screening	Number of participants	HCV incidence or prevalence (95% CI)*
IPERGAY: Molina, 2015 [12]	France and Canada	2012-2015	Reported overall number of acquired HCV infections.	At enrolment, every six months, and on indication if high ALT	199 on-demand PrEP-users and 201 placebo	**PrEP-users (cumulative incidence):** 1.3% (95% CI: 0.4-2.0)
Gras, 2018 [167]	France and Canada	2012-2016	Aim was to ascertain the sensitivity of different tests used for HV diagnoses. Presented HCV incidence.	At enrolment, every six months, and on indication if high ALT	428** participants (PrEP and placebo)	**PrEP-users (incidence):** 1.4 per 100 PY (95% CI: 0.7-2.4)
AmPrEP: Hoornenborg, 2017 [164]	Amsterdam, Netherlands	2015-2016	Estimated HCV prevalence in PrEP-users. Compared HCV isolates with HIV-positive MSM and other risk groups to identify clusters.	All screened at baseline	375 PrEP-initiators	**PrEP-initiators (prevalence):** 4.8% (95% CI: 2.9-7.5)
Hoornenborg, 2018 [168]	Amsterdam, Netherlands	2015-2017	Estimated overall HCV incidence and incidence was also calculated by PrEP regimen (daily or event-driven).	Quarterly	372 PrEP-users	**PrEP-users (incidence):** 1.51 per 100 PY (95% CI: 0.72-3.17) Daily PrEP: 1.16 per 100 PY (CI not reported) Event-driven PrEP: 1.68 per 100 PY (CI not reported)
Nguyen, 2018 [128]	Montreal, Canada	2010-2015	Estimated HCV incidence in the 12 months prior- and post-PrEP. Incidence was also compared between post-PrEP and PEP prescriptions.	**Year prior to PrEP:** at patients' discretion **Year on PrEP:** quarterly **PEP-users:** at patients' discretion	109 PrEP-users, 86 PEP-users	**Pre-PrEP (incidence):** 0 per 100 PY (95% CI: 0-3.4) **PrEP-users (incidence):** 0 per 100 PY (95% CI: 0-3.4) **Post-PEP (incidence):** 0 per 100 PY (95% CI: 0-4.3)
Volk, 2015 [166]	San Francisco, USA	2011-2014	Estimated HCV incidence among PrEP-users.	Not specified	485 participants, 304 person-years	**PrEP-users (incidence):** 0.7 per 100 PY (95% CI: 0.08-2.4)

Table continued on following page

Mikati, 2018 [169]	New York City, USA	2016-2017	Estimated HCV prevalence of PEP and PrEP-initiators.	99.7% of patients received a screen at PEP or PrEP initiation	381 PrEP-initiators 758 PEP-initiators	**PrEP-users (prevalence):** 0% (95% CI: 0-1.0) **PEP users (prevalence):** 0.4% (95% CI: 0.08-1.2)
Cotte, 2018 [167]	France	2016-2017	Estimated HCV prevalence and incidence among HIV-positive patients with serological follow-up in 2016, and PrEP-users between January 2016 and June 2017.	PrEP-users: quarterly HIV-positive: yearly	930 PrEP-users and 10049 HIV-positive	**PrEP-users:** Prevalence: 1.8% (95% CI: 1.1-2.9) Incidence: 1.2 per 100 PY (95% CI: 0.9-1.6) **HIV-positive MSM:** Prevalence: 6.8% (95% CI: 6.3-7.3) Incidence: 1.2 per 100 PY (95% CI: 0.6-2.2)

HCV, hepatitis C; CI, confidence interval; PY, person-years; PrEP, pre-exposure prophylaxis; P, *p*-value; PEP, post-exposure prophylaxis; USA, United States of America; ALT, Alanine transaminase;
*Exact confidence intervals for prevalence were calculated if studies did not report. Confidence intervals assuming a Poisson mean were calculated for incidence if studies did not report.
**Although not reported, different sample size to main study likely due to the difference in assessed for eligibility (*n*=445) and included in modified intention to treat analysis (*n*=400)

5.6 Data collection for HCV in PROUD

This section describes the HCV infection data collected in PROUD, the definitions used for seroprevalent and incident infections and the collection of HCV risk factor data.

5.6.1 HCV data collected during PROUD

Information on the screening and diagnosis of HCV was collected in a number of ways during PROUD (Table 5.3). Participants self-completed a baseline questionnaire which asked whether they had been diagnosed with HCV in the 12 months prior to enrolment (Form 2, Appendix 3). Further to this, the clinician reported whether the participant had ever been screened for, or diagnosed with, HCV (Form 1, Appendix 7).

At the start of PROUD, clinics were advised to follow guidelines and screen for HCV "if indicated". PROUD follow-up visits were scheduled quarterly, where information on the number of HCV screens and infections since the last visit were collected. In order to assess HCV seroprevalence, incidence and risk factors, from March 2015, PROUD acquired additional funding to reimburse clinics for screening participants at every study visit. The laboratory case report form (CRF) (Form 5, Appendix 5) did not distinguish between Ab and Ag tests, and, therefore, when an infection was reported the PROUD team contacted clinics directly to obtain further information. Upon indication of a new infection, clinics were asked to provide information, either via email or using an additional CRF (Appendix 7), on the dates of the last negative Ab/Ag test, viral load (VL) and injection drug use.

The PROUD protocol specified that in the event of HIV seroconversion, it was the choice of the participant to decide whether they wanted to continue with PROUD follow-up in addition to routine HIV-care. We therefore may have missed some HCV infections that post-dated an HIV infection.

Table 5.3: HCV infection information collected during PROUD

CRF/method	Information	Time-scale
Eligibility (clinician report)	Whether the participant has been screened for HCV or diagnosed with HCV	Any point before enrolment
Baseline (self-report)	Diagnosed with HCV	Past 12 months
Laboratory	Number of HCV screens and whether diagnosed with HCV	Since last visit
Contact with clinic	Precise dates of last negative and first positive Ab/Ag ALT and VL at/after diagnosis Treatment/spontaneous clearance details Injection drug use	NA

CRF, case report form; HCV, hepatitis; Ab, antibody; Ag, antigen; ALT, alanine aminotransferase; VL, viral load; NA, not applicable.

5.6.2 Defining seroprevalent and incident HCV infections

A seroprevalent infection was defined as evidence of a prior or current HCV infection at enrolment into the study. Specifically, the presence of HCV Ab/Ag/RNA at enrolment, or Ab/Ag/RNA identified shortly after randomisation, with other evidence to support recent acquisition. A clinician report of an infection prior to the study was also considered as a seroprevalent infection.

An incident HCV infection was defined by a positive Ab or Ag test in a previously Ab negative individual, or a positive Ag or RNA test in a participant who had cleared HCV. If an infection was diagnosed after randomisation on the first test during follow-up, the Trial Management Group (TMG) made a clinical decision based on ALT measures, VL at diagnosis, and time since randomisation.

5.6.3 Risk factor data collected during PROUD

Demographic, sexual and clinical information were collected in a number of ways during PROUD follow-up (Table 5.4). The self-completed questionnaire at baseline collected information on demographic factors, such as age, ethnicity, education, employment status, and relationship status (Form 2, Appendix 3). Participants were also asked to report which drugs they had used in the prior three months, although they were not asked how the drugs

were administered. This is important for HCV because of the transmission risk associated with injection drug use.

At the start of PROUD, the visit CRF asked whether ncAI had occurred since the last study visit. In March 2015, in line with the HCV sub-study, the visit CRF was updated to collect HCV-associated risk factors since the last visit (chemsex, injection drug use, snorting cocaine, group sex, use of sex toys and fisting (by glove use), Form 4, Appendix 10). The CRF was also updated to include the number of ncAI partners in the past 30 days. Drug use in follow-up and injecting had not been collected as part of the study up until this point. The visit and laboratory CRFs collected information on the number of PEP prescriptions since the last study visit, and STI screens and diagnoses since the last.

Participants were asked to complete an Adherence and Sexual Behaviour Questionnaire online on a monthly basis or on paper at a quarterly visit if they had not completed a form online (Form 3, Appendix 11). These were most frequently completed for the time period before the quarterly visits (Appendix 12). The monthly questionnaire focussed on the number of sexual partners in the prior 30 days, capturing: the total number of sexual partners; the number of partners with whom insertive anal intercourse without a condom (ncIAI) took place; and the number of partners with whom receptive anal intercourse without a condom (ncRAI) took place. Additional information was captured on the ncRAI partners: the number that they had engaged with previously; the number with an unknown HIV status; and the number that were known to be HIV-positive and not on treatment. The number of new ncRAI partners was derived from the total number of ncRAI partners within the last 30 days, and of those, the number of ncRAI partners that they had sex with previously. Participants were also asked for more detail about the last anal sex act in the 30 day period in terms of sexual position and condom use, and about the partner with whom they last had ncRAI (HIV status and whether they had previously had sex with this partner).

Table 5.4: Risk factor information collected during PROUD

CRF	Information	Time-scale
Baseline	Demographic information: education status; ethnicity; born in UK; age; relationship status; London site; employment status .	NA
	Drug use: chemsex associated drugs (methamphetamine, GHB, mephedrone or ketamine); and poppers.	Past three months
	Other factors: depression score; circumcision.	NA
Visit (pre-March and post-March 2015)	Has condomless anal sex occurred?	Since last visit
	Number of PEP prescriptions	Since last visit
Visit (post-March 2015)	How many condomless anal sex partners?	Past 30 days
	Drug use (chemsex, injecting drugs, snorting cocaine), group sex, sex toys, fisting (by glove use)?	Since last visit
Laboratory	STI screens and diagnoses (rectal/pharyngeal/rectal GC and CT, syphilis, HCV, hep B)	Since last visit
Monthly	Total number of partners, total receptive (ncRAI) and insertive (ncIAI) partners without a condom	Past 30 days
	Number of ncRAI partners with unknown HIV status	Past 30 days
	Number of ncRAI partner HIV-positive and not currently on treatment	Past 30 days
	Number of previous ncRAI partners	Past 30 days
	Condom use and position during the last AI	Past 30 days
	HIV status and treatment status of last ncRAI partner	Past 30 days

CRF, case report form; UK, United Kingdom; NA, not applicable; GHB, Gamma-hydroxybutyrate; PEP, post-exposure prophylaxis; PrEP, pre-exposure prophylaxis; chemsex, sexualised drug-use; STI, sexually transmitted infections; GC, gonorrhoea; CT, chlamydia; HCV, hepatitis C; hep B, hepatitis B; HIV, human immunodeficiency virus; ncRAI, receptive anal intercourse without a condom; AI, anal intercourse; ncAI, anal intercourse without a condom.

5.7 Screening for HCV

This section describes the HCV screening patterns during PROUD over time, by clinic, and a participant level. I also consider how the change to routine screening impacted ascertainment of HCV status and review the factors that predicted a screen prior to the change when screening was conducted "if indicated".

5.7.1 HCV screening patterns

Only 24.4% (133/544) of participants were screened for HCV at enrolment, but 91.7% (499/544) were screened at least once during the study. Nine of the 499 were screened only at baseline, and do not contribute to the incidence analysis (Section 5.9). Figure 5.3 illustrates, by time since enrolment, the cumulative number of participants who had received at least one HCV screen, demonstrating a number of participants had been in the study for a substantial amount of time before they were screened.

Figure 5.3: Cumulative number of participants with a HCV screen by study time

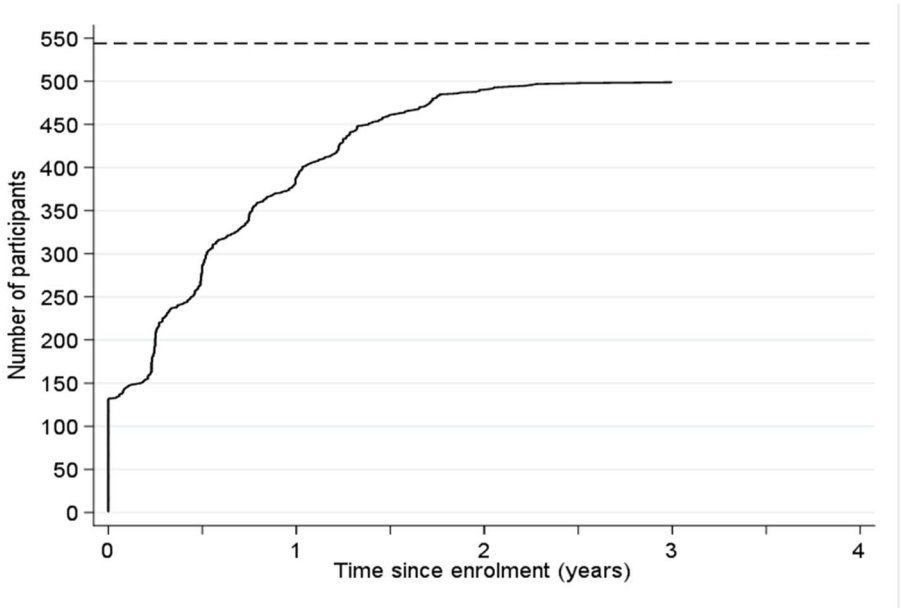
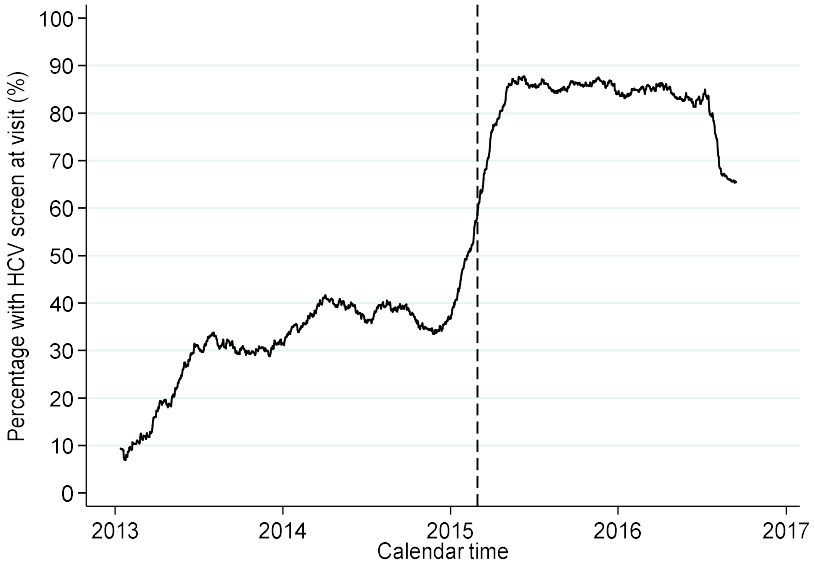


Figure legend: *Horizontal dashed line indicates the 544 participants recruited to PROUD. Vertical dotted line indicated the start of the HCV sub-study.*

Figure 5.4 demonstrates the probability (moving average) of having a HCV screen at a study visit over calendar time[15]. The average proportion screened at a visit before January 2015 was 33.8%. Testing increased from this point through to the start of the sub-study in March 2015, after which the proportion screening was 80.6%.

[15] The moving average was calculated as the proportion of visits with a HCV screen in the 90 day period (±45 days) around that particular time point.

Figure 5.4: Moving average of percentage of visits involving a HCV screen by calendar time



The percentage screening at each visit varied widely by clinic, ranging from 6.7% to 81.0% prior to the sub-study (p<0.001, Figure 5.5), with screening less likely in London clinics compared to non-London clinics (31.9% vs. 42.0%, p<0.001). After the sub-study began, the proportion of screening increased in all clinics (range: 56.3-95.6%, Figure 5.5), although the increase was relatively small in two clinics (Clinic 11 and 13), although their screening rate was already relatively high.

Figure 5.5: Proportion of visits with a HCV screen, by study clinic and HCV sub-study

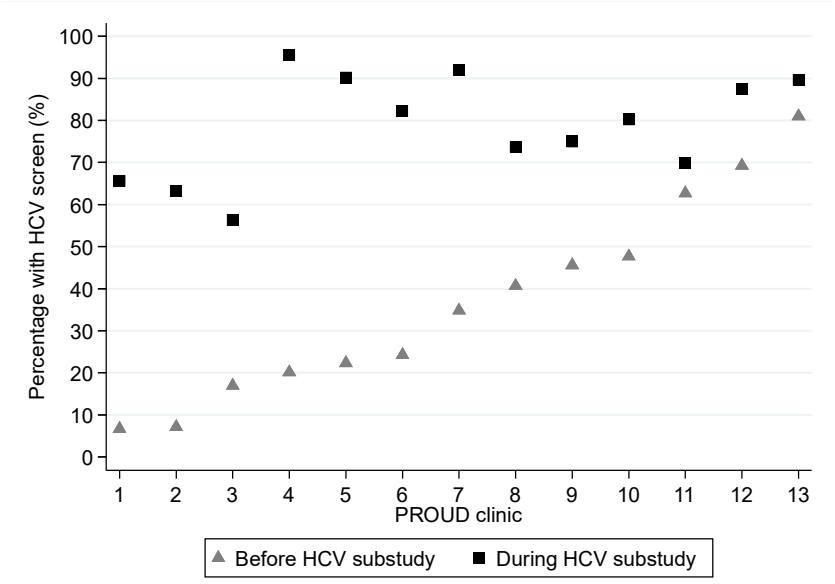
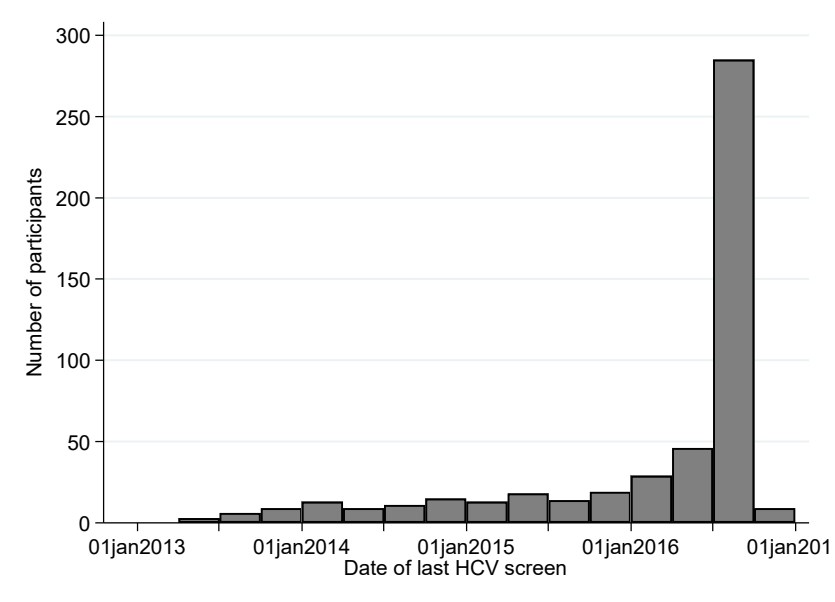


Figure legend: *London sites: 1, 2, 3, 5, 6, 7, 10, 11.*

Figure 5.6 shows the distribution of the date of the last HCV screen in the trial for the participants. 369 participants had a screen in the final calendar year of the study (2016) and 294 of those were from July onwards.

Given the nature of HCV, if a participant tests Ab negative towards the end of the study, we know that they could not have acquired the infection during the trial (and at randomisation). Clinical judgement was used to determine the likely timing of infections diagnosed shortly after enrolment. Therefore, under the assumption that the status was known for all participants at enrolment, participants could contribute person-years from randomisation until their last screen, regardless of whether they were screened at baseline. This approach also reduces bias, since incorporation into the analysis is not based on HCV screening frequency or HCV status. As a result, HCV status was known for 93.8% (1188.9/1267.1 PY) of the follow-up time.

Figure 5.6: Distribution of last HCV screen in PROUD



5.7.2 Individual predictors of having a HCV screen

I focused next on the participant characteristics that predicted HCV screening in the period when screening was conducted "if indicated" (pre-March 2015).

Statistical methods

To assess the predictors of receiving a HCV screen, I considered pertinent baseline and time-updated factors at each visit from the start of PROUD (November 2012) to the end of February 2015 (pre-HCV sub-study). Chemsex associated drug-use, popper-use, and relationship status were taken from the baseline questionnaire because they were not collected again during this period (Table 5.4). Time-updated factors were: PEP prescription since the last visit; a key STI diagnosis since the last visit; and the grouped number of ncRAI partners taken from the monthly questionnaire (0, 1, 2-4, 5-9, 10+). For time-updated variables, information was taken from the participants' most recently completed questionnaire.

To account for within-patient dependency, generalised estimating equations (GEEs) were used to model the association between risk factors and receiving a HCV screen. Logistic regression models were fitted using the binomial family and a logit link function. Due to the variability in HCV screening observed between clinics (Section 5.7.1), clinic was adjusted for in each model. Autocorrelation matrix structures (independent, exchangeable, and auto-regressive[16]) were compared using the 'quasilikelihood under the independence model criterion' (QIC). The model with the smallest QIC value indicated the best fit. Multivariable analysis was conducted by adjusting for all factors together in the model. For categorical

[16] Independent correlation matrix assumes that there is not dependency in HCV screens between visits (within a participant). Exchangeable correlation matrix assumes that the correlation is the same for any pair of visits. Auto-regressive correlation matrix assumes that the dependency is stronger for visits occurring closer together.

variables, the category with the highest number of HCV screens was chosen to be the reference category. For ordered categorical variables, *p*-values for trend were calculated.

Results

During the pre-sub-study period, 3457 study visits were conducted amongst the 544 participants (median visits per participant: 7, IQR: 5-8), over an average follow-up of 1.2 years (IQR: 0.9-1.5 years). A HCV screen was performed at 1208 of the visits (34.9%), with a median number of 2 (IQR: 1-3) screens per participant.

Statistically significant predictors of receiving a HCV screen at a given visit were: the use of chemsex associated drugs in the three months prior to enrolment, being single at baseline, diagnosis of a key STI since the last visit, and ten or more ncRAI partners in the prior 30 days (Table 5.5). The use of chemsex associated drugs was associated with a 30% higher odds in obtaining a screen (adjusted odds ratio (aOR)=1.3 [95% CI: 1.1-1.6], p=0.003). Participants reporting single relationship status at baseline were at a borderline-significant increase in obtaining a screen at each visit (p=0.04). The odds of receiving a HCV screen increased two-fold if a key STI had been diagnosed since the last visit (aOR=2.0 [95% CI: 1.6-2.5], p<0.001). After adjustment for other covariates, participants reporting ten or more ncRAI partners in the 30 days prior to the visit were at a nearly two-fold chance of getting a test (aOR=1.9 [95% CI: 1.4-2.6], p<0.001) compared to those reporting zero ncRAI partners.

Table 5.5: Predictors of HCV testing at each visit (pre-HCV sub-study)

Characteristic		Total visits	Total HCV screens (%)	OR (95% CI)	aOR (95% CI)	*p*-value*
Trial arm	Immediate	1875	636 (33.9)	1.0	1.0	0.11
	Deferred	1582	572 (36.2)	1.1 (0.9-1.3)	1.1 (1.0-1.3)	
Use of chemsex associated drugs[A]	No	1785	585 (32.8)	1.0	1.0	0.003
	Yes	1569	575 (36.7)	1.2 (1.0-1.4)	1.3 (1.1-1.6)	
Poppers[A]	No	1592	506 (31.8)	1.0	1.0	0.10
	Yes	1762	653 (37.1)	1.2 (1.0-1.5)	1.2 (1.0-1.4)	
Relationship status[A]	Not cohabiting	1044	351 (33.6)	0.9 (0.7-1.2)	0.8 (0.7-1.0)	0.04
	Cohabiting	494	164 (33.2)	0.9 (0.6-1.2)	0.9 (0.7-1.1)	
	Single	1899	687 (36.2)	1.0	1.0	
PEP use[B]	No	3093	1071 (34.6)	1.0	1.0	0.53
	Yes	364	137 (37.6)	1.0 (0.8-1.3)	1.1 (0.8-1.4)	
Key STI[B]	No	3024	989 (32.7)	1.0	1.0	<0.001
	Yes	433	219 (50.6)	2.0 (1.6-2.4)	2.0 (1.6-2.5)	
No. ncRAI partners[C]	0	939	288 (30.7)	1.0	1.0	0.001
	1	873	301 (34.5)	1.1 (0.9-1.3)	1.0 (0.8-1.2)	
	2-4	915	321 (35.1)	1.1 (0.9-1.4)	1.0 (0.8-1.3)	
	5-9	332	129 (38.9)	1.3 (0.9-1.7)	1.2 (0.9-1.5)	
	10+	252	128 (50.8)	2.3 (1.6-3.1)	1.9 (1.4-2.6)	

HCV, hepatitis C; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; chemsex associated drugs, methamphetamine, GHB, mephedrone or ketamine; PEP, post-exposure prophylaxis; key STI, rectal chlamydia, rectal gonorrhoea or syphilis; ncRAI, receptive anal intercourse without a partner.
aOR estimated from logistic regression model, adjusting for study site and other variables in factors
[A]Baseline questionnaire, [B]quarterly visits (time-updated), [C]most recent monthly questionnaire (time-updated)
p-values for relationship status calculated by comparing single and those in a relationship. *p*-value for trend presented for ncRAI.

5.8 HCV infections

5.8.1 Seroprevalent HCV infections

Of the 133 participants screened for HCV at enrolment, two were found to be HCV Ab positive and active infection was confirmed virologically. An additional eight participants were reported to have had a previous diagnosis of HCV by their clinician (Figure 5.8). Finally, two participants (who were not screened at baseline) were determined to be HCV viraemic at their first post-enrolment test. A definitive assessment of whether the infection occurred before or after enrolment was not possible. However, one case was judged by the clinicians on the Trial Management Group to have occurred before enrolment based on HCV RNA of 9006 copies/ml and ALT of 208 at 4 weeks, and the other to have occurred after enrolment based on HCV RNA of 1684020 and ALT=2763 at 8 weeks. This gives a total of 11 (2+8+1) seroprevalent infections at the time of enrolment.

45 participants were not screened for HCV during the study, 14 of whom did not provide a history of HCV at enrolment and therefore provide no information on HCV seroprevalence or incidence (Figure 5.8). 358 participants (who had not been screened at baseline) were found to be HCV Ab negative at their first post-enrolment test. It can be inferred that these participants would also have tested HCV Ab negative at baseline, and can be added to the 130 individuals who actually tested HCV Ab negative, giving a total of 488. An additional 30 participants did not receive a HCV screen during PROUD, but the clinician reported no prior history. Thus the denominator for the HCV seroprevalence rate at baseline is 530 (488+30+12 cases described above), giving an estimated seroprevalence of 2.1% (11/530, 95% CI: 1.0-3.7). It is noted that this includes individuals with active and cleared infections.

5.8.2 Incident HCV infections

There were 26 incident HCV infections in 25 of the 490 participants screened after baseline, including the case described above diagnosed at 8 weeks. 21 participants were diagnosed after a negative HCV Ab test during PROUD and three after detecting virus in a participant who had cleared HCV virus after an earlier infection. One participant had two incident infections during the study; the first was diagnosed in January 2014 and cleared after treatment, but he acquired a new infection in February 2016.

Counting only the first infection, the overall HCV incidence during follow-up in PROUD was 2.1 per 100 PY (25/1188.9, 95% CI: 1.4-3.1). Two of the participants described above acquired HCV infection after a diagnosis of HIV (three months and two years later). Excluding these cases from the HCV incidence calculation reduces the estimate only slightly (1.9 per 100 PY [95% CI: 1.2-2.9]), and they are therefore included in the remaining analyses.

At the time of the incident HCV diagnosis, a prior history of injection drug use was reported in 11 participants (44%, [Table 5.6]). However, it was unclear whether this was the mode of transmission rather than sexual acquisition.

A large proportion of the infections occurred towards the end of the study in 2015 and 2016 (2015 *n*=12, 2016 *n*=9). Figure 5.7 shows the date of the last negative serological or virological test result and the first positive test in the 25 incident infections. The large gap observed in some cases means we are unable to accurately pinpoint the time of infection, which complicates the analysis of calendar time trends (Section 5.9).

The wait-listed design of PROUD allows direct comparison of those taking PrEP (in the IMM group) to those that are not (in the DEF group). In theory, this provides an opportunity to assess whether PrEP influences HCV incidence. However, there were only three incident HCV infections reported during the deferred phase (one IMM, two DEF), precluding examination of this effect.

Figure 5.7: Date of last negative Ab (or Ag/RNA in a participant who had previously cleared HCV) and first the positive Ab or Ag

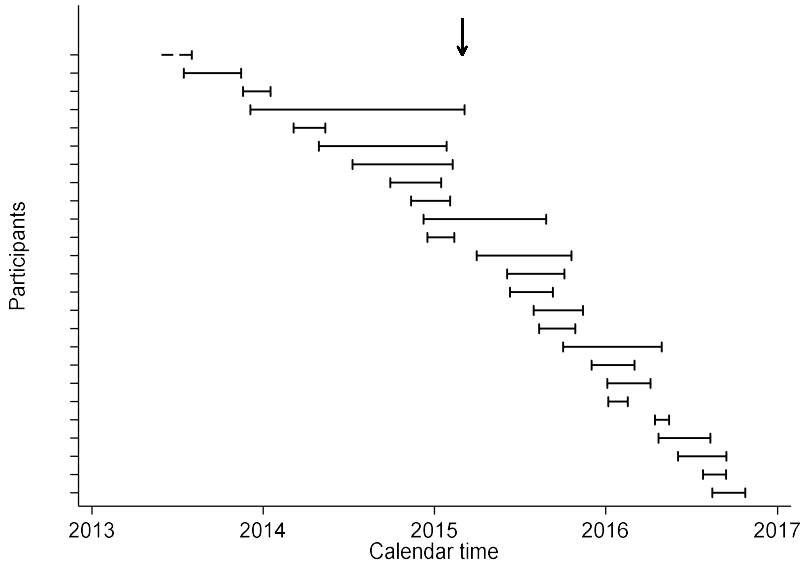


Figure legend: *Left bound indicates the date of the last negative HCV screen (Ag or Ag), right bound indicates the date of the first positive HCV screen (Ag or Ab), arrow indicates the start of the HCV sub-study.*

Table 5.6: Details of incident HCV seroconversions

Participant	Trial arm	Year of first positive	VL*	Injection drug use	Outcome (treatment or spontaneous clearance)
1**	DEF	2013	6.2	---	---
2**	IMM	2013	5.5	Y	Treatment
3**	DEF	2014	---	Y	Treatment
4	DEF	2014	6.0	---	---
5	DEF	2015	3.5	Y	Treatment
6	IMM	2015	---	Y	Treatment
7	IMM	2015	---	Y	Treatment
8	DEF	2015	---	N	Treatment
9	DEF	2015	7.2	Y	Neither
10	DEF	2015	---	Y	Spontaneous
11	DEF	2015	4.8	N	Treatment
12	IMM	2015	6.9	N	---
13	IMM	2015	4.6	Y	Spontaneous
14	DEF	2015	---	Y	---
15	IMM	2015	3.2	Y	---
16	IMM	2015	---	N	---
17	IMM	2016	7.0	N	Treatment
18	IMM	2016	4.1	N	Neither
19	IMM	2016	4.9	N	Neither
20	IMM	2016	---	Y	---
21	DEF	2016	---	N	Spontaneous
22	DEF	2016	5.7	N	Treatment
23	IMM	2016	6.7	N	---
24	IMM	2016	---	N	----
25	IMM	2016	---	N	Treatment

ID, participant identifier; VL, viral load; TMG, Trial management group; DEF, deferred; IMM, immediate; Y, yes; N, no.
*$\log_{10}$ viral load
**Acquired during deferred phase
Participant 1 required Trial Management Group judgement to reach conclusion on incident infection
Participants 5, 12 and 13 reported a previous infection prior to the incident infection during PROUD
Participant 3 went on to acquire an additional HCV infection during PROUD

Figure 5.8: Hepatitis C screening and infection consort diagram

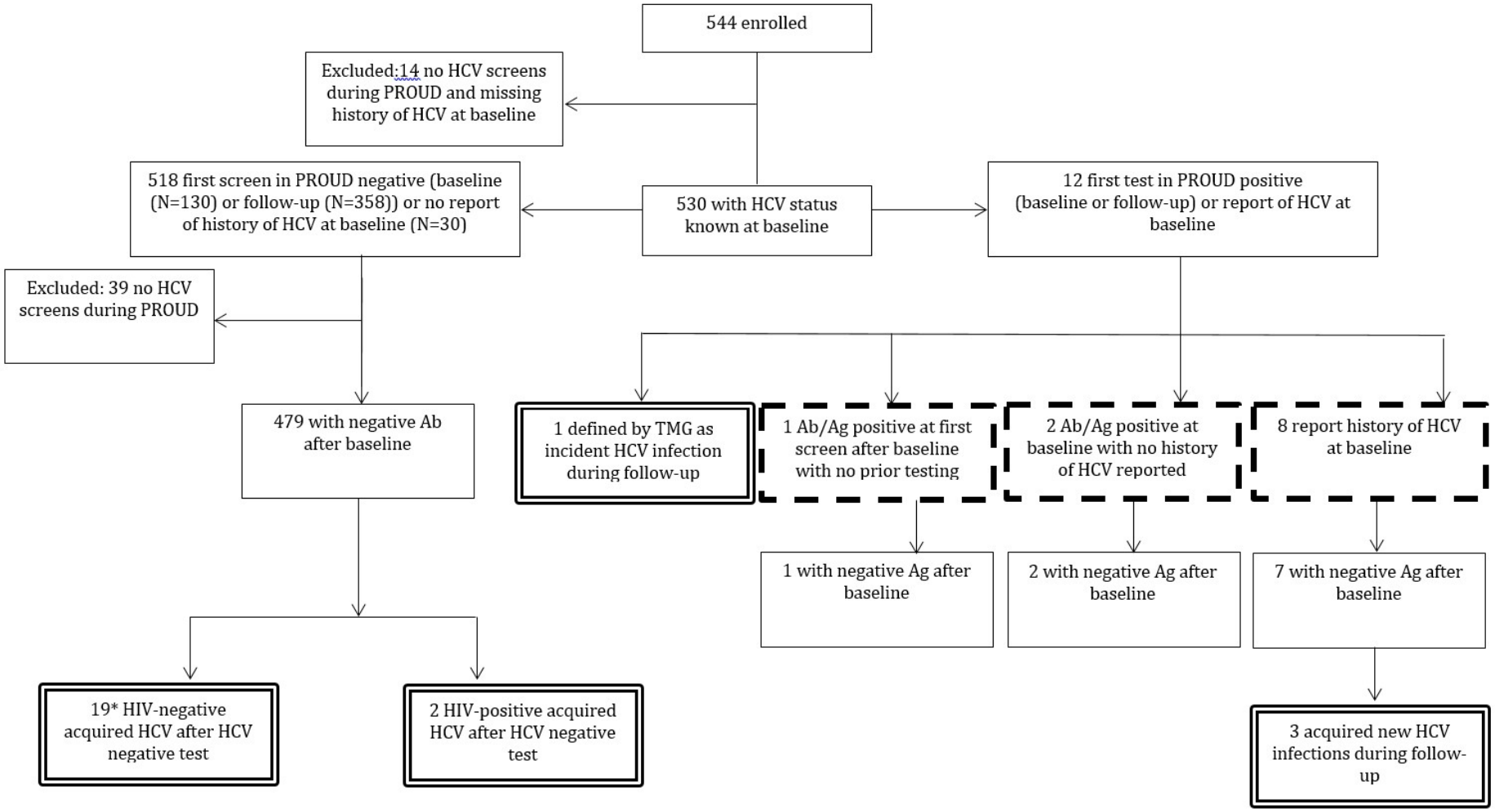


Figure legend: *Seroprevalent infections indicated by dashed box. Incidence infections indicated by double lined box. *One participant acquired two incident infections during follow-up (only first considered in analysis).*

5.9 Estimating HCV incidence over time

This section discusses methodological issues in calculating HCV incidence over time. I start by discussing the choice of time-scale (time since enrolment or calendar time), and then compare methods for calculating incidence when the precise time of infection is unknown.

5.9.1 Time-scales

Traditionally, clinical trials present data from the time of enrolment, given that the intervention is usually the key focus. In PROUD the majority of HCV infections occurred in the last two years of the study when everyone had access to the intervention (Figure 5.7 and Table 5.6). Therefore, we also need to consider the effect of calendar time. Two time-scales are possible:

1. **Time from enrolment** – the participants' origin in the analysis is the point at which they are enrolled.
2. **Calendar time** – the time-origin is from the start of the trial (29th November 2012), with participants entering the analysis when they are enrolled (delayed entry).

In both analyses, individuals are censored at the date of HCV diagnosis or their last HCV screen in the trial, whichever is earlier. The overall incidence in the two time-scales is equivalent because the amount of follow-up time contributed by each participant is the same.

Figure 5.9 illustrates the cumulative hazard of acquiring HCV from enrolment (stratified by trial arm). There was no evidence of a difference between the IMM and the DEF group (log-rank test, p=0.87). However, this does not imply that access to PrEP has no effect on HCV incidence since both groups had access to PrEP over most of the period of follow-up. Therefore, IMM and DEF groups were combined in all subsequent analyses.

Figure 5.10 illustrates that the HCV diagnoses appear to cluster by calendar time (e.g. beginning of 2015). This could be due to localised epidemics, or changes in screening patterns, e.g. the increase in testing that occurred around the introduction of the HCV sub-study. This suggests that, for this analysis, calculating HCV incidence over calendar time is the most appropriate and is the only time-scale presented for the remainder of the chapter.

Figure 5.9: Kaplan Meier analysis of time to HCV diagnosis (time from enrolment)

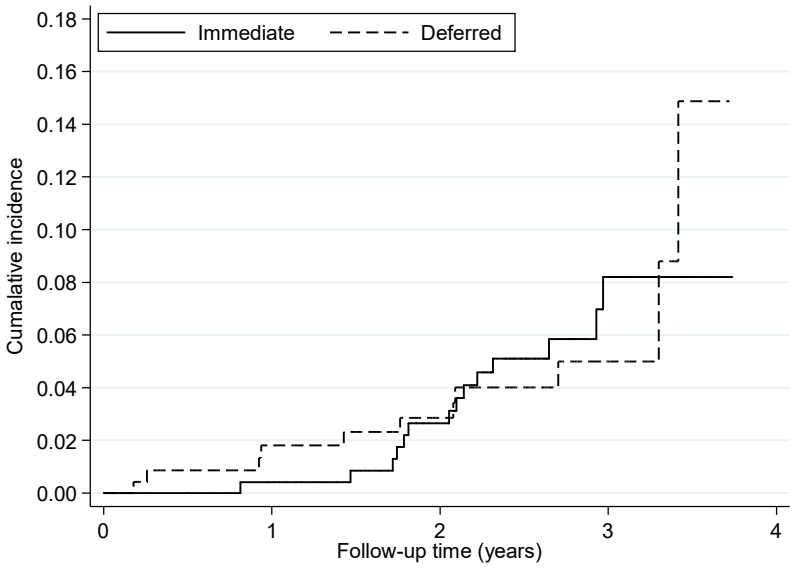


Figure 5.10: Kaplan Meier of the time to HCV over calendar time (with 95% confidence intervals)

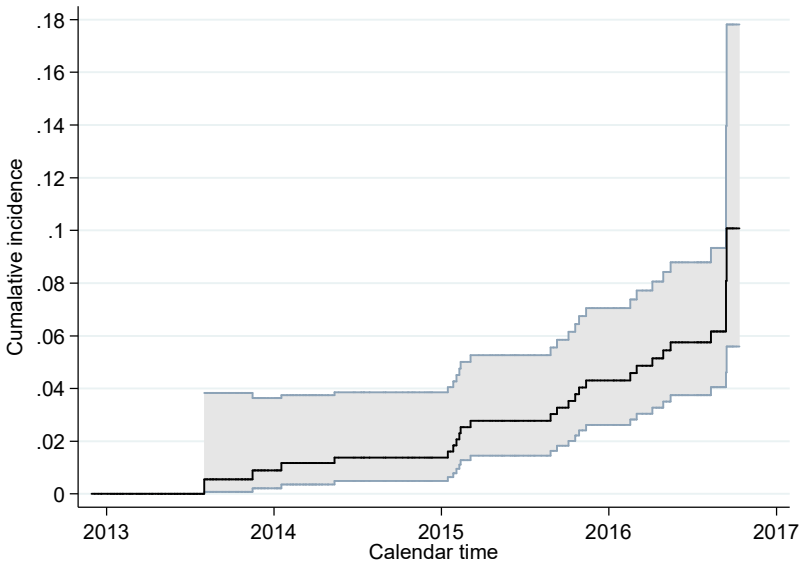


Figure legend: *For display purposes this figure excludes one participant with an infection occurring in October 2016. This infection was included in all analyses presented in this chapter.*

5.9.2 Estimating HCV incidence over calendar time

For some participants, there was a long interval between the last negative screen and first positive screen (Figure 5.7). This makes it difficult to pinpoint when the HCV infection occurred, which complicates the analysis assessing the change in incidence over calendar time. In PROUD, there were ten (40%) of 25 participants whose interval between the last negative and the first positive test spanned different calendar years, with one case, spanning three years (Figure 5.11).

Figure 5.11: HCV infections with an interval of infection spanning two or more calendar years

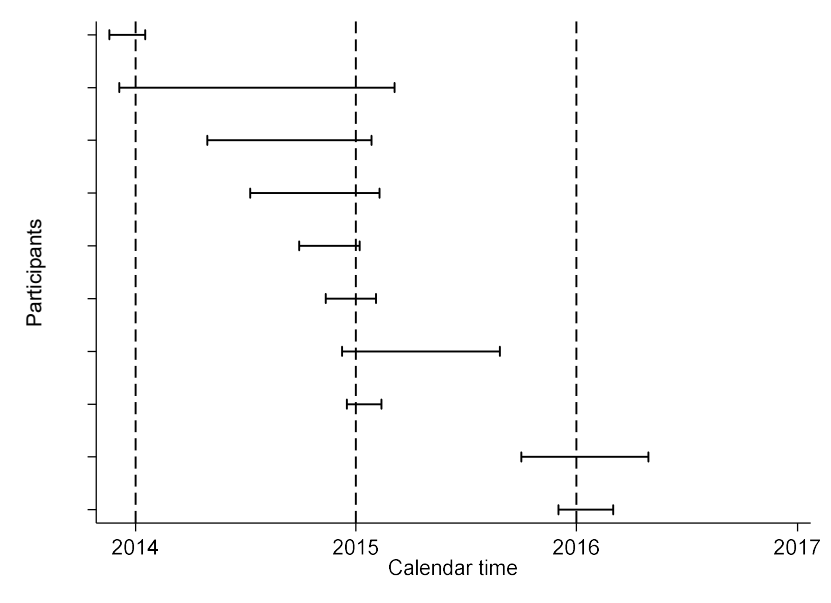


Figure legend: Dashed vertical lines represent the beginning of each calendar year

As incidence estimates are sensitive to the assumptions made about when each infection occurred, I compared the HCV incidence by calendar year based on four different assumptions of the date of HCV infection:

1. The date of the first positive test (date of diagnosis);

2. The day after the last negative test;
3. The mid-point between the last negative and the first positive test;
4. An imputed date between the last negative and the first positive test ("random-point" approach described later).

For the one participant with no previous negative screen in the study, the date of their negative test was assumed to have occurred at enrolment. For each of the methods, HCV incidence was calculated for each calendar year by dividing the number of infections by the total amount of follow-up in that calendar year. Given the small amount of follow-up in 2012 (0.3 PY), this was combined with the follow-up in 2013.

HCV incidence rates varied for each year depending on the assumption of the date of infection (Table 5.7). For instance, incidence in 2015 was estimated at 3.0 per 100 PY, 1.8 per 100 PY and 1.8 per 100 PY for the first positive, last negative and mid-point methods, respectively. In 2016, the incidence was 4.4 per 100 PY, 3.4 per 100 PY and 4.4 per 100 PY per 100 PY for each of the three methods.

Table 5.7: HCV incidence stratified by calendar year and according to assumed dates of infection

	First positive			**Last negative**		
	PY	***n***	**Rate per 100 PY (95% CI)**	**PY**	***n***	**Rate per 100 PY (95% CI)**
2013	155.1	2	1.3 (0.2-4.7)	154.5	4	2.6 (0.7-6.6)
2014	432.7	2	0.5 (0.06-1.7)	429.8	7	1.6 (0.7-3.4)
2015	394.9	12	3.0 (1.6-5.3)	391.7	7	1.8 (0.7-3.7)
2016	206.2	9	4.4 (2.0-8.3)	204.3	7	3.4 (1.4-7.1)
	Mid-point			**Random-point**		
	PY	***n***	**Rate per 100 PY (95% CI)**	**PY**	***n***	**Rate per 100 PY (95% CI)**
2013	154.9	3	1.9 (0.4-5.7)	154.8	2.8	1.8 (0.5-6.2)
2014	431.4	6	1.4 (0.5-3.0)	431.4	5.7	1.3 (0.5-3.3)
2015	393.2	7	1.8 (0.7-3.7)	393.2	8.2	2.1 (1.0-4.4)
2016	205.1	9	4.4 (2.0-8.3)	205.1	8.2	4.0 (2.0-8.1)

PY, person-years; *n*, number of HCV infections; CI, confidence intervals
* Average values calculated from 1000 repetitions and confidence intervals calculated using Rubin's Rule

Therefore, the incidence estimate is clearly sensitive to the interval between last negative and first positive test, and how these intervals overlap the start of the calendar year, rather than the approach used *per se*. This was a particular concern given the low number of HCV events. In addition, the mid-point assumption, although a common approach, does not reflect any information we hold on the participant, and is merely a function of the length of the interval between tests, rather than an estimate of when the infection could have occurred.

Given the pit-falls of these three assumptions, I explored the literature for an alternative approach. A simulation study investigated the use of the mid-point method to estimate HIV incidence when participants missed their scheduled HIV tests [172]. They reported that the mid-point approach under-estimated the true HIV incidence at the end of the follow-up period. Instead, they advocated for an approach which randomly assigns the date of infection between the last negative and first positive test, using a uniform distribution. I carried out this approach for the PROUD HCV data by imputing the date of HCV infection between the infection interval 1000 times for each individual with an infection. I then calculated the incidence for each calendar year in each imputed dataset, and then took the average incidence for each year. Confidence intervals were calculated by pooling the standard errors using Rubin's rule [173].

Using the random-point method, I found that the estimates were the most comparable to the mid-point method, but still differed. HCV incidence was estimated to be 1.8 per 100 PY (95% CI: 0.5-6.2), 1.3 per 100 PY (95% CI: 0.5-3.3), 2.1 per 100 PY (95% CI: 1.0-4.4) and 4.0 per 100 PY (95% CI: 2.0-8.1) per 100 PY in 2013-2016, respectively (Table 5.7). Therefore, there was an indication that HCV incidence was higher towards the end of the study (*p*-value for trend=0.09).

5.10 Predictors of incident HCV infection

5.10.1 Statistical methods

I conducted two separate analyses to assess the predictors of HCV acquisition. The first analysis considered the entirety of follow-up (from enrolment until last HCV screen). Demographic characteristics and popper-use were taken from the baseline questionnaire (they were not recorded again during follow-up). Data recorded in the monthly Adherence and Sexual Behaviour Questionnaire, such as number of sexual partners, and the HIV status of their last partner in the 30 days previous, were time-updated variables in the analysis. Information on STI diagnoses, and PEP prescriptions since the last visit (collected at quarterly visits) were also time-updated. Person-years of follow-up were attributed to the most recent risk-factors reported on the questionnaire (regardless of the length of time since the participants' last questionnaire). If a participant acquired HCV, but did not complete a questionnaire on the date of diagnosis, data were taken from the closest questionnaire completed prior to this. Analysis was performed on a calendar time scale with data censored at the last HCV screen or the first HCV infection, whichever was earlier.

The second analysis was restricted to follow-up after March 2015, when several questions (e.g. chemsex, injection drug use, snorting cocaine, group sex, and fisting) were added to the visit CRF. Again, analysis was performed on a calendar time scale (origin 1 March 2015) using the same censoring rule as above.

To account for the non-constant HCV incidence, time-updated Cox regression models were fitted for both analyses. The low number of HCV infections precluded a multivariable approach. Reference groups for categorical variables were chosen to be the group with the most person-years of follow-up to provide the most stable estimates of hazard ratios. *p*-values for trend were calculated for ordered categorical variables.

5.10.2 Results

Baseline and time-updated predictors of HCV (entire follow-up)

Of the 490 participants included in the HCV incidence analysis, 487 participants completed a questionnaire at baseline. However, data on age and clinic could still be used for the remaining three. During the course of the trial, 6099 monthly questionnaires were completed by 487 participants; an average of 11 (IQR: 7-16) questionnaires per participant. The total follow-up for individuals with at least one monthly questionnaire was 1187.7 PY, with an average of 4.4 (IQR: 3.2-6.6) questionnaires per year. The number of questionnaires did not vary according to HCV status. All 25 participants with an incident HCV infection had completed a baseline questionnaire and had at least one monthly questionnaire before their diagnosis (Figure 5.12). Seven participants (28.0%) completed a questionnaire on the date of HCV diagnosis, whereas five participants' (20.0%) most recent questionnaire was more than three months prior to the diagnosis.

Figure 5.12: Monthly questionnaires prior to incident HCV infection

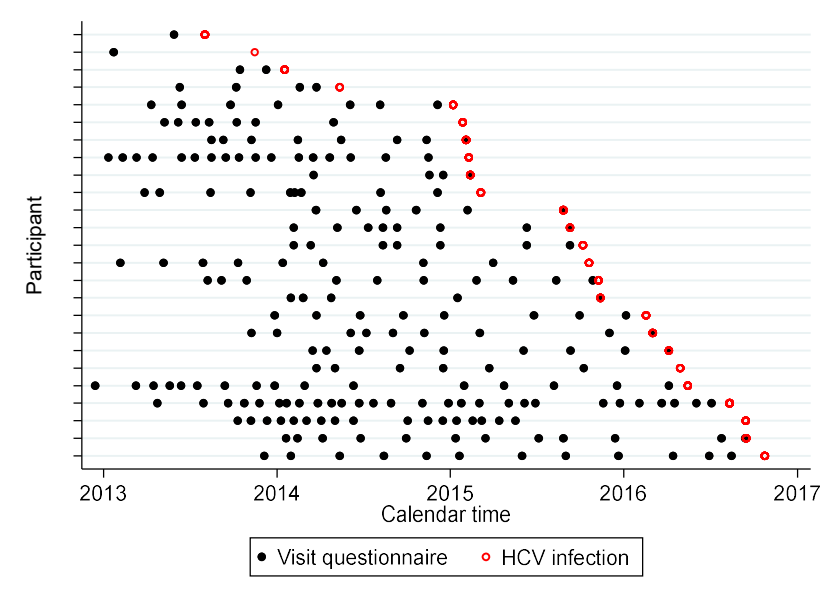


Figure legend: *black dots indicate the date of completion of the monthly questionnaire and red dots indicate the date of HCV diagnosis.*

Reporting the use of poppers in the three months prior to enrolment was significantly associated with a three-fold increased risk of HCV acquisition (HR=3.2 [95% CI: 1.3-8.1], *p*=0.01)(Table 5.8). Non-significant trends were observed for demographic factors. Those attending a London site at baseline (HR=1.5 [95% CI: 0.5-3.9], *p*=0.46) were at a higher risk. Similarly to predictors of HIV (Chapter 2), participants reporting that they were in a non-cohabiting relationship were at the lowest risk of HCV compared to those that were single or living with their partner (HR=0.5 [95% CI: 0.1-2.4], *p*=0.43). Participants in the 25-34 year age category at baseline were at a higher risk of HCV acquisition compared to other age groups.

In terms of time-updated sexual behaviour (in prior 30 days), reporting ncRAI of any kind put individuals at higher HCV risk, including: total number of ncRAI partners; number of new ncRAI partners; ncRAI with unknown HIV status; and the last sex act being ncRAI, although not all were statistically significant (Table 5.9). Participants reporting 10 or more ncRAI partners were at higher risk of HCV compared to those reporting zero ncRAI partners in the prior 30 days (HR=1.6 [95% CI: 1.0-2.6], *p*=0.08). HCV risk was particularly high for participants reporting ncRAI with five or more partners with unknown HIV status in the prior 30 days (HR=1.5 [95% CI: 1.1-2.0], *p*=0.016). Those reporting ten or more new ncRAI partners in the prior 30 days were at a 60% increased risk of HCV acquisition compared to those with zero new ncRAI partners (HR=1.6 [95% CI: 1.1-2.3], *p*=0.025). In contrast, the total number of sexual partners or the number of ncIAI partners had little impact on HCV risk, although clearly intrinsically associated with ncRAI.

HIV status of their last ncRAI partner was also associated with HCV risk; participants reporting that their ncRAI partner was negative were at the lowest risk, whereas those reporting either an unknown or HIV-positive status of their partner were at a more than three-fold greater risk (HR=3.3 [95% CI: 1.2-9.3], HR=3.4 [95% CI: 1.2-9.5], respectively). Although there was a suggestion that participants reporting no ncRAI were at a higher risk than those with a HIV-negative ncRAI partner (HR=2.2 [95% CI: 0.7-6.4], *p*=0.17), two of the

three individuals completed the questionnaire a substantial time prior to diagnosis (six and nine months) and behaviours may have changed.

The diagnosis of a key STI in the period since the last visit was associated with a 20% increase in hazard, but this was not statistically significant (HR=1.2 [95% CI: 0.8-1.6], p=0.37).

Table 5.8: Predictors of HCV during entire follow-up (baseline factors)

Characteristic		Participants, *n* (%)	PY (% total PY)	HCV infections	Incidence rate (per 100 PY)*	HR	95% CI	*p*-value**
Total		490 (100.0)	1188.9 (100.0)	25	2.1	---	---	---
Age, years	18-24	43 (8.8)	91.7 (7.7)	0	0	---	---	0.48
	25-34	190 (38.8)	446.1 (37.5)	12	2.7	1.3	0.6-2.9	
	35-49	210 (42.9)	530.7 (44.6)	11	2.1	1.0	---	
	50+	47 (9.6)	120.4 (10.1)	2	1.7	0.8	0.2-3.7	
University degree	No	183 (37.7)	437.3 (37.0)	5	1.1	1.0	---	0.11
	Yes	303 (62.3)	746.0 (63.0)	20	2.7	2.2	0.8-6.0	
Full-time employment	No	134 (27.6)	320.5 (27.2)	6	1.9	1.0	---	0.84
	Yes	351 (72.4)	859.0 (72.8)	19	2.2	1.1	0.4-2.8	
Born in UK	No	194 (39.9)	464.6 (39.3)	9	1.9	1.0	---	0.60
	Yes	292 (60.1)	718.6 (60.7)	16	2.2	1.3	0.5-2.9	
Ethnicity	White	395 (83.7)	963.5 (81.7)	22	2.3	1.0	---	0.39
	BAME	90 (18.3)	215.7 (18.3)	3	1.4	0.6	0.2-2.0	
London site (at baseline)	No	144 (29.4)	347.9 (29.3)	5	1.4	1.0	---	0.46
	Yes	346 (70.7)	840.9 (70.7)	20	2.4	1.5	0.5-3.9	
Circumcised	No	341 (70.6)	815.4 (69.4)	16	2.0	1.0	---	0.65
	Yes	142 (29.4)	359.7 (30.6)	8	2.2	1.2	0.5-2.9	
Relationship status	Living with partner	145 (29.8)	356.0 (30.1)	9	2.5	1.2	0.5-2.8	0.43
	Not living with partner	74 (15.2)	172.5 (14.6)	2	1.2	0.5	0.1-2.4	
	Single	267 (54.9)	653.7 (55.3)	14	2.1	1.0	---	
High depression score [D]	No	414 (90.3)	1006.3 (90.3)	24	2.4	---	---	---

Table continued on following page

	Yes	43 (9.7)	108.3 (9.7)	0	0	---	---	
Popper-use in 90 days before enrolment	No	228 (48.0)	555.1 (48.0)	6	1.1	1.0	---	0.01
	Yes	247 (52.0)	600.3 (52.0)	19	3.2	3.2	1.3-8.0	

n, number of participants; PY, person years; HCV, hepatitis C virus; CI, confidence interval; HR, hazard ratio; kSTI, key sexually transmitted infections (rectal chlamydia, rectal gonorrhoea or syphilis); BAME, black, Asian and minority ethnicity.

[D]Defined by the PHQ-9 score, high score ≥10

Missing data (Total, events lost due to missing exposure data: poppers (15, 0); circumcised (7, 1); education (4, 0); ethnicity (5, 0); depression (34, 1); born in UK (4, 0); relationship (4, 0); employment status (5, 0).

*CI not presented due to varying incidence over calendar time

**p*-value for trend calculated for ordered categorical variables: ncRAI partners, AI partners, age and HIV tests. *p*-value for relationship status compares single vs. not living with partner.

Table 5.9: Predictors of HCV during the entire follow-up (time-updated predictors)

Characteristic		PY (% of total)	HCV infections	Incidence rate (per 100PY) *	HR	95% CI	*p*-value**
Key STI[B]	No	973.7 (81.9)	18	1.8	1.0	---	0.36
	Yes	215.2 (18.1)	7	3.3	1.2	0.8-1.6	
Number of AI partners	0	79.6 (6.7)	2	2.5	1.2	0.7-2.2	0.69
	1	207.3 (17.5)	5	2.4	1.2	0.7-1.8	
	2-4	333.6 (28.2)	5	1.5	1.0	---	
	5-9	269.9 (22.8)	6	2.2	1.2	0.8-1.8	
	10-19	196.7 (16.6)	3	1.5	0.9	0.5-1.6	
	20+	96.1 (8.1)	4	4.2	1.5	0.9-2.4	
Number of ncIAI partners	0	287.7 (24.3)	6	2.1	1.0	0.7-1.6	0.48
	1	312.5 (26.4)	5	1.6	0.9	0.6-1.4	
	2-4	316.4 (26.8)	6	1.9	1.0	---	
	5-9	159.6 (13.5)	6	3.8	1.4	0.9-2.1	
	10+	105.8 (8.9)	2	1.9	1.0	0.6-1.6	
Number of ncRAI partners	0	320.3 (27.1)	3	0.9	1.0	---	0.08
	1	307.3 (26.0)	6	2.0	1.2	0.7-2.0	
	2-4	306.5 (25.9)	6	2.0	1.2	0.7-2.1	
	5-9	141.8 (12.0)	5	3.5	1.3	0.8-2.3	
	10+	107.1 (9.0)	5	4.7	1.6	1.0-2.6	
Number of ncRAI partners with unknown HIV status	0	645.9 (54.6)	10	1.5	1.0	---	0.04
	1	227.1 (19.2)	4	1.8	1.0	0.7-1.6	
	2-4	193.3 (16.3)	3	1.6	1.0	0.6-1.6	
	5-9	80.2 (6.8)	5	6.2	1.5	1.0-2.2	
	10+	36.6 (3.1)	3	8.2	1.6	1.0-2.4	

Table continued on following page

Number of ncRAI partners with HIV and not on treatment	0	1019.8 (86.4)	18	1.8	1.0	---	0.31
	1	97.6 (8.3)	4	4.1	1.2	0.8-1.8	
	2-4	47.0 (4.0)	1	2.1	1.0	0.5-1.9	
	5-9	12.4 (1.1)	1	8.1	1.3	0.6-2.9	
	10+	3.4 (0.3)	1	29.1	1.6	0.6-3.9	
Number of new ncRAI partners	0	657.6 (55.6)	10	1.5	1.0	---	0.08
	1	155.6 (13.2)	3	1.9	1.0	0.6-1.6	
	2-4	219.3 (18.5)	4	1.8	1.0	0.6-1.5	
	5-9	96.1 (8.1)	4	4.2	1.2	0.8-1.8	
	10+	53.9 (4.6)	4	7.4	1.6	1.1-2.3	
IAI last time had anal sex	No	379.1 (32.0)	12	3.2	1.2	0.9-1.5	0.28
	Yes–with a condom	114.7 (9.7)	0	0	---	---	
	Yes-without a condom	689.3 (58.3)	13	1.9	1.0	---	
RAI last time had anal sex	No	365.0 (30.9)	3	0.8	0.7	0.4-1.1	0.05
	Yes-with a condom	132.9 (11.2)	0	0	---	---	
	Yes-without a condom	685.2 (57.9)	22	3.2	1.0	---	
HIV status of last ncRAI partner	No ncRAI	320.3 (27.1)	3	0.9	2.2	0.7-6.4	0.17
	HIV–negative	398.2 (33.7)	2	0.5	1.0	---	
	Unknown	162.5 (13.7)	6	3.7	3.4	1.2-9.8	0.02
	HIV-positive	302.1 (25.5)	14	4.6	3.5	1.2-9.8	0.02

PY, person years; HCV, hepatitis C virus; CI, confidence interval; HR, hazard ratio; kSTI, key sexually transmitted infections (rectal chlamydia, rectal gonorrhoea or syphilis); AI, anal intercourse; ncRAI, receptive anal intercourse without a condom; ncIAI, insertive anal intercourse without a condom; PEP, post exposure prophylaxis.

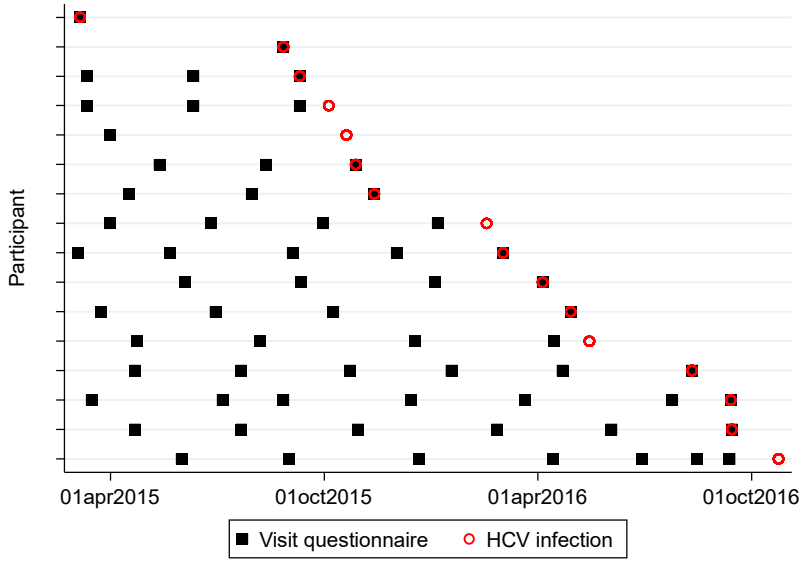
*CI not presented due to varying incidence over calendar time

***p*-value for trend calculated for ordered categorical variables: ncRAI partners, AI partners, age and HIV tests. *p*-value for relationship status compares single vs. not living with partner.

Time-updated predictors of HCV (follow-up from March 2015)

For the second analysis, 412 participants attended 2199 visits in the period after March 2015. Participants attended clinic an average of 6 times (IQR: 5-6) from this date until the end of the trial in October 2016. The quarterly visit schedule was adhered to during this period, with an average of 3.9 (IQR: 3.5-4.1) visits per year. 16 participants acquired HCV after March 2015, all of which had at least one visit questionnaire with the updated risk-factor questions (Figure 5.13). Nine (56.3%) had a trial visit on the day of HCV diagnosis; although, one participant's most recent visit was seven months prior. Over 532.1 PY of follow-up, the overall incidence during this period was 3.0 per 100 PY [95% CI: 1.7-4.9].

Figure 5.13: Visit questionnaires during HCV sub-study prior to HCV infection



Reporting fisting or the use of sex toys since the last visit put participants at significantly increased risk of HCV acquisition (Table 5.10). Participants reporting fisting were at a six-fold higher risk than those not reporting this since their last visit (HR=6.0 [95% CI: 2.1-16.8, p=0.001). There was no difference in hazard between those fisting with or without gloves (p=0.84). Participants reporting the use of sex toys were also at a significantly higher risk of becoming infected with HCV (HR=5.3 [95% CI: 1.8-15.6], p=0.002). Reporting group sex put participants at a two-fold HCV risk, but this was not statistically significant (HR=2.0

[95% CI: 0.7-5.7], p=0.19). There was no evidence to suggest that chemsex increased the risk of HCV (HR=1.1 [95% CI: 0.4-2.9]), similarly for snorting drugs (p=0.54). Injection drug use increased HCV risk by 60% (HR=1.6 [95% CI: 0.5-5.3]), but was not statistically significant (p=0.41). All five of the individuals reporting injection drug use reported ncAI during this time-period, and therefore the route of infection was unclear.

Reporting any one of the six risk factors (chemsex, injection drug use, snorting drugs, group sex, use of sex toys, or fisting) put participants at higher risk of HCV (HR=1.7 [95% CI: 0.6-4.7]), but this was not statistically significant (p=0.34). However, participants reporting any four or more of these had a significantly higher HCV incidence (HR=4.5 [95% CI: 1.5-13.1], p=0.006).

Table 5.10: Time-updated predictors of HCV during HCV sub-study

Characteristic		PY (% total)	HCV infections	Incidence rate per 100PY	HR	95% CI	*p*-value
Chemsex	No	325.6 (61.2)	8	2.5	1.0	---	0.86
	Yes	206.5 (38.8)	8	3.9	1.1	0.4-2.9	
Injection drug use	No	480.7 (90.3)	11	2.3	1.0	---	0.41
	Yes	51.4 (9.7)	5	9.7	1.6	0.5-5.3	
Snorted drugs	No	414.3 (77.9)	14	3.4	1.0	---	0.54
	Yes	117.7 (22.1)	2	1.7	0.7	0.2-2.6	
Group sex	No	304.2 (57.3)	7	2.3	1.0	---	0.19
	Yes	226.3 (42.7)	9	4.0	2.0	0.7-5.7	
Sex toy	No	413.7 (78.0)	5	1.2	1.0	---	0.002
	Yes	116.9 (22.0)	11	9.4	5.3	1.8-15.6	
Fisting	No	465.5 (87.8)	8	1.7	1.0	---	0.001
	Yes	65.0 (12.3)	8	12.3	6.0	2.1-16.8	
Fisting (by glove use)	No	465.6 (87.8)	8	1.7	1.0	---	0.84
	Yes-gloves	29.7 (5.6)	4	13.5	6.5	1.8-23.9	
	Yes-no gloves	35.3 (6.6)	4	11.3	5.6	1.6-20.0	
Number of risk factors*	0	180.9 (34.0)	3	1.7	1.0	---	0.04
	1	130.9 (24.6)	2	1.5	1.2	0.2-5.5	
	2	94.1 (17.7)	2	2.1	1.4	0.2-7.7	
	3	71.8 (13.5)	2	2.8	1.1	0.2-5.2	
	4	30.3 (5.7)	4	13.3	4.6	0.9-22.5	
	5	19.7 (3.7)	3	15.2	6.1	1.4-27.8	
	6	4.4 (0.8)	0	0	---	---	

PY, person-years; HCV, hepatitis C virus; HR, hazard ratio; CI, confidence interval.
* CI not presented due to varying incidence over calendar time
p-value for glove use whilst fisting compares those fisting with and without glove use
p-value for trend for number of risk factors

5.11 Are HCV risk factors changing over time?

5.11.1 Background

Section 5.9 showed that HCV incidence was increasing over time, and therefore it is of interest to establish whether there were behavioural changes over this period which could explain this change. For instance, the increase could be driven by an increase in: ncRAI partners over time, which could increase the transmission risk of HCV; ncRAI with HIV-positive partners due to the difference in HCV incidence between HIV-positive and HIV-negative MSM; or other risk factors such as, chemsex, injection drug use, fisting and the use of sex toys. I conducted exploratory analyses to examine whether there were calendar time trends in sexual behaviour that might explain the increase in HCV incidence.

5.11.2 Statistical methods

Using data from the monthly adherence and sexual behaviour questionnaire, I analysed calendar time trends either for the entire follow-up or from March 2015 onwards, depending on the specific variable. For each variable, the proportion of participants within each category at any given time was estimated by a moving average in the 90 day period (±45 days). Trial arms were combined for this analysis given the lack of difference in HCV risk.

5.11.3 Results

Although there were fluctuations, there were no clear trends in risk factors over time. The proportion of participants reporting five or more ncRAI partners experienced the most change over time - decreasing and increasing throughout follow-up (Figure 5.14). The proportion of participants reporting an HIV-positive most recent partner increased in the first year of the study and again around October 2014 (when DEF arm had access to PrEP),

but then remained relatively constant throughout the rest of the study. Although the population average did not show major changes, many individual participants switched between different categories (Appendix 13), maybe suggesting individual-level changes.

The number of HCV-associated risk factors reported at each PROUD visit remained relatively stable until around April 2016, when the proportion reporting one or more risk factors decreased (Figure 5.16). However, this change could be a reflection of the characteristics of the participants left in the study whilst clinics were phasing participants onto other sources of PrEP.

Figure 5.14: Number of ncRAI partners reported in the monthly questionnaires over time

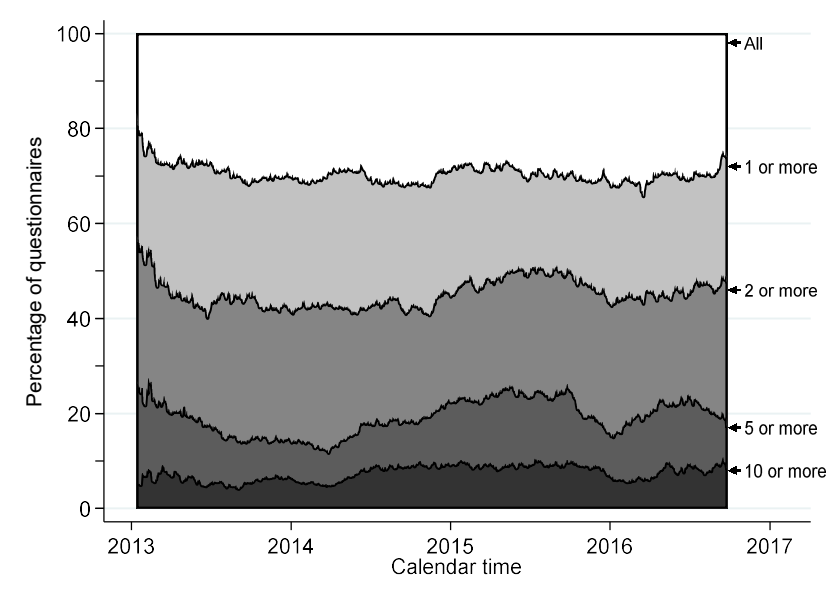


Figure 5.15: HIV status of last ncRAI partner reported in monthly questionnaires over time

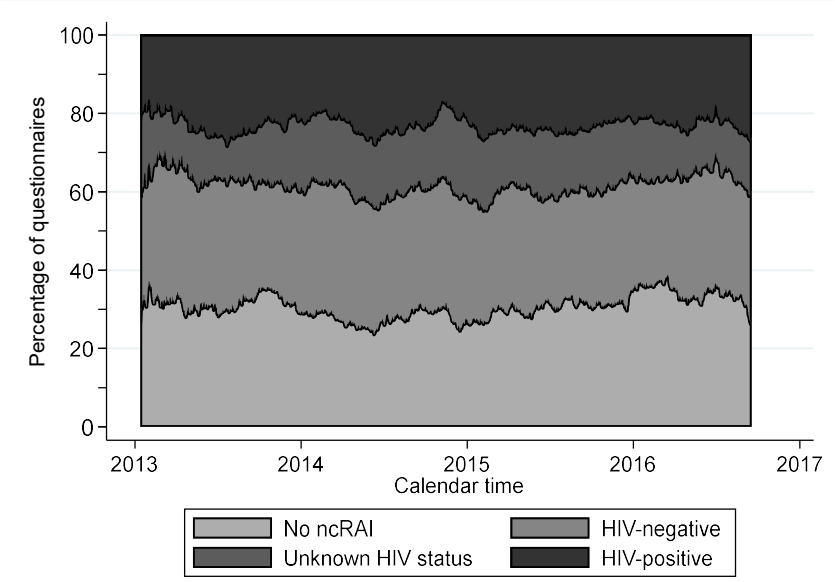


Figure 5.16: Number of HCV associated risk factors reported at PROUD study visits over time (during HCV sub-study)

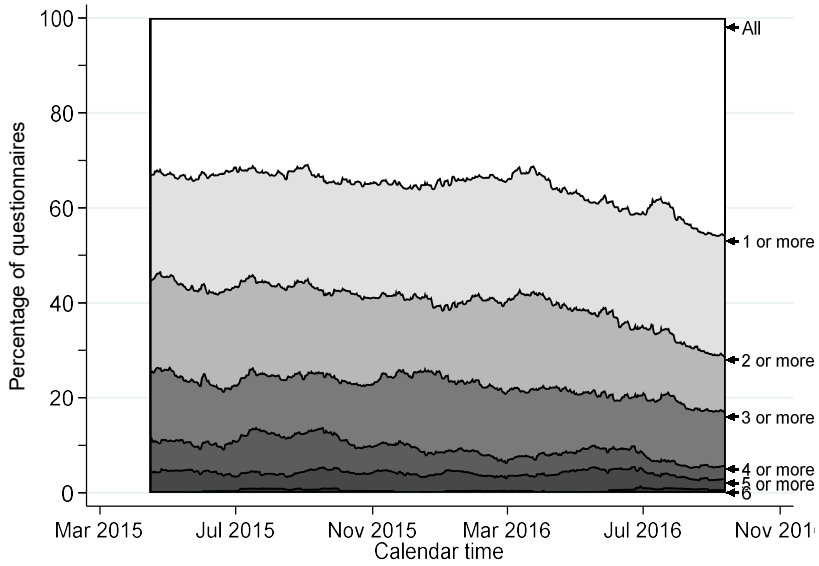


Figure legend: *Moving average calculated from 45 days before and after each time point. The height (rather than the line) of each colour block represents the proportion reporting each category. Risk factors collected at the visit were: chemsex, injection drug use, snorted drugs, group sex, sex toys and fisting.*

5.12 Discussion

5.12.1 Key findings

- HCV screening rates varied according to clinic and other reported risk factors. Not all participants were screened for HCV at baseline, but due to the nature of HCV screening, status can be ascertained from the first test if negative for Ab. I recommended that follow-up should be from randomisation (rather than first screen) until final screen to minimise bias
- Due to the low number of events in the deferred phase, I was unable to determine whether PrEP was driving HCV acquisition
- I concluded that the use of the random-point method was the most appropriate approach to account for the uncertainty around the date of HCV acquisition and to estimate HCV incidence over time
- There was an indication that HCV incidence increased with calendar time, which could explain the low seroprevalence relative to incidence. I could find little evidence of a change in risk factors so the increase was most likely to be due to an increase in background incidence in MSM during the study period
- HCV acquisition was associated with the total number and new ncRAI partners. Participants reporting partners with an unknown or positive HIV-status were also at an increased risk.
- Reporting the use of poppers at baseline, and fisting or the use of sex toys since the last visit, put participants at significantly increased risk of HCV acquisition. Reporting multiple high-risk activities i.e. drug use and other high risk sexual activities (fisting, sex toys) also put individuals at high risk of acquiring HCV. Injection drug use was reported by a number of participants acquiring HCV but was not the only transmission risk

5.12.2 Connection to other literature

HCV seroprevalence

The estimated HCV seroprevalence at enrolment into PROUD was 2.1% (95% CI: 1.0-3.7). Seroprevalence in PROUD was lower than that reported at entry to the AmPrEP demonstration project (4.8% [95% CI: 2.9-7.5]) [164]. This difference could be due to a number of factors, including a difference in year of enrolment between PROUD and AmPrEP (2012-2014 vs. 2015-2016).

In 2013, around the time of PROUD recruitment, a community sample estimated the same HCV seroprevalence (2.1%) among MSM attending London gay bars, clubs and saunas, although this differed according to HIV status (HIV-positive 7.7% [95% CI: 4.2-12.9] vs. HIV-negative 1.2% [95% CI: 0.6-2.1]) [174].

HCV incidence

HCV incidence was higher than expected in this HIV-negative MSM population (2.1 per 100 PY overall [95% CI: 1.4-3.1]), and indeed higher than that reported in HIV-positive populations in the UK, although this population was also heterogeneous in risk [155-157]. A number of studies have reported HCV incidence amongst PrEP-users and the incidence in PROUD was higher than, although compatible with, other studies in Europe [165-168].

Similar to seroprevalence, the disparity in HCV incidence seen between European and North American PrEP studies could be driven by a number of factors [12, 128, 164-169]. Background HCV incidence clearly differs between geographical locations [150]. PROUD participants were at high sexual risk upon entering the trial which may be due to appropriate targeting by clinic staff, or participant self-selection of PrEP in England [13, 175-177]. Furthermore, as PrEP has been available for a longer period of time in North America, the population on PrEP is likely to reflect a broader range of risk (and possibly reflects a lower background risk).

Phylogenetic studies have shown an overlap in HIV-positive and HIV-negative MSM in HCV clusters [164, 178]. A modelling study showed that differences in HCV transmission between HIV-positive and HIV-negative MSM were unlikely to be driven by biological factors, but, instead, driven by sexual behaviour or sexual mixing by HIV-status (serosorting) [151]. A study in France compared the HCV risk of HIV-positive individuals with HIV-negative PrEP-users, finding that the HCV incidence was similar between the two groups [165]. As PrEP rolls out, this is a concern for HCV because preferential mixing by HIV-status may reduce, and, therefore, HCV risk increases in the HIV-negative MSM. PROUD provides further evidence to support HIV-positive and PrEP-using MSM share similar sexual risk and practices.

In this chapter, I have shown that there is evidence to suggest an increase in HCV incidence over calendar time in MSM seeking PrEP. This was seen despite HCV prevalence in England having declined overall in recent years [179]. The increase observed in PROUD is most likely driven by an increase in background incidence in UK MSM, rather than the increase in HCV screening or risk factors. An increase in HCV incidence was also observed literature, as a systematic review of HCV incidence in high-income countries observed an increase in HCV incidence from 2000 through to 2010, although only a few studies had a follow-up period beyond 2010 [150]. Increasing incidence between 2012 and 2016 in a French HIV-infected cohort was reported more recently [180]. That said, small changes in the average number of sexual partners can have a substantial impact on the connectivity of a network at the population level [181], and the analysis of risk factors over time in the PROUD population is unlikely to capture small changes in behaviour that could still be important.

Predictors of HCV and HCV testing guidelines

Predictors of HCV identified in PROUD largely confirm those described in the literature prior to the availability of PrEP (Section 5.4) [150]. HCV acquisition was associated with a high number of ncRAI partners (ten of more), and not knowing the HIV status of a number of their ncRAI partners (five or more) put individuals at an even higher risk. The use of

poppers, sex toys and engaging in fisting were strongly associated with HCV acquisition, which had not been consistently identified in the previous literature [150]. Reporting a number of high-risk activities, i.e. drug use, and other high-risk sexual activities (fisting, sex toys), also put individuals at a particularly high risk of acquiring HCV. Injection drug use increased the risk of HCV acquisition but did not explain all infections, which were likely acquired sexually.

Guidelines released in 2012 recommended HCV screening for HIV-positive individuals, injection drug users and individuals engaging in fisting, but were not explicit for other risk behaviours in HIV-negative MSM [46, 147]. Therefore, guidelines did not include a recommendation for screening individuals who are HIV-negative MSM and reporting condomless anal sex without any other risk factors. Updated guidelines in 2018 for MSM using PrEP recommended quarterly HCV screening to reflect the high HCV seroprevalence in some PrEP studies [42, 149, 164]. However, my analysis has demonstrated that some individuals accessing PrEP are at a much higher risk of HCV compared to others. The key driver of HCV risk appeared to be calendar time, with diagnoses appearing in clusters and concentrated in the latter two years of PROUD. Therefore, quarterly screening is unlikely to be warranted in all MSM accessing PrEP, unless there is evidence that a localised epidemic is ongoing. In the absence of an epidemic, individuals reporting high-risk behaviours such as injecting drugs, fisting and use of sex toys or multiple risk factors should continue to be monitored for HCV. Solely reporting a number of ncRAI partners may not indicate screening at each visit, but would provide a key marker for screening during periods of high HCV incidence. Yearly screening should still be implemented to continue monitoring HCV epidemics in the PrEP-using MSM population. Efforts should also be targeted towards contact tracing of sexual partners to limit onward transmission from undiagnosed cases. HCV treatment is an important component of epidemic control, but this may not always be available.

5.12.3 Strengths and limitations

It was clear that prior to the HCV sub-study, as expected, HCV screening was being conducted in a non-systematic way based on behavioural and clinical risk factors. The change in the PROUD protocol meant that HCV testing was conducted across the cohort, regardless of perceived HCV risk in clinic. Due to the increase in HCV testing in the latter part of the study, a vast proportion of the follow-up (94%) was covered by a HCV screen, and, therefore, HCV status was known for the majority of participants during the study. If a participant was Ab negative, we knew that they had not acquired an infection before, so could infer that individuals negative at first test during PROUD were also negative at randomisation.

Data from PROUD has allowed estimation of HCV incidence with reasonable precision overall, and identified changes in incidence over time, adding to the literature globally, as well as in the UK. Although the PROUD cohort was small, the risk behaviours were diverse, albeit skewed towards higher risk.

Throughout PROUD, a considerable amount of risk factor data, including demographic, sexual behaviour, drug-use and STIs were collected. This enabled consideration of predictors of HCV acquisition within this population, with limitations, as the small number of infections precluded both a randomised comparison and a multivariable analysis to adjust for confounders. In addition, completion dates of questionnaires, especially the monthly questionnaires, meant that risk factors were not always collected around the time of infection which could be misleading. The self-selected nature of the monthly questionnaires is likely to introduce further reporting bias, since participants completing questionnaires frequently were likely to be at lower sexual risk. Baseline and visit questionnaires were less susceptible to this kind of bias because they were completed for all participants who were still attending clinic.

In contrast to the STI analyses presented in Chapter 4, detection bias is not a concern for HCV. By testing more frequently, the gain is in the accuracy in the time of acquisition, rather than identifying more infections. I discussed that the random-point approach was the best way to account for residual uncertainty about the date of acquisition.

Eight percent (8.3%) of participants were not screened for HCV at all during PROUD, and therefore, we could not ascertain their status during follow-up. For the participants who did not receive a HCV screen, previous history of HCV relied on clinician reporting, which would only be based on virological results if the participant had been diagnosed in the recruiting clinic. Both of which could influence the seroprevalence and incidence estimated in the study.

5.12.4 Conclusion

Analyses presented in this chapter suggest that MSM seeking PrEP are at high risk of HCV, similar that of HIV-positive MSM. Individuals initiating PrEP are likely to be aware that their risk of HIV is significant, but may not be aware that they are at risk of acquiring HCV. HCV testing is advisable amongst individuals who are starting PrEP because it provides an ideal opportunity to ascertain HCV status. Clinicians should actively ask individuals about a range of risk factors and screen quarterly when these are reported.

However, HCV appears to be influenced by location and time, therefore, quarterly screening may only be justified for all MSM accessing PrEP when there is evidence of increasing incidence in the population with additional risk factors. Surveillance systems should be put in place to identify clusters of new HCV diagnoses and implement more frequent HCV testing in a timely manner when this is required.

6 Concluding remarks

This chapter summarises the work discussed throughout this thesis. Table 6.1 outlines, for each substantive chapter, the key findings, limitations and potential future work. I also discuss general strengths and limitations of using PROUD data.

6.1 Key findings and guidance for practice

6.1.1 Chapter 2: Baseline predictors of HIV incidence

PrEP initiation guidelines in the UK are broad [42]. My work in Chapter 2 aimed to examine the relative importance of the recommended eligibility criteria. I presented an analysis based on participants in the deferred arm, before they had access to PrEP, and evaluated HIV incidence according to baseline characteristics.

I identified two highly significant predictors of HIV acquisition. First, participants reporting a diagnosis of syphilis, rectal chlamydia or rectal gonorrhoea (a "key STI") in the previous twelve months had an incidence of 17.2 per 100 PY (95% CI: 9.7-28.5), 4.8 fold-higher (95% CI: 1.8-14.9) than those without such a diagnosis. Second, those reporting two or more receptive anal sex partners without a condom (ncRAI) in the previous three months had a HIV incidence of 13.6 per 100 PY (95% CI: 7.9-21.7), and were at a 4.6-fold higher risk than those reporting fewer partners. By contrast, the incidence rate among participants lacking both of these risk factors was 1.1 per 100 PY (1/87.6, 95% CI: 0.03-6.4), falling below the 3% WHO threshold for PrEP initiation [39].

Using a diagnosis of a key STI as an indicator for risky sex and a proxy for HIV risk, I was able to conduct a multivariable analysis. I found other baseline characteristics, including: full-time employment; drug-use associated with chemsex; use of poppers; living with a partner; being born in the UK; and, younger age were associated with the increased risk of

acquiring a key STI. These characteristics, most of which make sense as signals of engagement in high-risk sexual networks, could also be used to identify those who will benefit from PrEP.

Whilst my work supports keeping the eligibility criteria for a PrEP programme broad, a recent history of a key STI, or recent multiple ncRAI partners indicates a high imminent risk of HIV infection. MSM with either of these risk factors should be offered PrEP as a matter of urgency.

6.1.2 Chapter 3: Critique of epidemiological measures used in PrEP research

A number of PrEP and other HIV prevention studies have reported the number needed to treat (NNT) and the population attributable fraction (PAF). However, different approaches have been used to calculate these measures.

I described why the most appropriate NNT calculation should use HIV incidence to reflect the person-years of PrEP care required to prevent an infection. NNT can also be scaled by the amount of PrEP prescribed to give an "on treatment" metric. However, caution should be exercised when generalising NNT to other populations as it may need to be scaled up (or down) to reflect that HIV incidence in the wider population which may differ to that of the trial population.

Although several HIV prevention studies have presented PAF [62, 63, 70, 76, 108, 109], primarily as a measure to identify subgroups for PrEP prioritisation, I argued that this measure is misleading for this purpose. This is because PAF does not reflect the impact of PrEP on averted HIV infections as it does not account for the effectiveness of PrEP. Instead, I proposed the use of an alternative measure, the proportion of potential averted infections (PPAI), which incorporates PrEP effectiveness and uptake. PPAI can be generalised to populations with a different underlying HIV incidence, and different estimates of effectiveness can be incorporated into the formula.

I described that NNT and PPAI can be used in conjunction to identify characteristics that predict those who are most likely to benefit from PrEP. However, both are univariable measures. I therefore explored the use of a stepwise approach, proposed by Poynten et al., to identify multiple characteristics when a multivariable analysis was not feasible [82]. An attractive feature of this approach is that it reflects how a clinician might identify potential PrEP-initiators, e.g. participants with a key STI or multiple ncRAI partners.

NNT and PPAI do not incorporate the number of onward transmissions that can be prevented as a result of PrEP. To estimate the impact of PrEP at a population level comprehensive cost-effectiveness models, ideally incorporating sexual network models, are required.

6.1.3 Chapter 4: Assessing whether access to PrEP increases STI incidence

In 2018, a meta-analysis incorporated eight open-label PrEP studies and found that STI risk was higher among PrEP-users [120]. However, I pointed out that the meta-analysis had a number of limitations, including the inappropriate use of control groups and statistical methods. PROUD was the only study identified that was both randomised and open-label, and provided the highest quality of evidence on the impact of PrEP on STIs.

I discussed methodological considerations around analyses of STI data in PrEP studies. Analyses need to pay careful attention to selection of the control group, risk of detection bias from more frequent screening, choice of statistical model, managing concurrent diagnoses (more than one anatomical site, more than one pathogen) and repeat infections, as well as changes in background STI incidence over calendar time. Estimating STI incidence is more appropriate than cumulative incidence, and negative-binomial models gave the best formulation of heterogeneity in risk between participants in the PROUD data. I also concluded that detection bias is not sufficiently accounted for by simply adjusting for the number of STI screens in the statistical model.

I conducted a number of analyses to estimate the STI incidence in PROUD, including a re-analysis of the deferred phase and analyses by phase and over calendar time. STI incidence was high, estimated at 114.7 per 100 PY (95% CI: 99.4-132.3) and 94.3 per 100 PY (95% CI: 80.1-110.9) during the deferred phase in the immediate and deferred arms, respectively. I found that the incidence of STIs, particularly chlamydia, was higher among PROUD participants with access to PrEP, demonstrated in both the randomised comparison of the deferred phase (IRR (chlamydia)=1.4 [95% CI: 1.0-2.0], p=0.027) and the pre-/post-PrEP comparison in the deferred arm (IRR (chlamydia)=1.4 [95% CI: 1.0-1.9], p=0.061). However, it was unclear whether this was driven by a difference in STI screening or behaviour change (risk compensation). There were clear changes in STI incidence over calendar time for some individual STIs, probably reflecting changes in the wider population in the UK [142].

I concluded that, regardless of whether or not "risk compensation" was driving the increase in STI incidence, MSM seeking PrEP are at high risk of STIs, and quarterly screening is justified [42].

6.1.4 Chapter 5: HCV risk and predictors in PrEP-users

I conducted a literature review and found that European MSM accessing PrEP experience a higher HCV risk than MSM in North America [12, 128, 164-169]. I estimated seroprevalence, incidence, and predictors of HCV among PROUD participants, the first such estimates of HCV risk among MSM accessing PrEP in the UK.

I found that HCV incidence was both high and increasing over calendar time, supported by the low seroprevalence at enrolment (2.1% [95% CI: 1.0-3.7]) relative to the high incidence during the trial (2.1 per 100 PY [95% CI: 1.4-3.1]). Using the random-point method to account for the uncertainty around the date of HCV acquisition, I estimated that HCV incidence increased from 1.8 per 100 PY [95% CI: 0.5-6.2] in 2013 to 4.0 per 100 PY [95%

CI: 2.0-8.1] in 2016. During the deferred phase, there were only three incident HCV infections (one IMM, two DEF), precluding a randomised comparison.

Participants reporting popper use in the prior three months at baseline were at a significantly higher risk of HCV compared to those with no popper use. In a time-updated analysis, I found that HCV acquisition was associated with a high number of ncRAI partners and new ncRAI partners. Participants reporting partners with an unknown or positive HIV-status were also at an increased risk. Individuals reporting fisting or the use of sex toys, since the last visit, were at significantly increased risk of HCV acquisition, and those reporting multiple high-risk activities since the last visit i.e. drug use and other high-risk sexual activities (fisting, sex toys) were also at high risk of acquiring HCV. Although 44% of participants acquiring HCV had a history of injecting drugs, it was not clear whether this was the route of transmission, and reporting this behaviour did not significantly increase the risk of HCV acquisition in PROUD. I have also shown that the increase in HCV incidence during PROUD was likely driven by an increase in background incidence. This did not appear to be explained by a change in risk factors, however, the analysis did not capture individual-level changes.

As HCV risk varied according to both individual- and population-level risk factors, BHIVA's quarterly screening recommendations may not be warranted or necessary in all MSM seeking PrEP [42]. My results suggest that individuals reporting high-risk behaviours should continue to be offered quarterly screening, however, in the absence of a localised epidemic, for those at lower risk (i.e. those solely reporting ncRAI), annual screening may be sufficient.

6.2 Strengths and limitations

6.2.1 PROUD design

PROUD was pivotal in demonstrating the high effectiveness of PrEP in MSM in a sexual health clinic setting. This is particularly impressive given that it was designed as a pilot study for a larger trial. The consent obtained from participants at enrolment for data linkage allowed the matching exercise with the national database of HIV diagnoses. HIV status was ascertained for all participants, and a further five HIV seroconversions that were unknown to PROUD were identified. The wait-listed, open-label design of PROUD allowed a randomised comparison of outcomes in a setting where participants were aware of their PrEP status. The randomised control and open-label nature of PROUD were key strengths compared to other PrEP trials and particularly relevant for evaluating the predictors of HIV acquisition and the effect of PrEP on STIs.

Throughout PROUD, a large amount of sexual behaviour data were collected through self-report using questionnaires. These data informed the analyses of baseline predictors of HIV and time-updated predictors of HCV. However, participants willing to complete questionnaires frequently may differ in their risk profile from those who do not, leading to selection bias. This could result in lower estimates for the association between risk factors and infections.

I identified the importance in the use of a key STI diagnosis (rectal STI or syphilis) in establishing whether an individual should initiate PrEP. The PROUD protocol made this analysis feasible due to the collection of STIs by anatomical site, which is not always collected or reported in PrEP studies.

A limitation of this pragmatically designed trial was that participants receiving PrEP were seen in clinic more often than participants in the deferred arm during the deferred phase, leading to detection bias in both the randomised comparison and pre-/post-PrEP

comparison. The change in screening guidelines for bacterial STIs and HCV during the trial also contributed to this. The laboratory CRF, as designed, did not allow collection of the date of STI screening, reason for screening, or details about treatment and clearance of the infection; this information could have helped to better separate the effects of detection bias from a true increase in sexual behaviour and STI risk.

6.2.2 Generalisability

The high rates of HIV, STIs and HCV amongst PROUD participants raises the question of generalisability of these results to the general MSM population, as these early adopters of PrEP clearly had differential risk behaviours to the wider clinic population [176]. Nevertheless, the trends (rather than quantitative estimates) should be broadly applicable to other MSM accessing PrEP in the UK or similar settings elsewhere (e.g. Europe).

Furthermore, PROUD was conducted during a period when the effectiveness of PrEP was not widely known, which may have affected the way participants behaved. If the study were repeated now, participants may engage in even higher risk sexual practices. In addition, the recent large reduction in HIV diagnoses in the UK is likely to have reduced the strength of the associations seen between risk factors and sexual outcomes described in this thesis (e.g. HIV and STIs). If the HIV incidence continues to reduce, and STI incidence continues to increase in the UK, an STI may become less predictive of HIV risk in future years.

6.2.3 Low number of HIV and HCV diagnoses

Given the nature of this pilot study, a number of analyses were restricted by low numbers of HIV and HCV diagnoses. Standard multivariable analyses were not feasible for these outcomes, and therefore a risk score could not be developed for PrEP eligibility. Nevertheless, the diagnosis of a key STI was used as a proxy for HIV risk. Given that NNT and PPAI are univariable measures, I also proposed the use of an iterative approach to identify multiple baseline characteristics that put participants at highest HIV risk. However,

the low number of events also made this approach prone to variable selection bias, where less frequent characteristics are more sensitive to this.

Calculating HCV incidence by calendar year was also compromised because estimates varied according to the assumption made about the time of infection. I used an imputation approach, proposed by Vandormael et al., to account for the unknown interval of HCV infection [172].

6.2.4 Long follow-up

The long follow-up of PROUD (up to four years) meant that calendar trends in clinical outcomes for participants with access to PrEP could be examined. Longitudinal information on participants not receiving PrEP was more limited (up to one year).

6.3 Possibilities for future work

At some point in the future, HIV incidence could reduce to the extent that some MSM will no longer be at sufficiently high risk to warrant receiving PrEP. Although it would be very useful to study this, it is difficult to conceive how this could be done without a no-PrEP control group. The PrEP Impact study in the UK collects information on individuals who initiate PrEP within the programme. It collects data on STI diagnoses made in sexual health clinics but does not collect data on sexual behaviour.

My work in Chapter 2 focused solely on baseline predictors of HIV to ascertain who should initiate PrEP. However, time-updated HIV predictive analyses could help inform whether individuals should remain on PrEP, and whether adherence support is necessary. In addition, time-updated predictive analyses (rather than baseline risk factors) of STI acquisition would help to identify characteristics of MSM at highest risk, and those who would most benefit from risk-reduction strategy counselling.

To understand whether PrEP increases the risk of STIs, causal models would be required. However, these would require complex datasets, including the reasons for screening, treatment of infections, and clearance. This may not be achievable given time pressure in sexual health clinics and the accuracy of clinic notes.

Given the continued reductions in the cost of Truvada and changes in the underlying HIV risk, there is a need to update cost-effectiveness analyses of a UK PrEP programme, building upon the work by Cambiano et al. and Ong et al. [53, 54]. It is important that these models consider both directly and indirectly averted HIV infections.

The PROUD dataset is unique with a no-PrEP randomised comparison. The next-generation PrEP trials, such as DISCOVER (F/TAF vs. F/TDF), are designed as double-blind and double-dummy non-inferiority designs with an active control. These studies will be restricted in the analyses that can be performed. In addition, given the high effectiveness of current PrEP regimens, very few HIV outcomes are expected in these trials, suggesting there is a need for alternative approaches to trial design and statistical analyses [182-185].

6.4 Conclusion

The findings presented in this thesis have confirmed that PROUD participants were at very high risk of acquiring sexually transmitted diseases, including HIV, bacterial STIs, and HCV. As early adopters of PrEP, PROUD participants may have been a sub-population at extreme risk. Nonetheless, future PrEP programmes need to include sufficient resources to screen and treat clinical outcomes.

The risk of STIs was highly heterogeneous between individuals, with wide variation in the number of diagnosed infections (some with zero infections over three and half years of follow-up). Heterogeneity in HIV risk cannot be directly observed since the infection is acquired only once. However, it can be inferred because of the wide range in predicted risk according to baseline factors e.g. almost five-fold higher for participants reporting a recent

key STI diagnosis and for those with two or more ncRAI partners in the previous three months. Similarly, HCV risk also varied according to risk factors, for example, the risk was six-fold higher among those reporting fisting since the last visit. Identifying potential risk factors of clinical outcomes may enable health-care providers to give the most appropriate care for individuals seeking PrEP.

My thesis has shown that epidemics of STIs can vary markedly with calendar time. For instance, incidence of syphilis in PROUD increased more than three-fold between 2013 and 2015 while HCV incidence more than doubled between 2013 and 2016. These trends were most likely due to changes in background rates in UK MSM over the same time period. This supports the need for ongoing surveillance, including flexibility to amend the frequency of screening. This also highlights the danger in attributing time changes observed in cohorts of PrEP-users to the effect of PrEP itself. More generally, my work has highlighted that researchers should take care in the design, analysis and interpretation of PrEP studies to ensure the most robust conclusions.

Table 6.1: Summary of key findings, limitations and possibilities for future work

Objectives	Key findings	Limitations	Future work
Chapter 2 To identify MSM at the greatest risk of HIV for PrEP initiation	• Matching with the national database of HIV diagnoses enhanced the analysis of HIV incidence • MSM seeking PrEP are at high risk of acquiring HIV • Highest HIV risk was amongst MSM reporting a rectal STI or syphilis diagnosis in the previous twelve months, or reporting condomless receptive anal intercourse with two or more partners in the past three months • Participants reporting neither of these risk factors were at substantially lower risk of HIV • Other baseline characteristics, such as: full-time employment; chemsex; poppers; living with partner; born in the UK; and younger age, were associated with the risk of acquiring a key STI, and are likely to be associated with a high risk of HIV.	• Conclusions are most applicable to those already willing to accept the offer PrEP, rather than who to offer it in the first place • The high HIV incidence in PROUD raises concerns about whether results are generalisable to wider MSM population • HIV diagnoses identified outside the UK could be missing from matching exercise • Low number of events resulted in imprecise HIV incidence estimates and restricted multivariable analyses • A high number of PEP prescriptions were taken in the deferred arm during this period which could have underestimated HIV incidence • Binary analysis for STI proxy analysis did not incorporate repeated STIs	• If possible, continue to monitor predictors of HIV acquisition as the use of PrEP expands in the MSM community and HIV incidence decreases • Time-updated HIV predictive analyses could help inform whether individuals should remain on PrEP, and inform whether adherence support is necessary
Chapter 3 To critique epidemiological measures used in PrEP research	• In the context of PrEP research, NNT calculations should be based on estimates of HIV incidence rather than cumulative incidence. It may be helpful to present two different values, one based on total person-years of follow-up and a second scaled by the medication possession ratio to reflect the amount of drug prescribed • NNT is not generalisable to a population with a different HIV incidence but can be scaled up or down if the incidence in the wider population is known • The use of PAF to measure the impact of PrEP on population HIV incidence is misleading and should be avoided. PPAI is an appropriate alternative measure.	• NNT and PPAI are univariable measures and do not account for confounding risk factors • PrEP-initiators may find NNT difficult to understand. • Generalisability of NNT needs to be considered carefully in settings outside of the trial because it incorporates baseline HIV risk • NNT and PPAI do not incorporate the onward transmissions prevented as a result of PrEP	• Given the newly reduced cost of Truvada and changes in underlying HIV risk, updated modelling would be required to estimate the cost-effectiveness of a PrEP programme and estimate the directly and indirectly averted infections in the UK.

	• PPAI and NNT can be used in conjunction to identify characteristics of MSM most in need of PrEP prioritisation • A step-wise approach can be used to identify a set of characteristics at high risk of HIV when multivariable analysis is not feasible	• A step-wise approach to identify multiple characteristics at high risk of HIV is highly unstable with a small number of outcomes	
Chapter 4 To assess whether access to PrEP increases STI incidence	• Although there are several open-label studies in PrEP-users, PROUD is the only open-label study with a randomised design to evaluate the impact of daily PrEP on STIs • Reported studies and PROUD confirm that MSM seeking PrEP are also at high risk of STIs and frequent screening is clinically justified • Analyses need to pay careful attention to selection of the control group, risk of detection bias, choice of statistical model, managing concurrent diagnoses (more than one anatomical site, more than one pathogen) and repeat infections, and changes in background STI incidence over calendar time • Estimating STI incidence is more appropriate than estimating that probability of ever being diagnosed, and the negative-binomial model was the best fit for the PROUD data due to the heterogeneity in risk between participants • Using these methods, I conclude that the incidence of STIs, particularly rectal chlamydia, was higher among PROUD participants with access to PrEP • Detection bias may have inflated the observed STI incidence in PrEP-users compared to non-users • The fact that STI incidence was high in PROUD participants before they enrolled in the trial may limit the ability to assess whether PrEP increases STI incidence	• Unable to separate out the effects of risk compensation and detection bias given the level of data collected • The randomised comparison was limited by unknown high effectiveness of PrEP in preventing HIV during this period, therefore sexual behaviour could have differed once this was known. Therefore, generalisation may be a concern during this period. • The pre- and post-PrEP comparison in deferred arm must be interpreted considering change over calendar period in background STI risk	• Time-updated predictive analyses of STI acquisition would help to identify characteristics of MSM at highest risk of STI diagnosis, and who would most benefit from risk reduction strategy counselling. • If possible, causal models should be conducted to ascertain whether PrEP increases the risk of STIs.
Chapter 5 To estimate the hepatitis C risk and predictors in PrEP-users	• HCV screening rates varied according to clinic and other reported risk factors. Not all participants were screened for HCV at baseline, but due to the nature of HCV screening, status can be ascertained from the first test if negative for Ab. I recommended that follow-up should be from randomisation (rather than first screen) until final screen to minimise bias • Due to the low number of events in the deferred phase, I was unable to determine whether PrEP was driving HCV acquisition	• Small number of HCV outcomes reduced precision, and precluded randomised PrEP comparison and multivariable predictive analyses • Completion dates of questionnaires meant that risk factors were not always collected around the time of infection. In addition, the self-selected nature of the monthly	• National surveillance of localised HCV epidemics should help inform frequency of screening among MSM using PrEP

	• I concluded the random-point method was the most appropriate approach to account for the uncertainty around the date of HCV acquisition and to estimate HCV incidence over time • HCV incidence increased with calendar time, which could explain the low seroprevalence relative to incidence. I could find little evidence of a change in risk factors so the increase was most likely to be due to an increase in background incidence during the study period • HCV acquisition was associated with the total number and new condomless receptive anal intercourse partners, and participants reporting this with an unknown or positive HIV-status were also at an increased risk. • Reporting the use of poppers at baseline, and fisting or the use of sex toys since the last visit, put participants at significantly increased risk of HCV acquisition. Reporting multiple high-risk activities i.e. drug use and other high risk sexual activities (fisting, sex toys) also put individuals at high risk of acquiring HCV. Injection drug use was reported by a number of participants acquiring HCV but was not the only transmission risk	questionnaires is likely to introduce bias into the analysis. • 8% of participants were not screened for HCV during the trial, therefore their status was unknown which could influence seroprevalence and incidence estimates

MSM, men who have sex with men; HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection; UK, United Kingdom; NNT, number needed to treat; PAF, population attributable fraction; PPAI, proportion of potentially averted infections; HCV, hepatitis C.

Table 6.2: General strengths and limitations of using PROUD data in thesis

Strengths	Limitations
PROUD included MSM seeking PrEP in a pragmatically designed trial to reflect real-life; this enable conclusions to influence future PrEP guidelines	Self-completed nature of sexual behaviour questionnaires could introduce bias, especially for HCV predictors analysis
Consent obtained from participants allowed ascertainment of missing HIV status via national database of HIV diagnoses	STI screening by indication incorporates detection bias, which differs according to PrEP status. Information on reason for screening was not collected in order to separate these effects
The wait-listed design of PROUD allowed open-label randomised and pre-/post-PrEP comparisons	Changes in protocol/recommendation of screening guidelines (STIs and HCV) could also impact the ascertainment (/detection bias) of these outcomes over time
Vast amount of data collected on clinical outcomes (including STIs by anatomical site), and sexual behaviour which allowed predictive analyses	The high-risk participants, possibly driven by the differential risk behaviours of early adopters of PrEP, raises questions around the generalisability of conclusions from PROUD
PROUD participants were at high risk of HIV, therefore, conclusions are most applicable to individuals in the most need of PrEP, in the UK and other similar healthcare settings	The randomised period was when the high effectiveness of PrEP was unknown, and therefore participants could have behaved differently during this period compared to the post-deferred phase or if the study was conducted now
Long follow-up and high adherence to PrEP allowed key analyses of the long-term effects of PrEP, including the prevention of HIV, and estimating the risk of other sexual outcomes	The recent reduction in HIV diagnoses in the UK is likely to reduce the strength of associations between risk factors and clinical outcomes.
	Given the nature of the pilot study, the number of HIV and HCV outcomes were low, precluding multivariable analysis, and a randomised comparison of HCV incidence
	Missing HCV clinical outcomes for 8% of participants

MM, men who have sex with men; PrEP, pre-exposure prophylaxis; HCV, hepatitis C virus, HIV, human immunodeficiency virus; STI, sexually transmitted infections; UK, United Kingdom.

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Appendices

Appendix 1 Publication in Sexually Transmitted Infections journal relating to the work in Chapter 2 (image redacted due to copyright)

Appendix 2 Submitted paper to Journal of Viral Hepatitis relating to the work presented in Chapter 5 (image redacted due to copyright)

Appendix 3 PROUD Study Team

The PROUD study group:

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Gilead Sciences:

Rich Clarke and Jim Rooney.

Appendix 4 PROUD trial Baseline Sexual Behaviour Questionnaire (Form 2)

Baseline Sexual Behaviour Questionnaire

Trial no:	Initials:	Date of birth:	Date form completed:

Patient Questions

1. **Are you:** Male ☐ Transgender ☐
2. **How would you describe your sexuality?**

   Gay/Homosexual ☐ Straight/heterosexual ☐ Bisexual ☐ Other (please specify) _____
3. **To which of these ethnic groups do you consider yourself to belong?**

White ☐	Chinese ☐	Irish ☐	Irish Traveller ☐
Indian ☐	Pakistani ☐	Bangladeshi ☐	Black Caribbean ☐
Black African ☐	Black Other ☐	Mixed Ethnic Group_____	Other _____

4. **Were you born in the UK?** Yes ☐ No ☐ *(If yes skip to question 6)*
5. **If no, which country were you born in?** _____
6. **What is your date of birth?** __/__/____ *(please fill as DD/MM/YYYY)*
7. **At what level did you complete your education?**
   - ☐ Finished education with no qualifications
   - ☐ O levels/GCSEs (or equivalent qualifications at age 16)
   - ☐ A levels (or equivalent qualification at age 18)
   - ☐ University degree or above
   - ☐ Still in full-time education
   - ☐ Vocational Training
   - ☐ Other qualifications *(please specify)* _____
8. **What is your current work situation?**
   - ☐ Employed or self-employed FULL-TIME (at least 30 hours a week)
   - ☐ Employed or self-employed PART-TIME (less than 30 hours a week)
   - ☐ Part/full time student/education/training
   - ☐ Unemployed
   - ☐ Retired
   - ☐ Other *(please specify)*_____
9. **Are you currently in an ongoing relationship with a partner (wife/husband or civil partner or girlfriend/boyfriend)?**
   - ☐ Yes, I am in a relationship and living with my partner
   - ☐ Yes, I am in a relationship but not living with my partner
   - ☐ No, I am not currently in an ongoing relationship with a partner
10. **Have you been circumcised?** Yes ☐ No ☐

Sexual Behaviour Questions

11. **With how many different men have you had either been bottom (receptive, passive, he fucked you) or top (insertive, active, you fucked him) during anal sex in the last 90 days?** ☐☐

12. With how many different men have you been bottom (passive) during anal sex in the last 90 days? ☐☐ *(If 0 please skip to question 16)*

13. Of the men in question 12, with how many were you bottom without using a condom?
☐☐ *(If 0 please skip to question 16)*

14. Of the men in question 13, how many did you know were HIV positive?
☐☐ *(If 0 please skip to question 16)*

15. Of the men in question 14, how many did you know were on HIV treatment? ☐☐

16. With how many different men have you been top (active) during anal sex in the last 90 days? ☐☐ *(If 0 please skip to question 20)*

17. Of the men in question 16, with how many were you top without using a condom?
☐☐ *(If 0 please skip to question 20)*

18. Of the men in question 17, how many did you know were HIV positive?
☐☐ *(If 0 please skip to question 20)*

19. Of the men in question 18, how many did you know were on HIV treatment? ☐☐

20. Of the men you've been either top or bottom with during anal sex in the last 90 days, how many were new partners? ☐☐ (This means men you had not had sex with before)

21. Think of the last time you had anal sex (top or bottom) with a man without a condom. These are reasons other men have given for not using condoms, please tick all that apply.
☐I don't like using condoms
☐He doesn't like using condoms
☐Condoms weren't discussed
☐We don't use condoms with each other but do with other partners
☐Neither of us had any condoms
☐I didn't consider myself at risk of HIV
☐I was under the influence of alcohol
☐I was under the influence of drugs
☐I am faithful to him
☐He is faithful to me
☐It is more enjoyable without a condom
☐I was only dipping
☐Other _____

22. Think of the last time you had anal sex (top or bottom) with a man without a condom. What was his HIV status?
☐I don't know
☐I thought he was HIV negative
☐I thought he was HIV positive and on treatment
☐I thought he was HIV positive and not on treatment
☐I thought he was HIV positive and did not consider whether he was on treatment

23. In general, when you have anal sex (top or bottom) without using a condom to what extent do you consider yourself at risk of getting HIV?

☐ Not applicable	☐ No risk	☐ A little risk
☐ Somewhat at risk	☐ Large risk	☐ Very large risk

24. In general, how do you manage your risk of getting HIV? *(Tick all that apply)*

- ☐ I frequently ask my partner to use a condom for anal sex
- ☐ I frequently use condoms
- ☐ I choose partners based on their negative HIV status
- ☐ I seek partners who I know are on HIV treatment
- ☐ I think about strategic positioning (I try to be top if I'm not sure about my partner's HIV status)
- ☐ I don't think about these risk reduction strategies

25. How many times in the past 12 months have you attended a clinic for a HIV test? ☐

26. How many times in the past 12 months have you attended a clinic for a STI test? ☐

27. How many times in the past 12 months have you been prescribed a course of post-exposure prophylaxis (PEP, taking antiretroviral (anti-HIV) drugs soon after potential HIV exposure for 4 weeks to reduce the risk of becoming infected with HIV)? ☐

28. In the past 12 months have you been diagnosed with any of the following?

	Yes	No		Yes	No
Rectal Gonorrhoea	☐	☐	Syphilis	☐	☐
Urethral Gonorrhoea	☐	☐	Hepatitis B	☐	☐
Oral Gonorrhoea	☐	☐	Hepatitis C	☐	☐
Rectal Chlamydia	☐	☐	Genital warts (new or recurrent)	☐	☐
Urethral Chlamydia	☐	☐	Genital herpes (new or recurrent)	☐	☐
Oral Chlamydia	☐	☐	Trichomonas	☐	☐
LGV	☐	☐			

Health and wellbeing Questions

29. Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Not at all	Several days	More than half the days	Nearly every day
a) Little interest or pleasure in doing things	☐	☐	☐	☐
b) Feeling down, depressed or hopeless	☐	☐	☐	☐
c) Trouble falling or staying asleep, or sleeping too much	☐	☐	☐	☐
d) Feeling tired or having little energy	☐	☐	☐	☐
e) Poor appetite or overeating	☐	☐	☐	☐
f) Feeling bad about yourself – or that you are a failure or have let yourself or your family down	☐	☐	☐	☐
g) Trouble concentrating on things, such as reading the newspaper or watching television	☐	☐	☐	☐
h) Moving or speaking so slowly that other people could have noticed. Or the opposite being so fidgety or restless that you have been moving around a lot more than usual	☐	☐	☐	☐
i) Thoughts that you would be better off dead, or of hurting yourself in some way	☐	☐	☐	☐

Lifestyle Questions

30. In the past 3 months have you used recreational drugs (e.g. poppers, cannabis, cocaine)?
Yes ☐ No ☐ *(If no, go to question 32)*

31. If yes, which drugs have you used?

Acid/LSD/magic mushrooms	☐	Heroin	☐
Anabolic steroids	☐	Ketamine (K)	☐
Cannabis (marijuana, grass)	☐	Khat (chat)	☐
Cocaine (coke)	☐	Mephedrone	☐
Crack	☐	Morphine	☐
Codeine	☐	Opium	☐
Crystal meth (methamphetamine)	☐	Poppers (amyl nitrate)	☐
Ecstasy (E)	☐	Speed (amphetamine)	☐
GHB (liquid ecstasy)	☐	Viagra	☐
		Other (please specify)_____	

32. How often have you had a drink containing alcohol (beer/wine/spirits/mixed drink) in the last 90 days?

Daily ☐ Nearly every day ☐ 3 or 4 times a week ☐
Once or twice a week ☐ 2 or 3 times a month ☐ Once ☐
Never ☐ *go to question 34*

33. How many units of alcohol do you drink on a typical day when you are drinking?
(One unit=half a pint of beer/cider or a small glass of wine or a single measure of spirits) ☐☐

34. Other men have suggested the following reasons as motivation for taking part in this trial. *Please tick all the statements that you agree with.*
☐ I want to contribute to scientific research
☐ I want to receive the regular sexual counselling to help me understand and reduce my risk
☐ I feel pressured to have sex without a condom
☐ My partner is already in this trial
☐ Taking PrEP would reduce my risk of getting HIV
☐ I will be able to have more sex without condoms
☐ I want to help the gay community
☐ Other _____

35. PrEP will be prescribed to men participating in this trial, either now or in the future, as a DAILY medication. When you are offered PrEP how often do you think you'll miss a tablet?
☐ I will find it easy to remember to take my drug daily
☐ I might forget to take my pill at my scheduled time but will remember to take it within a few hours
☐ I might occasionally forget to take a dose
☐ I might forget to take my drug once or twice a week
☐ I will remember to take my pill if I know I am going to be having sex in a couple of days
☐ I will find a daily dosing schedule very difficult to follow

Thank you for finishing the questionnaire.
Please place in the provided envelope and hand to a doctor or nurse

Appendix 5 Values for ncRAI and STI data in baseline questionnaire

Table 6.3: Values for ncRAI and STI data in baseline questionnaire

ncRAI≥2	key STI	No. participants	No. HIV infections
Y	Y	70	12
Y	N	73	4
Y	.	3	1
N	Y	30	3
.	Y	1	0
N	N	76	0
N	.	4	0
.	N	6	1
.	.	5	0

Y, participant reported behaviour/infection at baseline; N, participant reported that they had not had behaviour/ infection; ".", no information reported

Appendix 6 PROUD trial laboratory CRF (Form 5)

Form 5 PROUD laboratory results

Laboratory results

Trial no: P ☐☐☐☐☐☐	Initials: ☐☐☐	Date of birth: ☐☐/☐☐/☐☐	Date of visit: ☐☐/☐☐/☐☐

Month of visit

1 ☐ 3 ☐ 6 ☐ 9 ☐ 12 ☐ 13 ☐ 15 ☐ 18 ☐ 21 ☐ 24 ☐ 27 ☐ 30 ☐ 33 ☐

36 ☐ 39 ☐ 42 ☐ **Unscheduled** ☐ **reason** .....

1. **Serum creatinine** Not done ☐ Done ☐ result ☐☐☐ µmol/L

2. **Is urinary creatinine :protein ratio > 20?**
   Not done ☐ No ☐ Yes ☐ *if yes, check diet and repeat; Truvada may need to be interrupted if confirmed*

3. **HIV result**
   Not done ☐ Date sample collected: ☐☐/☐☐/☐☐
   Negative ☐ Positive ☐ Indeterminate ☐

4. **Any STI results at this visit or since last study visit? :** No ☐ Yes ☐ *if yes complete below*

	Number of screens	Number of infections
a. Rectal Gonorrhoea	☐	☐
b. Urethral Gonorrhoea	☐	☐
c. Oral Gonorrhoea	☐	☐
d. Rectal Chlamydia	☐	☐
e. Urethral Chlamydia	☐	☐
f. Oral Chlamydia	☐	☐
g. LGV	☐	☐
h. Syphilis	☐	☐
i. Hepatitis B	☐	☐
j. Hepatitis C	☐	☐
	New	Recurrent
k. Genital warts	☐	☐
l. Genital herpes	☐	☐

Researcher completing this form. I confirm that this is a true record

Signature	Print name	Date

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Appendix 7 PROUD trial Baseline eligibility and enrolment CRF (Form 1)

Form 1 PROUD Baseline eligibility & enrolment

Baseline eligibility and enrolment

Trial no:	Initials:	Date of birth:	Date of visit:
P ☐☐☐☐☐☐	☐☐☐	☐☐/☐☐/☐☐	☐☐/☐☐/☐☐

Clinic Number : ☐☐☐☐☐☐☐☐☐☐☐☐

1. **When did this participant first attend this clinic?** ☐☐/☐☐/☐☐
2. **When was his most recent attendance before today?** ☐☐/☐☐/☐☐
3. **When was his last negative HIV test?** ☐☐/☐☐/☐☐
4. **When was his last STI screen?** ☐☐/☐☐/☐☐
5. **What is the participant's weight?** ☐☐☐.☐ **kg**
6. **What is the participant's height?** ☐.☐☐ **m**

7. **STI history** – please complete the following table answering yes or no for each of the columns

	Ever tested	**Previously tested positive** (include smear positive)
a. Rectal Gonorrhoea	Yes ☐ No ☐	Yes ☐ No ☐
b. Urethral Gonorrhoea	Yes ☐ No ☐	Yes ☐ No ☐
c. Oral Gonorrhoea	Yes ☐ No ☐	Yes ☐ No ☐
d. Rectal Chlamydia	Yes ☐ No ☐	Yes ☐ No ☐
e. Urethral Chlamydia	Yes ☐ No ☐	Yes ☐ No ☐
f. Oral Chlamydia	Yes ☐ No ☐	Yes ☐ No ☐
g. LGV	Yes ☐ No ☐	Yes ☐ No ☐
h. Syphilis	Yes ☐ No ☐	Yes ☐ No ☐
i. Hepatitis C	Yes ☐ No ☐	Yes ☐ No ☐
		Previous history
j. Genital warts (new or recurrent)		Yes ☐ No ☐
k. Genital herpes (new or recurrent)		Yes ☐ No ☐

l. **Hepatitis B**: is the participant immune to hepatitis B following natural infection or immunisation ?
Yes ☐ No ☐ Not clear ☐

8. **Was there 1+ protein in the absence of nitrites on urinalysis in clinic today?** Yes ☐ No ☐
If yes consider other causes (eg protein supplements) and the need for further investigation

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9. What drugs has the participant taken in the last 6 months?
(include recreational & over the counter drugs)

regularly = every day/every week
frequently = at least every month
occasionally = less than once a month

Drug name	regularly	frequently	occasionally
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

10. Have any risk reduction interventions been offered today and taken up?

Strategy	Offered today		Taken up		
a. Counselling (health advisor or referral)	Yes ☐	No ☐	Yes ☐	No ☐	Already on ☐
b. Motivational interviews	Yes ☐	No ☐	Yes ☐	No ☐	Already on ☐
c. Psychotherapy/cognitive behaviour therapy	Yes ☐	No ☐	Yes ☐	No ☐	Already on ☐
d. Addiction services	Yes ☐	No ☐	Yes ☐	No ☐	Already on ☐
e. Other *specify* _____	Yes ☐	No ☐	Yes ☐	No ☐	Already on ☐

Explain the long and short behavioural questionnaires and diary card, and confirm the participant is willing to try and complete these in follow-up.

The participant should be given privacy to complete the first set and place them in a sealed envelope to send to MRC CTU whilst you randomise

11. Will he be able to complete these online in future? Yes ☐ No ☐

Eligibility check

12. Inclusion Criteria (All must be Yes)

The volunteer:-		Yes	No
a)	Was born to male gender	☐	☐
b)	Is aged 18 or more	☐	☐
c)	Has attended clinic on at least one previous occasion	☐	☐
d)	Has completed a screen for HIV & STI	☐	☐
e)	Is HIV negative by routinely used assay at this site within the last 4 weeks or today	☐	☐
f)	Has had unprotected anal intercourse on more than 1 occasion in the last 90 days	☐	☐
g)	Is likely to have unprotected anal intercourse in the next 90 days	☐	☐
h)	Is willing to complete monthly questionnaires on sexual behaviour and adherence	☐	☐
i)	Is willing and able to comply with the visit schedule throughout the follow-up period	☐	☐
j)	Has signed the consent form [Date signed ___/___/___]	☐	☐

13. Exclusion criteria (All must be No)

		Yes	No
a)	Has had an acute viral illness that could be due to HIV seroconversion	☐	☐
b)	Are there any contraindications to Truvada? *(e.g. renal tubular disease)*	☐	☐
c)	Is treatment for hepatitis B indicated or currently ongoing	☐	☐
d)	Is unlikely to comply with the randomised allocation	☐	☐

If any of the shaded boxes have been ticked the subject is currently ineligible

14. Does he have a regular sexual partner who has been enrolled in this study?
No ☐ **Yes** ☐ *if Yes* **Partner's Trial number** **P** ☐☐☐☐☐☐

If eligible the volunteer can now be randomised

Randomised to: **Arm A** – Immediate PrEP ☐ **Arm B** – Deferred PrEP ☐

15. Has HIV serology for antigen/antibody testing been collected today? Yes ☐ **No** ☐ *if No please collect this now*

If randomised to Immediate PrEP:

16. How many Truvada have been prescribed today? ☐☐ **pills**

Go through the instructions for the use of Truvada and collect serum for creatinine

Researcher completing this form. I confirm that this is a true record

Signature	Print name	Date

Appendix 8 Example of the use of *nlcom* to calculate NNT confidence intervals

```
*************************************************************************************
poisson hiv i.trlarm, offset(off)

**calculate confidence intervals for NNT by survival function using incidence rates (SD method)

nlcom   (Surv_IMM: exp(-exp(_b[_cons]))) ///
        (Surv_DEF: exp(-exp(_b[_cons]+_b[2.trlarm]))), post

nlcom   NNT: 1/(_b[Surv_IMM]-_b[Surv_DEF]), level(95)
```

Appendix 9 PROUD trial First Positive HCV CRF

FIRST POSITIVE HCV Clinic reporting form

Trial no:	Initials:	Date of birth:	Date of visit:
P ☐☐☐☐☐☐	☐☐☐	☐☐/☐☐/☐☐	☐☐/☐☐/☐☐

Month of visit

1 ☐ 3 ☐ 6 ☐ 9 ☐ 12 ☐ 13 ☐ 15 ☐ 18 ☐ 21 ☐ 24 ☐ 27 ☐ 30 ☐ 33 ☐
36 ☐ 39 ☐ 42 ☐ **Unscheduled** ☐ **reason** .....

Diagnosis of hepatitis C

1. **Any previous episodes of HCV infection prior to this new diagnosis?** No ☐ Yes ☐
2. **Date of current HCV diagnosis:** ☐☐/☐☐/☐☐
3. **Suspected date of infection (if known):** ☐☐/☐☐/☐☐ Answer Q7 and 8 based on this date.
4. **Symptomatic at time of probable infection or at time of diagnosis?** No ☐ Yes ☐ Unknown ☐
5. **Method of HCV diagnosis**
   HCV antibody ☐ HCV antigen ☐ HCV PCR ☐
   Date last negative: ☐☐/☐☐/☐☐

   Has the last negative sample been stored and available for retrospective testing? No ☐ Yes ☐

6. **Any abnormal LFTs noted?** No ☐ Yes ☐
   List 3 most recent LFT results (if available)

Date	ALT	AST	ALP	GGT	Bilirubin	Albumin	HCV RNA

Risk assessment

7. **Has the participant engaged in any of the following at suspected time of HCV infection:**
   (i) Recreational drugs during sex? No ☐ Yes ☐
   If yes, which of the following?

Anabolic steroids	☐	Crack	☐
Acid/LSD	☐	Crystal meth	☐
Amyl nitrates (poppers)	☐	Ecstasy	☐
Cannabis	☐	GBL/GHB	☐
Cocaine	☐	Mephedrone	☐
Other non-prescribed:	☐		

   (ii) Injected drugs excluding prescribed medicines? No ☐ Yes ☐
   (iii) Group sex (2 or more partners)? No ☐ Yes ☐

   (iv) Fisting? No ☐ Yes ☐

	With gloves	Without gloves
Receptive?	No ☐ Yes ☐	No ☐ Yes ☐
Insertive?	No ☐ Yes ☐	No ☐ Yes ☐

   (v) Using sex toys No ☐ Yes ☐

With gloves	Without gloves

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Receptive? No ☐ Yes ☐ No ☐ Yes ☐
Insertive? No ☐ Yes ☐ No ☐ Yes ☐

8. **Has unprotected anal sex occurred at suspected time of infection?** No ☐ Yes ☐
If yes, how many **condomless anal** sex partners in the past 30 days? _____

9. **Has the participant been diagnosed with any of the following within the 90 days since HCV diagnosis:**

Gonorrhoea: No ☐ Yes ☐

If yes: Date: ☐☐/☐☐/☐☐ Rectal? No ☐ Yes ☐

Pharyngeal? No ☐ Yes ☐

Urethral? No ☐ Yes ☐

Chlamydia: No ☐ Yes ☐

If yes: Date: ☐☐/☐☐/☐☐ Rectal? No ☐ Yes ☐

Pharyngeal? No ☐ Yes ☐

Urethral? No ☐ Yes ☐

LGV: No ☐ Yes ☐ If yes, Date: ☐☐/☐☐/☐☐

Syphilis: No ☐ Yes ☐ If yes, Date: ☐☐/☐☐/☐☐

Hepatitis B: No ☐ Yes ☐ If yes, Date: ☐☐/☐☐/☐☐

Genital warts: No ☐ Yes ☐ If yes: New diagnosis ☐ Or recurrence ☐ Date: ☐☐/☐☐/☐[

Genital herpes: No ☐ Yes ☐ If yes: New diagnosis ☐ Or recurrence ☐ Date: ☐☐/☐☐/☐[

Researcher completing this form. I confirm that this is a true record

Signature	**Print name**	**Date**

Appendix 10 PROUD trial visit CRF (Form 4)

Form 4 PROUD visit

Visit

Trial no: P ☐☐☐☐☐☐	Initials: ☐☐☐	Date of birth: ☐☐/☐☐/☐☐	Date of visit: ☐☐/☐☐/☐☐

Month of visit

1 ☐ 3 ☐ 6 ☐ 9 ☐ 12 ☐ 13 ☐ 15 ☐ 18 ☐ 21 ☐ 24 ☐ 27 ☐ 30 ☐ 33 ☐

36 ☐ 39 ☐ 42 ☐ **Unscheduled** ☐ **reason** .....

For all participants throughout follow-up

1. **Has the participant been admitted to hospital since last study visit (excluding elective surgery and social admissions)?**
   No ☐ Yes ☐ *If Yes complete SAE form 6*
2. **Has the participant suffered any illness that PREVENTED them from undertaking their usual daily activities AND sought medical attention since last study visit?**
   No ☐ Yes ☐ **a. Did this meet the definition of an SAE?** No ☐ Yes ☐ *If Yes complete SAE form 6*
3. **Has the participant been prescribed post-exposure prophylaxis (PEP, anti-HIV medication after potential HIV exposure) since the last study visit?** No ☐ Yes ☐ *If Yes, how many courses* ☐
4. **Has the monthly sexual behaviour questionnaire been completed in the last month?**
   No ☐ Yes ☐ *If no please give reason and ask participant to complete in clinic* _____
5. **Has condomless anal sex occurred since the last study visit?** No ☐ Yes ☐
   If yes, how many **condomless anal** sex partners in the past 30 days? _____

5a. Has the participant engaged in any of the following since their last visit:

Crystal meth, GHB/GBL or mephedrone immediately prior to, or during, sex ("chemsex")	☐No ☐Yes
Injection drugs (including injecting "chemsex drugs", excluding anabolic steroids or medicine)	☐No ☐Yes
Snorted cocaine	☐No ☐Yes
Group sex (sex with more than one other man at the same time)	☐No ☐Yes
Use of sex toys, such as dildos or vibrators	☐No ☐Yes
Fisting (receptive or insertive)	☐No ☐Yes
If yes, have they engaged in fisting without the use of protective gloves?	☐No ☐Yes

6. **Has an HIV test been performed since the last visit, including today?**
   No ☐ Yes ☐ *if Yes complete laboratory CRF form 5*
7. **Has an STI screen been performed since the last visit, including today?**
   No ☐ Yes ☐ *if Yes complete laboratory CRF form 5*
8. **Has serum creatinine (12,24,36m,exit) or urinary creatinine:protein ratio been collected?**
   No ☐ Yes ☐ *if Yes complete laboratory CRF form 5*
9. **What was the result of urinalysis today?**
   - ☐ No protein
   - ☐ Trace protein
   - ☐ 1+protein or more *further action may be required*
   - ☐ Urinalysis not indicated *eg unscheduled visit*
   - ☐ Urine not collected in error*
   - ☐ Could not pass urine today*

   **if baseline creatinine clearance result >90ml/min no action; if 50-90ml/min then reschedule urinalysis if taking Truvada*

10. **What is the participant's current weight?** ☐☐☐.☐ **kg**

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Form 4 **visit**

11. Risk reduction interventions offered today or already being undertaken:

Strategy	Offered today		Taken up		
a. Counselling (health advisor or referral)	Yes ☐	No ☐	Yes ☐	No ☐	Already on ☐
b. Motivational interviews	Yes ☐	No ☐	Yes ☐	No ☐	Already on ☐
c. Psychotherapy/cognitive behaviour therapy	Yes ☐	No ☐	Yes ☐	No ☐	Already on ☐
d. Addiction services	Yes ☐	No ☐	Yes ☐	No ☐	Already on ☐
e. Other *specify* _____	Yes ☐	No ☐	Yes ☐	No ☐	Already on ☐

For participants taking Truvada

Is the participant on Truvada/starting? No ☐ Yes ☐ Starting ☐

12. Does the investigator wish to report an adverse event to MRC because it is relevant to the safety evaluation of Truvada? (***please capture bone fractures, clinical renal events, and unexplained abdominal pain/nausea/headaches***)
No ☐ Yes ☐ *If Yes complete AE form 8*

13. Has the participant DISCONTINUED Truvada for a medical event (excluding HIV)**?**
No ☐ Yes ☐ *If Yes complete SAE form 6*

14. Has the participant had any side effects to Truvada in the last 30 days?
☐ No
☐ Yes but not enough to miss any tablets
☐ Yes enough to miss tablets *complete AE form 8*

15. How well is the participant managing on a scale of 1 to 10, where 10 = no missed pills?

0 1 2 3 4 5 6 7 8 9 10

16. How likely is the participant to miss pills at the weekend, where 10 = almost certainly?

0 1 2 3 4 5 6 7 8 9 10

17. How many pills were dispensed last time? ☐☐☐

18. How many pills should the participant have left? ☐☐☐

19. How many pills does the participant have left? ☐☐☐

20. Did the participant bring these to clinic today? No ☐ Yes ☐

21. How many Truvada have been prescribed today? ☐☐☐

If adherence support was offered, go back and check that your answer to question 11

Researcher completing this form. I confirm that this is a true record

Signature	Print name	Date

Appendix 11 PROUD trial Adherence and Sexual Behaviour CRF (Form 3)

Form 3 — PROUD — Adherence and sexual behaviour

Adherence and Sexual Behaviour Questionnaire

Trial no:	Initials:	Date of birth:	Date form completed:

This form should be completed monthly and just before your 3-monthly clinic visit; you will be sent a reminder. Please bring all completed forms with you to you clinic appointment for discussion with your nurse/doctor.

Sexual Behaviour

This section is about your sexual behaviour in general over the last 30 days. Unless otherwise specified "sex" means anal intercourse (including "dipping"), either as bottom (receptive, passive, he fucked you) or as top (insertive, active, you fucked him). Approximate answers are fine.

1. **How many different men did you have sex with in the last 30 days?** ☐☐ *if '0' go to q14 if currently prescribed PrEP tablets or to end of this questionnaire if you are not currently prescribed PrEP*
2. **With how many different men have you been a top during anal sex without a condom in the last 30 days?** ☐☐
3. **With how many different men have you been a bottom during anal sex without a condom in the last 30 days?** ☐☐ *if 0 go to question 7*
4. **Of the men in question 3, how many men did you not know their HIV status?** ☐☐
5. **Of the men in question 3, how many did you think to be HIV positive and not currently on treatment?** ☐☐
6. **Of the men in question 3, how many have you previously had sex with?** ☐☐

Recent Sexual history

This section is about your recent sexual history. It can include partners who you have already included in question 3.

7. **Think of the last time you had anal sex in the last 30 days.**
   For each statement please tick one box on each row

a) **I was top (active) during anal sex**
No ☐ Yes with a condom ☐ Yes without a condom ☐

b) **I was bottom (passive) during anal sex**
No ☐ Yes with a condom ☐ Yes without a condom ☐

8. **How many days ago was this?** ☐☐ days
9. **Think of the last time you were bottom (passive) during anal sex without a condom. When was this?** ☐☐ days ago
10. **What was the HIV status of this partner?**
    - ☐ I don't know
    - ☐ I thought he was HIV negative
    - ☐ I thought he was HIV positive and on treatment
    - ☐ I thought he was HIV positive and not on treatment
    - ☐ I thought he was HIV positive and did not consider whether he was on treatment
11. **Was this a partner who you have previously had sex with?** Yes ☐ No ☐

Please skip to the end of this questionnaire if you are not currently prescribed PrEP tablets or if you are currently prescribed PrEP tablets but have not had sex without a condom in the last 30 days go to qu14

12. In the 7 days before you had sex without a condom how many days did you miss PrEP tablets? 0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐ 7☐

13. In the 7 days after you had sex without a condom how many days did you miss PrEP tablets? 0☐ 1☐ 2☐ 3☐ 4☐ 5☐ 6☐ 7☐ *If it has not yet been a full 7 days since you had sex without a condom please estimate how many PrEP tablets you expect to miss*

Your experience of using PrEP

Many people miss tablets for a variety of reasons

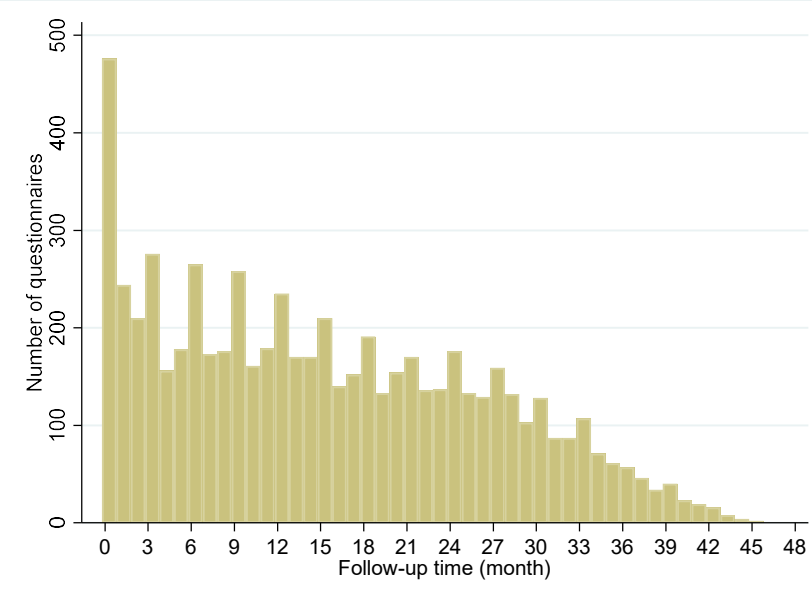
14. Approximately what percentage of days in the last 30 have you missed PrEP tablets? *Please mark on the line below*

15. These are reasons other people have given for missing PrEP tablets. For each reason, please show how often they apply to you by ticking the box that fits

Reasons for missing PrEP tablets	Always	Often	Sometimes	Rarely	Never
a) I forgot	☐	☐	☐	☐	☐
b) I am not convinced I needed PrEP	☐	☐	☐	☐	☐
c) I decided to stop altogether	☐	☐	☐	☐	☐
d) I am using other protection	☐	☐	☐	☐	☐
e) I had a bad side effect to PrEP	☐	☐	☐	☐	☐
f) I lost my PrEP tablets	☐	☐	☐	☐	☐
g) I decided to give myself a break from PrEP	☐	☐	☐	☐	☐
h) I did not have my PrEP tablets with me	☐	☐	☐	☐	☐
i) I am not currently having sex	☐	☐	☐	☐	☐
j) I was concerned that PrEP might be harmful	☐	☐	☐	☐	☐
k) I don't like the idea of taking PrEP all the time	☐	☐	☐	☐	☐

Thank you for finishing the questionnaire.
Please place in the provided envelope and hand to a doctor or nurse during your next clinic visit.

Appendix 12 Distribution of date of completion for monthly questionnaires



Appendix 13 Number of unique participants reporting risk factors for the first time during PROUD

Figure 6.1: Number of unique participants reporting category of number of ncRAI partner for the first time during PROUD

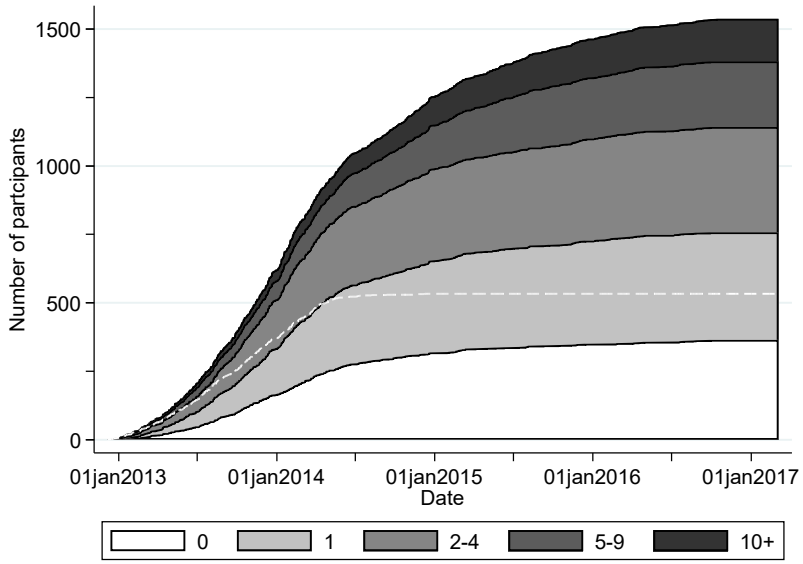


Figure 6.2: Number of unique participants reporting HIV status of ncRAI partner for the first time during PROUD

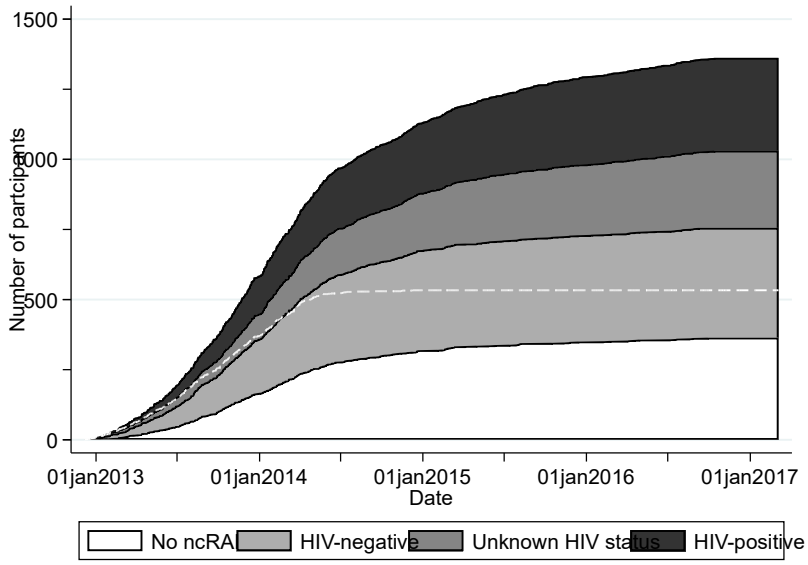


Figure legend: The number of participants reporting each behaviour is represented by the difference between the category lines. White line represents the total number of participants with at least one questionnaire completed at that time point (*n*=533).

Appendix 14 International Workshop on HIV Observational Databases 2016 oral presentation on baseline predictors of HIV infection

Baseline Predictors of Incident HIV Infections in the no-PrEP Group in the PROUD Trial

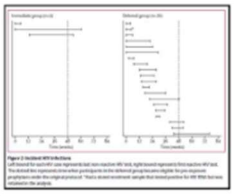
Ellen White and David Dunn on behalf of the PROUD team

International Workshop on HIV Observational Databases
7th-9th April 2016

The PROUD trial

- 544 men who have sex with men (MSM) in the UK
- Immediate vs. deferred PrEP
- Inclusion criteria - condomless anal intercourse
  a) In 3 month prior to enrolment
  b) Anticipate again in next 3 months
- HIV test every 3 months
- Primary endpoint: compared HIV incidence between arms

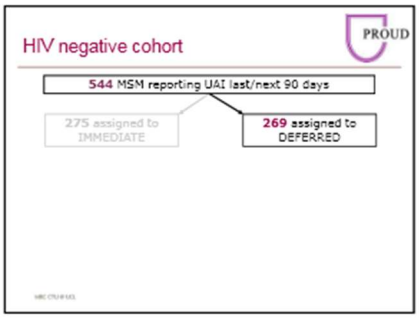
The PROUD trial

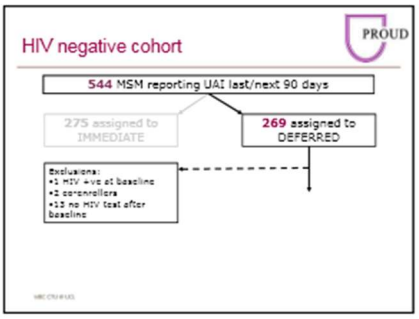


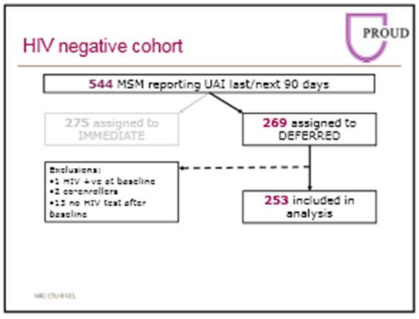
Aim

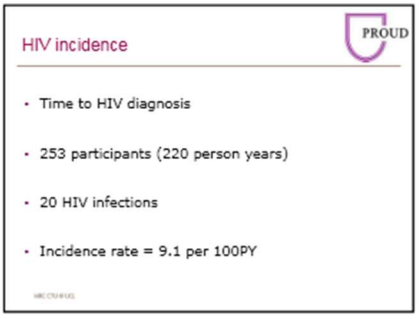
To identify characteristics of men who are at the highest risk of HIV infection

1

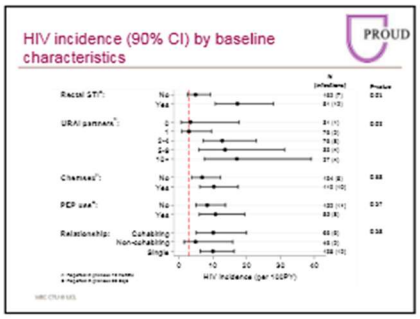

HIV negative cohort
PROUD
544 MSM reporting UAI last/next 90 days
275 assigned to IMMEDIATE
269 assigned to DEFERRED

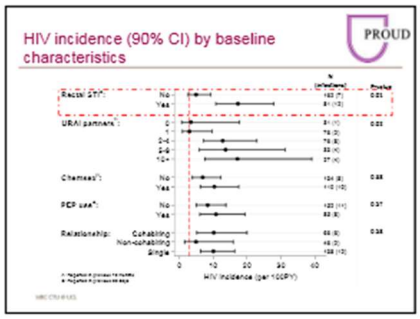

HIV negative cohort
PROUD
544 MSM reporting UAI last/next 90 days
275 assigned to IMMEDIATE
269 assigned to DEFERRED
Exclusions:
•1 HIV +ve at baseline
•2 seroreviters
•12 no HIV test after baseline

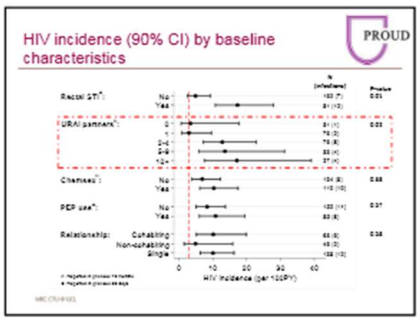

HIV negative cohort
PROUD
544 MSM reporting UAI last/next 90 days
275 assigned to IMMEDIATE
269 assigned to DEFERRED
Exclusions:
•1 HIV +ve at baseline
•2 seroreviters
•12 no HIV test after baseline
253 included in analysis

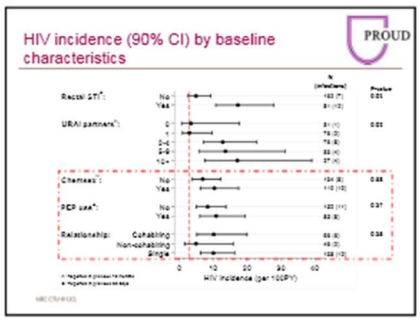

HIV incidence
PROUD
• Time to HIV diagnosis
• 253 participants (220 person years)
• 20 HIV infections
• Incidence rate = 9.1 per 100PY

2


HIV incidence (90% CI) by baseline characteristics
PROUD


HIV incidence (90% CI) by baseline characteristics
PROUD


HIV incidence (90% CI) by baseline characteristics
PROUD


HIV incidence (90% CI) by baseline characteristics
PROUD

3

Who is most at risk?

PROUD

ORIGINAL RESEARCH

Defining high HIV incidence subgroups of Australian homosexual men: implications for conducting HIV prevention trials in low HIV prevalence settings

- Simple approach
- No statistical modelling
- Inclusion criteria: A **or** B **or** C **or** ..

Who is most at risk?

PROUD

Rank:

1. Rectal STI	17.4
2. 2+ URAI	13.9
3. PEP	10.9
4. Chemsex	10.4

Predictors of high risk	Number of seroconversion for each risk factor (total no. of seroconversions)	Total PY of follow up	Combined HIV incidence per 100PY
Overall	30 (30)	330.1	9.1
Rectal STI	11 (11)	63.1	17.4

Who is most at risk?

PROUD

Exclude with STI

Rank:

1. 2+ URAI	9.5
2. PEP	9.4
3. Chemsex	7.1

Predictors of high risk	Number of seroconversion for each risk factor (total no. of seroconversions)	Total PY of follow up	Combined HIV incidence per 100PY
Overall	30 (30)	330.1	9.1
Rectal STI	11 (11)	63.1	17.4
2+ URAI partners	6 (18)	132.1	13.6

Who is most at risk?

PROUD

Exclude with 2+ URAI partners

Rank:

1. PEP	5.1
2. Chemsex	3.5

Predictors of high risk	Number of seroconversion for each risk factor (total no. of seroconversions)	Total PY of follow up	Combined HIV incidence per 100PY
Overall	30 (30)	330.1	9.1
Rectal STI	11 (11)	63.1	17.4
2+ URAI partners	6 (24)	132.1	13.6
PEP usage	1 (19)	152.0	12.5

Who is most at risk?

PROUD

Exclude with PEP usage

Rank:

1. Chemsex 4.9

Predictors of high risk	Number of seroconversion for each risk factor (total no. of seroconversions)	Total PY of follow up	Combined HIV incidence per 100PY
Overall	20 (20)	220.1	9.1
Rectal STI	11 (11)	63.1	17.4
2+ URAI partners	6 (18)	132.1	13.6
PEP usage	1 (19)	153.0	12.5
Chemsex	1 (20)	172.8	11.6

MRC CTU at UCL

Conclusions

PROUD

- No individual factor identified men who were below the level of "substantial risk", defined by WHO
- Highest risk – bacterial rectal STI or 2+ anal sex partners with no condom
- If PrEP needs to be prioritised then targeting these groups would be the most effective use of limited resources

MRC CTU at UCL

Acknowledgements

PROUD

Study participants

MRC CTU at UCL
Sarah Fenbury, Us Eraćinski, Christine Chung, Yolande Calleja-Moreca, Monica Desai, David Dolling, David Dunn, Mikey Gafos, Sajad Khan, Brendan Maugan, Shiona McCormack, Yinka Sowunmi, Ellen White, Gemma Wood

HIV & STI Dept, PHE
Monica Desai, Sarika Desai, Noel Gill, Anthony Nardone, GUMCAD team, HIV team

Clinics
Vanessa Apea, John Saunders, Mags Portman (Barts Health NHS Trust), Christine Bowman (Sheffield Teaching Hospitals NHS Foundation Trust), Michael Brady (Kings College Hospital NHS Foundation Trust), Martin Fisher, Amanda Clarke (Claude Nichol Centre), Julie Fox (Guy's and St Thomas's NHS Foundation Trust), Richard Gilson (The Mortimer Market Centre), Charles Lacey (York Hospitals NHS Foundation Trust), Nneka Nadoie (St Mary's Hospital), Alan McOwan, Simone Antonucci (56 Dean Street), Iain Reeves (Homerton University Hospital NHS Foundation Trust), Gabriel Schembri (Manchester Centre for Sexual Health), Ann Sullivan (John Hunter Clinic for Sexual Health), Steve Taylor, David White (Heart of England NHS Foundation Trust)

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Appendix 15 International Workshop on HIV and Hepatitis Observational Databases 2017 abstract submission

Abstract submission form

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Do **NOT** alter this form by deleting parts of it or adding new boxes.
Save this file in **.doc or .docx** format.

Title:

- ✓ Please do not add the names of authors or affiliations on this form.
- ✓ Please capitalise the first letter of the title and use lower case for the rest of the title (with the exception of proper nouns or abbreviations).

Different methods and their interpretation for Number Needed to Treat (NNT) in HIV pre-exposure prophylaxis (PrEP) trials

Abstract:

- ✓ Your abstract **must use Arial 10** and **single line spacing**.
- ✓ Your abstract (including tables and figures) **must fit** into the space below and must not exceed **500 words**.
- ✓ **Tables and figure must have a title** and will be printed in **black and white only.**
- ✓ Please follow the general outline **Background, Methods, Results and Conclusion** where applicable.

Background: Number needed to treat (NNT) is a well-known epidemiological construct that denotes the average number of people that require treatment in order to prevent one additional outcome. Originally developed for binary outcomes, the calculation of NNT is more complex for time-to-event outcomes and continuous treatment, such as pre-exposure prophylaxis (PrEP) to prevent the acquisition of HIV infection. Several methods have been proposed, but it is not necessarily clear which method is the most relevant. We illustrate various methods using data from the PROUD trial, discuss differences in their interpretation, and highlight the one we consider to most pertinent for assessing the cost-effectiveness of PrEP.

Methods: PROUD participants (N=544) were randomised to receive PrEP immediately (IMM) or deferred (DEF) PrEP starting one year later. The primary analysis compared HIV infection rates between the two trial arms during the DEF period. We compared 4 methods proposed in the literature for calculating NNT with time-to-event outcomes (Table 1). The first three methods are based on HIV endpoints only. Despite PROUD evaluating a daily regimen, there were a number of participants who interrupted or discontinued PrEP. Therefore we considered a fourth method which scaled ID by the medicine possession ratio (ID_{MPR}), defined as the total number of pills prescribed divided by the total number of days follow-up.

Results: The HIV incidence rate was 1.2 (3 infections, 243 person-years (PY)) in the IMM group and 9.0 (20, 222) per 100 PY in DEF. KM and SD values of 13.9 and 13.5, respectively, have the same interpretation and indicate the number of patients that need to be initially offered PrEP in order to avert one additional infection by 1 year. Unlike the SD method, KM is sensitive to the precise timing of HIV diagnoses occurring around the 1 year time point; this is reflected in the wider confidence interval. The measure based on incidence rates (ID) is more relevant for implementation since PrEP is an ongoing intervention. It indicates the number of person-years of PrEP care that need to be offered to prevent one additional HIV infection. The MPR during the DEF phase was 0.88. The ID_{MPR} value of 11.3 indicates the estimated person-years of PrEP treatment that needs to be prescribed.

Discussion: Although the NNT estimates based on the survival function and incidence rates are quantitatively similar they are conceptually different and it is important to choose the method that is most relevant to the question being addressed. In the context of PrEP implementation, as drug needs to be provided on a long-term basis, calculating NNT in terms of person-years follow-up (ID and ID_{MPR}) is the most appropriate. As many patients do not need to take PrEP continuously, and as drug is the major cost component of PrEP programmes, ID_{MPR} is the most relevant measure for assessing cost-effectiveness.

Table 1: Comparison of NNT calculation methods for preventing one HIV infection in PROUD

NNT = the reciprocal of the difference in :	Acronym	NNT (90% CI)
Survival functions at 1 year estimated from Kaplan-Meier curves	KM	13.9 patients (9.3-27.7)
Survival functions at 1 year inferred assuming exponential distributions	SD	13.5 patients (8.7-21.0)
Incidence rates	ID	12.9 PY (8.2-20.2)
Incidence rates adjusted for medicine possession ratio	ID_{MPR}	11.3 PY (7.2-17.8)

Appendix 16 International Workshop on HIV and Hepatitis Observational Databases 2017 poster presentation

PROUD

MRC Clinical Trials Unit

UCL

Different methods and their interpretation for Number Needed to Treat (NNT) in HIV pre-exposure prophylaxis (PrEP) trials

Ellen White, Sheena McCormack, David Dunn
MRC CTU at UCL

Background

- Pre-exposure prophylaxis (PrEP) is a drug used to prevent HIV infection; it stops the virus taking hold after entering the body.
- There have been a number of PrEP trials (IPrEX, PROUD, IPERGAY) which demonstrated the effectiveness of this treatment in preventing HIV in men who have sex with men (MSM).
- A popular epidemiological construct "Number needed to treat" (NNT) formed part of these trials' analyses. NNT is defined as the average number of patients who need to be treated to avoid one additional outcome.
- PrEP trials have calculated NNT in a number of different ways which makes it difficult to compare between trials

Aims

- Using data from the PROUD trial, we aimed to identify how NNT should be calculated in PrEP trials and whether this value can be generalised to the general population outside of a trial setting.
- It is important to establish whether PrEP is delaying or preventing HIV as these are conceptually different. We also want to quantify the extent to which PrEP can impact others in the population.

Different methods for NNT calculation

- NNT was originally developed for binary outcomes, calculated by taking the reciprocal of the difference in risk.
- Although CONSORT guidelines recommend use of NNT for survival outcomes it is not clear how best to calculate this.
- Appropriate methods and interpretation depend on predefined vs. variable (risk-related) duration of treatment and binary vs. survival outcomes. We compared a number of different calculation methods (see table) using data from the PROUD trial.
- NNT_{KM} and NNT_{EC} have the same interpretation. Unlike the SD method, KM is sensitive to the precise timing of HIV diagnoses occurring around the 1 year time point; this is reflected in the wider confidence interval.
- NNT_{PY} is more relevant for PrEP implementation since it is an ongoing intervention. It indicates the number of person years of PrEP care that need to be offered to prevent one additional HIV infection.
- Despite protocol, not all PROUD participants took PrEP daily. Since drug forms a major part of the cost of care, we want to take into account the actual amount of drug prescribed rather just the time in follow-up.
- The MPR for the PrEP arm during PROUD was 0.88. The NNT_{MPR} value of 11.3 indicates the estimated person-years of PrEP treatment that needs to be prescribed.

Acronym	Calculation method	Interpretation	NNT values from the PROUD trial
	Reciprocal of the difference in:	On average, provide...	
NNT_{KM}	Survival functions at 1 year estimated from Kaplan-Meier curves	PrEP care for 1 man to prevent 1 additional HIV infection for 1 year	13.9 men (6.9-27.7)
NNT_{EC}	Survival functions at 1 year assuming exponential distributions	PrEP care for 1 man to prevent 1 additional HIV infection for 1 year	14.5 men (6.7-31.0)
NNT_{PY}	Incidence rates	X person-years (PY) of PrEP care to prevent 1 additional HIV infection	13.8 PY (6.2-30.2)
NNT_{MPR}	Incidence rates adjusted for medicine possession ratio (MPR)	X person-years of PrEP prescribed to prevent 1 additional HIV infection	11.3 PY (5.1-17.8)

Table: Comparison of NNT calculation methods for time-to-event outcomes

Conclusions:

- Although the NNT estimates based on the survival function and incidence rates are quantitatively similar they are conceptually different and it is important to choose the method that is most relevant to the question being addressed.
- In the context of PrEP implementation, as drug needs to be provided on a long-term basis, calculating NNT in terms of person-years follow-up (NNT_{EC}, NNT_{MPR}) is the most appropriate.
- As many patients do not need to take PrEP continuously, and as drug is the major cost component of PrEP programmes, NNT_{MPR} is the most relevant measure for assessing cost-effectiveness.

NNT in the population

- The underlying HIV incidence may be different in the trial population compared to the general population
- The PROUD trial had incidence 7 times higher than GUM clinic attenders in the UK
- Unlike relative risk reduction (RRR), NNT is affected by baseline incidence
- Therefore, when generalising to a wider population we should scale the estimated NNT:

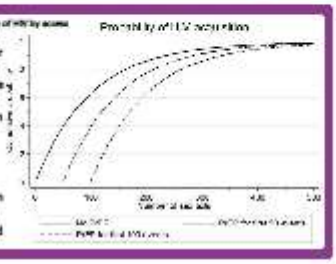
$$RRR_T = \frac{\lambda_{GT} - \lambda_{IT}}{\lambda_{GT}} = \frac{\alpha\lambda_{GT} - \alpha\lambda_{IT}}{\alpha\lambda_{GT}} = \frac{\lambda_{GT} - \lambda_{IT}}{\lambda_{GT}} = RRR_T$$ (T = incidence in the trial and general population)

$$NNT_T = \frac{1}{\lambda_{GT} - \lambda_{IT}} = \frac{1}{\alpha\lambda_{GT} - \alpha\lambda_{IT}} = \frac{NNT_T}{\alpha}$$ (λ_{IT} = incidence in no PrEP and PrEP group; α = ratio of incidence in trial and general population)

Does PrEP prevent or delay HIV?

- It is not clear in the context of PrEP whether we should use the terminology "prevents" or "delays" HIV infection.
- After discontinuing PrEP, an individual is at risk of HIV again. Was it a waste of resources if the individual subsequently acquires HIV?
- We consider a hypothetical scenario to argue that we are preventing HIV when giving an individual PrEP. Consider the following assumptions:
  1. HIV is only acquired by receptive anal intercourse without a condom
  2. Probability of acquisition is constant at 1% per sex act (following negative binomial distribution)
  3. The risk of HIV acquisition is zero when taking PrEP
  4. PrEP use covers the first 0, 50 or 100 sex acts
- The figure demonstrates that the cumulative probability of acquiring HIV differs largely between groups when there are a small number of events.
- Even after a large number of sexual acts, the cumulative risk of HIV can never be equal and therefore HIV is not inevitable and is prevented at a population level.

Figure: Cumulative probability of HIV by access to PrEP



Indirect effect of PrEP

- Individuals taking PrEP and using other HIV prevention strategies are protecting themselves from the infection along with their future partners
- HIV risk is not just based on an individual's behaviour but also their partners' and in turn their partners'
- When looking at the effect of PrEP in the population it is important to take sexual networks into account
- Quantifying NNT in this context can be challenging
- NNT calculated in a trial is actually an upper bound for the true NNT since PrEP can impact more individuals than those directly treated

Figure: Illustration to demonstrate the effect PrEP in a sexual network

Summary

1. Use **incidence rates** to calculate NNT since PrEP is used for a variable duration
2. In terms of cost –effectiveness, the most appropriate NNT would adjust for **amount of drug** prescribed rather than just attendance in clinic
3. When applying NNT calculated in trials to the general population we should **adjust for** differences in the **baseline incidence**
4. It is valid to say that PrEP prevents HIV at a population level rather than just delays it

Appendix 17 Abstract submission to British Assoiation for Sexual Health and HIV Conference (2017)

BASHH 2017_PROUD STIs_Final

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Title:

Impact of PrEP on sexual behaviour? Significantly lower rate of rectal CT in non-PrEP users in the deferred phase of PROUD disappeared when everyone had access to PrEP.

Abstract: **(Your abstract must use Normal style and must fit into the box. Do not enter author details)**

Introduction:
PROUD is uniquely placed to compare rates of STIs between PrEP users and non-PrEP users, and to provide longitudinal data in PrEP users between Nov12-Nov16. We describe reported STIs in the year prior to enrolment, and rates during the deferred and post-deferred phases of PROUD when all participants had access to PrEP.

Methods:
Data were extracted from baseline self-completed questionnaires. Staff were asked to capture STI screens and diagnoses from quarterly study and interim routine clinic visits. We compared incidence rates of selected STIs for those with immediate (IMM) access to deferred (DEF) access during the deferred and post-deferred phase.

Results:
517 participants completed the STI baseline questions, reporting a median (IQR) of 3 (2-4) screens in the 12m prior to enrolment; 172 (89 IMM, 83 DEF) reported a rectal infection. Rectal STI rates were similar by phase and arm with the exception of lower rates of rectal CT in the DEF arm during the deferred phase (p-value=0.024):

	Deferred Phase		Post-deferred Phase	
Rate (N/pyrs)	IMM	DEF	IMM	DEF
Rectal GC	35.3 (81/229)	33.7 (67/203)	31.4 (129/411)	32.7 (116/355)
Rectal CT	33.6 (77/229)	21.2 (43/203)	33.1 (136/411)	29.9 (106/355)

Discussion:
The ongoing high rates of rectal infections show that participants remaining in follow-up continued to need PrEP. The significantly reduced incidence of rectal CT in those allocated to deferred PrEP was not observed in the post-deferred phase when everyone had access to PrEP. This may be chance or may reflect an influence of PrEP on sexual practices.

Appendix 18 Abstract submission to International Clinical Trials Methodology Conference (2019)

Ascertainment bias: accounting for differential STI screening frequency in a HIV prevention trial

Background

Ascertainment bias is a phenomenon whereby the more screening that is conducted, the larger the number of outcomes detected. PROUD, a pragmatic trial, investigated the effectiveness of pre-exposure prophylaxis (PrEP) in preventing HIV acquisition. A key secondary outcome was sexually transmitted infection (STI) diagnoses. However, clinic attendance, and therefore STI screening frequency, was higher amongst participants receiving PrEP. We describe the impact and relevance of adjusting for the number of screens in an analysis.

Methods

PROUD randomised participants to receive PrEP immediately (IMM) or after a twelve month deferral period (DEF). The outcome was defined as the total number of STIs (chlamydia, gonorrhoea, or syphilis) detected during the randomised phase. Negative binomial models were used to allow for heterogeneity between participants. Unadjusted models and models adjusting for the number of STI screens (as a linear term) were compared.

Results

There was a significant difference in the number of screens between IMM and DEF (mean 4.1 vs. 3.6, P<0.001). STI incidence was higher amongst the IMM group (114.7 vs. 94.3/100PY). After adjustment, the incidence rate ratio (IRR) shifted towards the null (IRR=1.2 (95% CI:1.0-1.5), P=0.08 to aIRR=1.1 (95% CI:0.9-1.4), P=0.28).

Conclusions

Adjusting for the number of screens has been used in several PrEP studies to account for ascertainment bias. However, it can be seen as an external confounder (e.g. additional screening driven by clinic attendance for PrEP - which we want to adjust for) or a variable that lies on the causal pathway (e.g. clinic attendance driven by symptoms, which we do not want to adjust for). Simple statistical adjustment that does not discriminate between reasons for screening is likely to over-adjust for factors related to STI risk. Therefore unadjusted analyses provide a more clinically relevant insight into the PrEP effect on STIs.

Appendix 19 Abstract submission to International Workshop on HIV and Hepatitis Observational Databases (2018)

Submission Id: 97

Hepatitis C incidence in PrEP users: the importance of considering different time-scales

Ellen White[1], Monica Desai[2], Nina Vora[3], Sheena McCormack[1], David Dunn[1]

[1]MRC CTU at UCL, London, United Kingdom. [2]National Institute for Health and Care Excellence, Manchester, United Kingdom. [3]IGH at UCL, London, United Kingdom.

Abstract

Background

In the past decade, hepatitis C (HCV) infection has been on the rise in men who have sex with men (MSM). There is concern that the initiation of pre-exposure prophylaxis (PrEP) will bridge the gap between the high HCV incidence in HIV-positive MSM and the lower incidence in HIV-negative individuals. PROUD provides an opportunity to estimate HCV incidence among MSM on PrEP. We explore the most appropriate way to calculate HCV incidence in this scenario.

Method

PROUD ran between 2012 and 2016 and recruited MSM reporting anal sex without a condom. Participants were randomised to receive immediate PrEP (IMM) or deferred initiation for another 12 months (DEF). HCV screening occurred according to individual site practice. HCV incidence was calculated from study enrolment to the date of a new infection indicated by a positive antibody or antigen in a previously antibody negative individual or antigen/RNA in a participant who had previously cleared HCV. Negative individuals were censored at the date of their last HCV screening during PROUD. We explore the use of two different time-scales: time from enrolment (T1) and calendar time (T2, equivalent to time from the start of the study [29Nov12]) allowing for individual late entry. Flexible parametric models (Royston-Parmar) were fitted to model the change in incidence over time.

Results

Of the 544 participants of PROUD, 490 (90%) were screened for HCV at least once during the study. During the course of PROUD there were 22 incident infections, 3 (1 IMM vs. 2 DEF) of which occurred during the deferred phase. Infections clustered in the years 2015 (n=12) and 2016 (n=6). The overall HCV incidence was 1.85 per 100 PY (IMM 1.87 vs. DEF 1.82) but the rate increased significantly over time according to both timescales (T1, P=0.013; T2, P=0.016). Cumulative incidence varied according to the method, 0.90%, 2.89%, 6.08% and 0.91%, 1.71%, 4.13% at 1, 2 and 3 years after randomisation (T1) and start of study (T2) respectively (Figure).

Conclusion

Within this group of individuals that have self-selected to access PrEP, HCV incidence was much higher than general HIV-negative MSM populations attending GUM clinics. During the deferred phase, the number of HCV infections was small, precluding reliable analysis of the impact of PrEP per se. There was strong evidence to suggest that the rate was increasing over time. It is not possible to separate the two explanations for this: either incidence was increasing over calendar time or individuals are at greater risk the longer they take PrEP. The former explanation is the more plausible. This should be a consideration before attributing differences in incidence to participant characteristics i.e. PrEP initiation or other such risk factors.

Appendix 20 International Workshop on HIV and Hepatitis Observational Databases 2018 poster presentation

HCV incidence in PrEP users: the importance of considering different time-scales

Ellen White[1], Monica Desai[2], Nina Vora[3], Sheena McCormack[1], David Dunn[1]

[1]MRC CTU at UCL, [2]The National Institute for Health and Care Excellence, [3]Intstitue for Global Health, UCL

Background

- In the past decade, hepatitis C (HCV) infection has been on the rise in men who have sex with men (MSM)
- There is concern that the initiation of pre-exposure prophylaxis (PrEP) will bridge the gap between the high HCV incidence in HIV-positive MSM and the lower incidence in HIV-negative individuals
- PROUD provides an opportunity to estimate HCV incidence among MSM on PrEP
- We explore the most appropriate way to calculate HCV incidence in this scenario

Methods

- PROUD ran between 2012 and 2016 and recruited MSM reporting anal sex without a condom
- Participants were randomised to receive immediate PrEP (IMM) or deferred initiation for another 12 months (DEF)
- HCV screening occurred according to individual site practice
- HCV incidence was calculated from study enrolment to the date of a new infection indicated by a positive antibody or antigen in a previously antibody negative individual or antigen/RNA in a participant who had previously cleared HCV. Negative individuals were censored at the date of their last HCV screening during PROUD
- We explore the use of two different time-scales: time from enrolment (T1) and calendar time (T2, equivalent to time from the start of the study [29Nov12]) allowing for individual late entry
- Flexible parametric models (Royston-Parmar) were fitted to model the change in incidence over time

Results

HCV screening

- Of the 544 participants of PROUD, 490 (90%) were screened for HCV at least once during the study
- Median follow-up for individuals 2.6 (IQR: 2.1-3.0)

HCV infections

- During the course of PROUD there were 22 incident infections
- 3 (1 IMM vs. 2 DEF) of which occurred during the deferred phase
- Infections clustered in the years 2015 (n=12) and 2016 (n=6)

HCV incidence

- Total follow-up =
- The overall HCV incidence was 1.85 per 100 PY (IMM 1.87 vs. DEF 1.82)
- Incidence rate increased significantly over time according to both timescales (T1, P=0.013; T2, P=0.016)

Timescales

- Cumulative incidence varied according to the timescales

Figure: Estimated cumulative HCV incidence by time-scale

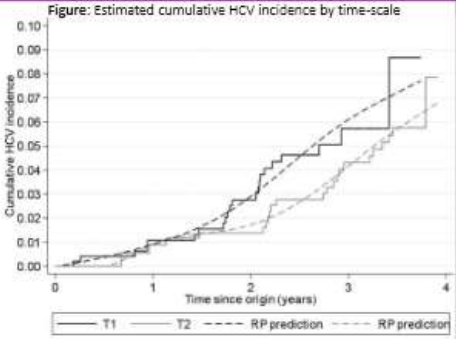

Table: Estimated cumulative HCV incidence (per 100 PY) by time-scale

	Time since origin (years)		
	1	2	3
Time-scale			
T1	0.9	2.9	6.0
T2	0.9	1.7	4.1

T1, time from enrolment; T2, calendar time

Summary

- Within this group of individuals that have self-selected to access PrEP, HCV incidence was much higher than general HIV-negative MSM populations attending GUM clinics
- During the deferred phase, the number of HCV infections was small, precluding reliable analysis of the impact of PrEP per se. There was strong evidence to suggest that the rate was increasing over time
- It is not possible to separate the two explanations for this: either incidence was increasing over calendar time or individuals are at greater risk the longer they take PrEP. The former explanation is the more plausible
- This should be a consideration before attributing differences in incidence to participant characteristics i.e. PrEP initiation or other such risk factors