The public health utility of assays to test for recent HIV infection: an evaluation on UK case-based surveillance data.

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Declaration of originality

I, Adamma Aghaizu declare that the work presented in this thesis is my own. All contributors have been indicated appropriately and references cited. The thesis was supervised by Professor Helen Ward, Imperial College London and Dr Valerie Delpech, Head of HIV Surveillance, Public Health England.

Copyright Declaration

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Abstract

Determining accurate, real-time epidemic trends for HIV is an ongoing challenge due to the lengthy asymptomatic period of infection. Current available methods to determine the number of new infections are based on back calculation models of diagnosis data and/or simulation models of behavioural data. Both approaches do not provide timely estimates for recent years or estimates for risk groups other than gay, bisexual and men who have sex with men (MSM), for whom there are less published data on risk behaviours. The aim of this thesis is to explore the public health utility of serological HIV incidence assays applied to case-based surveillance data in the UK.

For the first five years of Public Health England's surveillance programme, I determined demographic predictors for a recent infection diagnosis and estimated HIV incidence in both sexual health clinic attendees and the general population. I also undertook a feasibility study for enhanced behavioural surveillance among MSM with incident infection to explore if this could highlight new trends in risk behaviours or if more traditional infectious disease control methods, such as active case finding, could become more applicable to HIV.

Between 2009 and 2013, I found predictors for a recent infection diagnosis to have been younger age (15-24 years compared to + 50 years) (adjusted odd ratio (AOR) 2.8 95% C.I 2.2-3.7), the UK as probable country of infection (AOR 1.4 95% C.I 1.2-1.6) and higher CD4 counts (>1000 cells/mm^3 compared to >50≤200 cells/mm^3, AOR: 14.3, 95% C.I. 8.9-22.8) in MSM, and UK country of birth (AOR: 1.7, 95% C.I. 1.2-2.3) and UK country of infection (AOR: 1.4 95% C.I. 1.1-1.8) in heterosexuals. HIV incidence was up to 30-fold higher in sexual health clinic attendees (130 per 100,000 person years (pys) in 2009 increasing to 200 per 100,000 pys in 2013) compared to the general population (between 6 and 6.5 per 100,000 over the years), with little change over the period. The two key populations most affected were MSM, with approximately 300 infections per 100,000 pys, and black African heterosexuals, with between 45 and 70 infections per 100,000 pys. The number of new HIV

infections was five-fold higher in London compared to outside London. The behavioural surveillance data showed that nearly all men had exhibited high risk behaviours in the six months before diagnosis; half had had a sexually transmitted infection (STI) in the previous year. Men had met partners mainly via mobile phone dating apps. Despite two thirds of sexual partners having been contactable, only one in five had been contacted with men indicating preference to notify partners themselves.

Findings from this thesis show serological HIV incidence assays applied to case-based surveillance data in the UK can produce timely estimates of HIV incidence for the whole population. It is currently the only method allowing comparisons by geography which may enable prevention resources to be targeted more effectively. In light of the ongoing decline in new HIV diagnoses and likely transmission, and the roll out of a new biomedical intervention (pre-exposure prophylaxis (PrEP)), all sources of HIV epidemic intelligence will be crucial to work towards the elimination of HIV.

Whilst the enhanced behavioural surveillance was feasible in this group, it is unlikely to discover new risk behaviours or facilitate active case finding. However, there is a role for this approach of data collection among recent seroconverters; the surveillance scheme, now referred to as SHARE (Surveillance of HIV Acquired Recently: Enhanced), has been modified and rolled out on a national scale to obtain insights into how new infections may or may not relate to exposure of PrEP in light of the ongoing PrEP trial (https://www.prepimpacttrial.org.uk/). Findings of this new initiative will feed into future evaluations of PrEP use in the UK.

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Table of Abbreviations

AIDS	Acquired immunodeficiency syndrome
AOR	Adjusted odds ratio
ART	Antiretroviral therapy
ARV	Antiretroviral therapy
ASTRA	Antiretrovirals, Sexual Transmission Risk and Attitutes Study
BED CEIA	BED capture immunoassay
BHIVA	British HIV Association
CASCADE	Concerted Action on SeroConversion to AIDS and Death in Europe
CDC	Centers for Disease Control and Prevention
CEPHIA	Consortium for the Evaluation and Perfermance of HIV Incidence Assays
CHIPS	Collaborative HIV Paediatric Study
CIs	Confidence intervals
DNA	Deoxyribonucleic acid
ECDC	European Centre for Disease Prevention and Control
EIA	Enzyme immuno assay
EPP	Epidemic Projection Package
FRR	False recent rate
GUM	Genitourinary medicine clinic
GUMCAD	Genitourinary Medicine Clinic Activity Dataset
HANDD	HIV and AIDS New Diagnoses and Deaths
HARS	HIV and AIDS Reporting System
HCV	Hepatitis C infection
HIV	Human immunodefiency virus
HRM	High resolution melting
IQR	Interquartile range
KS	Kaposi's sarcoma
LGV	Lymphogranuloma venerum
MAR	Missing at random
MDRI	Mean duration of recent infection
MI	Multiple imputation
MOT	Mode of transmission model
MSM	Men who have sex with men
MTCT	Mother-to-child-transmission
NATSAL	National Survey of Sexual Attitudes and Lifestyles
NICE	National Institute for Health and Care Excellence
NGS	Next generation sequencing
NRES	National Research Ethics Service
NSHPC	National Study of HIV in Pregnancy and Childhood
OD	Optical denisty
ODn	Normalised optical density
ONS	Office for National Statitics
PASH	Pleasure and Sexual Health Study (PAH)
PCP	Pneumocytis pneumonia (PCP)
PEP	Post-exposure prophylaxis for HIV

PHE	Public Health England
PHI	Primary HIV infection
PIs	Protease inhibitors
PN	Partner notification
PrEP	Pre-exposure prophylaxis
PROUD	Pre-exposure Option for reducing HIV in the UK: an open-label randomisation to immediate or Deferred daily Truvada for HIV negative gay men
PWIDs	People who inject drugs
RITA	Recent Infection Testing Algorithm
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase polymerase chain reaction
SD	Standard deviation
SHARE	Surveillance of HIV Acquired Recently: Enhanced
SOPHID	Survey of Prevalent HIV infections Diagnosed
SPARTAC	Short Pulse Anti-Retroviral Therapy at Seroconversion
STIs	Sexually transmitted infections
TasP	Treatment as prevention
THT	Terrance Higgins Trust
UAI	Unprotected anal intercourse
UCL	University College London
UK	United Kingdom
UNAIDS	The Joint United Nations Programme on HIV/AIDS
US	United States
VRD	Virus Reference Department
WHO	World Health Organisation

1. Introduction

Control of human immunodeficiency virus (HIV) infection remains a public health priority in the UK. It was estimated that by the end of 2015, there were over 100,000 people living with HIV in the UK, of which approximately 13,500 were undiagnosed.(1, 2) Over the last decade, there have been around 6000 new HIV diagnoses each year, however in 2016, for the first time in the 30 years since the beginning of the epidemic, a reduction in this number was observed in gay, bisexual and other men who have sex with men (MSM).(1) This reduction continued into 2017.(3) The fall may have been due to a reduction in incidence or changes in HIV testing behaviours. Currently it is suspected that it was due to a real reduction in transmission brought about by combination prevention, including behavioural, biological and structural HIV prevention interventions.(4, 5) To establish if this is true, HIV incidence, the rate of new infections, must be determined which has been an ongoing challenge due to the prolonged asymptomatic period of infection (approximately 10 years).(6) Conventional methods used to estimate the number of new HIV infections, such as population cohort studies and cross-sectional, serial prevalence surveys, are costly and challenging, particularly in relation to measurements in harder to reach, stigmatised groups.(7) Attempts have been made to develop incidence estimation methods based on modelling and back projecting data routinely collected for HIV case-based surveillance. These however often rely heavily on the availability of high quality sexual behavioural data which are only currently available for MSM populations.(8)

An HIV incidence estimation approach which has been of interest in recent years is based on serological assays which, when used in combination with other clinical data, can distinguish newly acquired from established HIV infections in people diagnosed with HIV for the first time.(9) Integrating these assays into routine case-based surveillance may provide an opportunity to conduct real-time estimations of incidence.

In addition, with the possibility of identifying new infections in real-time and thus groups at most risk of acquiring HIV, conventional infectious disease measures could become more applicable to HIV. These include the detection of infection clusters in real-time indicating outbreaks, the identification of new risk behaviours, and being able to undertake active case finding and contract tracing activities.

To explore the utility of serological HIV incidence assays, Public Health England (PHE) in 2009, then known as the Health Protection Agency (HPA), introduced a nationwide programme. This followed on from studies by Dr Gary Murphy, the Joint Lead of Clinic Services Unit at the Virus Reference Department (VRD) at PHE, of laboratory aspects of the serological assays and estimated HIV incidence in MSM attending a group of Genitourinary Medicine (GUM) clinics between 1995 and 2001.(10) Introducing a nationwide programme entailed encouraging sexual health clinics throughout the country to submit specimens from people newly diagnosed to PHE. This was undertaken by one of my research supervisors, Dr Valerie Delpech and my predecessors in my role as lead scientist for the surveillance of recent HIV infections at PHE, Dr Sam Lattimore and Dr Ruth Simmons. The setup of the programme required vast amounts of effort to recruit clinics and laboratories which involved site visits and a series of presentations to communicate the purpose and required logistics of the programme. Coming into my role in July 2011, after the surveillance initiative had been running for two years, I was offered the opportunity to explore the public health utility of the HIV incidence assays by examining the contribution the surveillance scheme makes towards providing insights to the epidemic. This was considered an academic exercise best undertaken in the format of a doctoral thesis. Here, I present my findings and make recommendations regarding the pursue and any modifications of the programme from a scientific perspective.

1.1 Aims

The aims of the PhD are:

1. To utilise PHE's recent HIV infection testing data to estimate HIV incidence.
2. To assess the validity of HIV incidence measurements and compare these against existing methods for determining incidence in the UK.
3. To explore if recent HIV infection data can enable the collection of additional behavioural information facilitating the application of more conventional infectious disease control measures.

Recommendations at the end of the thesis are based on the programme's ability to provide significant new insights into the epidemic and if and how outputs may contribute to public health policy.

1.2 Thesis structure

This thesis is based on the analysis of routinely collected HIV case-based surveillance data at PHE and the analysis of primary data collected in the form of a pilot study. As the scientific lead for the surveillance of recent HIV infections at PHE, my day-to-day role was to manage these data and produce what were considered routine outputs which were data tables presenting the proportion of new HIV diagnoses that were likely recently acquired.(5, 11-13) Below, I outline the chapters for the additional academic work undertaken alongside which constitute the thesis. As a basis for evaluating the utility of the surveillance system, the structure of my thesis broadly follows the Centres for Disease Control (CDC) guidelines for evaluating surveillance systems (e.g. describing the objectives and the public health importance of the data collected and reviewing the quality, representativeness, timeliness, and usefulness of the data as well as the resources required).(14) The thesis outline is as follows:

Chapter 1 (current chapter)

Chapter 2 provides the research background giving an overview of the HIV epidemic both in the UK and worldwide, illustrates the challenges in determining HIV incidence, describes conventional incidence estimation methods and those more recently developed for HIV, and explores the role for outbreak investigations in the control of HIV.

Chapter 3 presents the methods used for data collection and analyses. I provide a detailed description of the datasets used and their limitations, the methods applied for the descriptive analysis in Chapter 5 and the HIV incidence estimation methods in Chapters 6 and 7. I also present the study procedures for the pilot of enhanced surveillance in MSM diagnosed with incident infection.

Chapter 4 describes the Recent Infection Testing Algorithm (RITA) programme data from 2009-September 2013 including the coverage and representativeness in relation to all people newly diagnosed with HIV. Here I also explore the impact of using different recent infection testing algorithms on the fraction of people classified as having been recently infected and calculate the false recent rate (FRR) of the chosen RITA. In addition, I conduct exploratory analyses on the correlation between results of the serological HIV incidence tests (avidity scores) and other clinical markers of early stage infection.

Chapter 5 explores the prevalence and predictors of people diagnosed with recently acquired HIV, presented separately for the two largest transmission risk groups, MSM and heterosexuals.

Chapter 6 uses national data on sexual health clinic attendance in combination with RITA to estimate HIV incidence in this healthcare seeking population.

Chapter 7 applies the approach developed by the US Centers for Disease Control (CDC) to the RITA data which uses a survey sample model combined with weighting to obtain population-based HIV incidence estimates.

Chapter 8 presents data collected from my pilot of enhanced surveillance in people with incident HIV infection exploring the feasibility in collecting data directly from patients for surveillance, and the potential value of a scale up of this activity.

Chapter 9 provides a critical appraisal of my findings and discusses the public health utility of the serological incidence assay data and the implications findings have on the control of HIV infection and public health policy more broadly.

2 Background

In this Chapter I provide an overview of the UK and global epidemiology of HIV infection and present the challenges and current methods available for determining the number of new infections in a timely manner. I discuss the rational for having introduced the surveillance programme of serological HIV incidence assays in England, Wales and Northern Ireland for i.) incidence estimation and ii.) enhancing infection control activities for HIV such as contact tracing and partner notification.

2.1 Global history of HIV

HIV was first documented in the United States in 1981 when an unexplained increase in fatal, opportunistic infections such as Kaposi's sarcoma (KS) and Pneumocystis carinii pneumonia (PCP) was noted in New York and Los Angeles among gay men.(15-17) This was followed by further reports of unusual cases throughout the world, particularly among homosexuals, haemophiliacs, injecting drug users, recipients of blood transfusions, female sexual partners of men who had the virus and Africans.(8, 17-22) In 1983, the human retrovirus was isolated.(23)

In the absence of an assay to test for the virus, the extent of the epidemic was unknown. People who presented with symptoms of the infection were classified as having acquired immunodeficiency syndrome (AIDS).(24) A range of indicator conditions fell under this umbrella term and included next to KS and PCP, cytomegalovirus infections and oral candidiasis.(25, 26) In 1984, a serological assay to test for the infection was developed allowing the identification of asymptomatic infections and screening of blood donations to prevent transmission via blood transfusions.(27) This was approved for use in 1985 and subsequently the routine screening of blood donations was introduced by all blood transfusion centres in the UK.(28)

The first successes in drug discovery demonstrating a sustained effect on disease progression did not occur until a decade later in 1995, by which time the World Health Organisation (WHO) reported the HIV/AIDS pandemic had affected over 18 million adults and 1.5 million children worldwide.(29) New treatments consisted of combinations of antiretroviral therapy (ART) based on protease inhibitors (PIS)(30, 31), which soon became widely available in most developed countries, and had a dramatic effect on improving the rates of morbidity and mortality in people infected with HIV.(1, 32, 33)

However, some initial drawbacks of the treatment use were severe side effects, the emergence of resistant strains, high costs and challenging treatment regimens. As a consequence, the recommendation was introduced to prescribe ART only to individuals with late stage infection and low immunity, indicated by low CD4 T-lymphocyte cell counts.(34) However, with the more recent development of newer ARTs with fewer side effects(35), and a number of trials showing that earlier initiation of ART improved prognosis(36) and vastly reduced the likelihood of onward transmission (due to lower infectivity by suppressed viral loads),(37-39) 'test and treat' strategies are now recommended by the WHO initiating people on ART as soon as possible for treatment as prevention (TasP).(40) Important landmark trials included that of Cohen et al. which explored the effect of early ART initiation in serodiscordant couples (clinical trials number HPTN 052) across nine countries. Among 1763 couples, a total of 28 virologically linked HIV transmissions were observed of which only one was in the early therapy group, reducing cases of onward transmission by 96%(37). The PARTNER study conducted in 2014 across 14 European countries and included over 1000 serodiscordant couples similarly found no transmissions within these couples when the viral load of the positive partner was undetectable.(41) The collection of evidence to determine the effectiveness of test and treat interventions (i.e. in a real-world setting) in addition to the efficacy studied in randomised controlled trials is ongoing. For example, a study using the Africa Centre for Population Health's demographic and HIV surveillance programme assessed the effect of ART uptake on serodiscordant couples and at household

level in KwaZulu-Natal, South Africa.(42) It was found that the use of immediate ART was associated with a 77% reduction in HIV acquisition and the effect in households was 53%. However, another larger study in this setting, ANRS 12249 which examined the population impact of scaling up treatment as prevention found that despite increased access to testing and treatment, only half of all people diagnosed started treatment and among those that did, linkage to care often took many months, limiting any population level benefits.(43) The outcome of one of the largest studies (HPTN 071, PopART) being conducted in 21 communities across South Africa and Zambia which will measure the potential benefits of door-to-door test and treat interventions will be available soon.(44) Studies from other parts of the world include one from Canada which reviewed the impact of ART on HIV incidence and estimated that for each increase of 100 individuals on ART, the estimated incidence decreased by 1.2%, and for every 1% increase in the number of individual supressed on ART, the estimated incidence also decreased by 1%.(45) In San Francisco, Das et al. studied community viral load levels (the mean viral load in a community) and found that a reduction in the mean community viral load was significantly associated with fewer new HIV cases again suggesting that wide-spread ART in the population is likely to reduce HIV transmissions.(39) This has resulted in the latest campaign which is U=U, and denotes undetectable = untransmissible or (uninfectious).(46) Further evidence supporting this is a study conducted in a Ugandan cohort in Rakai(47) a cohort in Spain studying serodiscordant couples(48) and a multi-country study in Australia, Thailand and Brazil in 2017 named 'Opposites Attract (49).

Progress in the development of biological interventions with the availability of pre-exposure prophylaxis (PrEP) has further dramatically changed the landscape of HIV prevention. A ground-breaking trial revealed HIV negative people who take antiretrovirals (ARVs) (either daily or event-based) can reduce their chance of HIV infection to close to zero.(50-52) The randomised controlled trial by Grant et al conducted in 2010 in 2499 MSM found that, among participants with detectable study drug levels in the intervention arm and no detectable drug

levels in the control arm, the relative reduction in HIV risk was 92%.(46) This effect has also been reproduced in heterosexual populations (38)(53) and among people who inject drugs (PWIDS) (54). Further studies also examined the combined effect of TasP and PrEP strategies for mixed-status couples and found a 95% reduction in incidence relative to the estimated HIV incidence for the population in the absence of PrEP integrated into HIV treatment services.(55) Consequently, the WHO now also recommends PrEP should be offered to people considerably at risk of infection as part of a combination prevention package including regular HIV testing and other behavioural interventions.(56) Other interventions include post-exposure prophylaxis (PEP)or PEPSE (Post-exposure Prophylaxis after Sexual Exposure) which is the use of ARV shortly after a risk exposure (normally within 72 hours).However, the clinical effectiveness has not been well established thus far (ref 96 SD PhD).(57) The efficacy of PEP relies heavily on how soon after the exposure the ARVs are taken. Studies have shown that among people who use PEP effectively, the incidence of HIV can be reduced up to 83%.(58) The mechanism is the same as for PrEP in that if taken promptly it can inhibit replication of the virus to avoid permanent infection. However, the study also showed that HIV incidence among the whole study population was not significantly different to the general population leading the authors to conclude that the participants may not have always identified an exposure to have been high risk. In addition, condoms are one of the most effective ways to prevent HIV infection (can reduce incidence up to 78-85%), as well as other STIs when used correctly and consistently.(59) However, the use of condoms is influenced by the type of partnership, availability and individual personal preferences.(60) In addition, even when used correctly condoms may ‘slip off’ or break.(61) Observational studies have found that couples are unlikely to use condoms consistently over long periods of time and in some instances have found inconsistent use can in fact increase the risk of HIV acquisition.(62)

With the powerful tools of TaSP, PrEP and advances in technologies which are key to enabling prompt diagnosis such as rapid testing, home sampling and self-testing kits, there

is a move towards eliminating AIDS as a public health threat. The United Nations Programme on HIV/AIDS (UNAIDS) set ambitious global treatments targets to end the epidemic, termed 90-90-90, calling for 90% of people living with HIV to know their status, 90% of all people with diagnosed HIV to receive sustained ART and 90% of all people receiving ART to have viral suppression by 2020.(63) These targets are based on modelling work by Granich et al. which looked at a theoretical HIV test and treat strategy to eliminate HIV.(64) Granich et al. studied the long-term dynamics of a HIV epidemic using data from South Africa assuming that all transmission stemmed from heterosexual sex; he found that a fully implemented HIV test and treat strategy in 2008, such that most adults with HIV are on ART and yearly HIV testing was conducted, could reduce HIV incidence and mortality to less than 1 per 1000 per year by 2016, which was what he chose as the threshold for the elimination for HIV. Further he found that this strategy could reduce the prevalence of HIV to less than 1% within 50 years from the assumed 11% at baseline. The end of AIDS is defined as low HIV incidence and AIDS-related mortality which to achieve globally will require a close to doubling in the number of people on treatment.(65) HIV eradication is not considered possible in the absence of a vaccine or a cure in addition to the available treatment.

To measure progress towards the 90-90-90 targets, countries as well as cities are producing HIV care cascades which start with an estimate of the number of people of living with HIV and the fraction of those diagnosed, and explores among those diagnosed how many are linked to care and receiving ART and the proportion that are virally supressed.(66, 67) The 90-90-90 targets are equivalent to 86% of all people living with HIV being on ART and 73% having undetectable viral load. An example of this from the US in 2014 (estimates published in 2017) is that there were an estimated 1.1 million people living with HIV, 85% were diagnosed, 62% were receiving care and 49% were virally supressed which is quite a way off the UNAIDS target.(68) In 2016, 18 of 28 EU countries were able to report data on all four stages of the continuum of care, with the most difficult part estimating the number of people

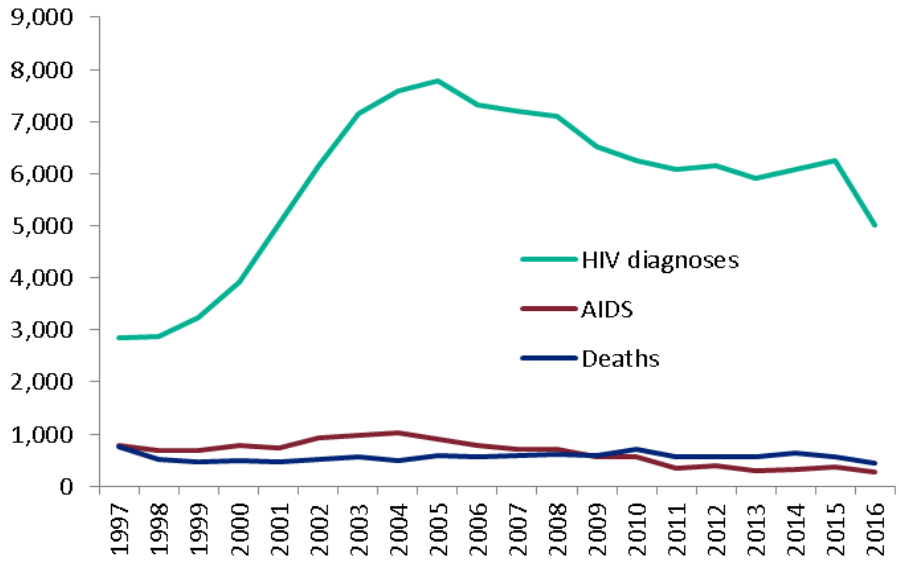
living with HIV as the undiagnosed fraction needs to be known.(69) As countries have different health and data capturing systems, there are limitations as to which modelling tools they are able to use to conduct these estimations. For the countries that were able to do this, on average 17% of people were undiagnosed ranging from 2-43%.(69) Data from South Africa show that an estimated 86% of people living with HIV had been diagnosed and 59% were receiving ART and of those 78% virally supressed.(70) As South Africa has the largest HIV epidemic in the world, this translates into very large numbers of people undiagnosed, and not virally supressed. By mid-2015, it was estimated that 3.4 million people were on ART which was equivalent to just under half of the HIV positive population.(70)

2.2 HIV in the UK

As in the US, the first case of HIV documented in the UK was in 1981, with further cases of immune deficiency identified mostly in gay men and then in people who injected drugs (PWIDs) and haemophiliacs.(71) Subsequently, the national public surveillance of AIDS was initiated followed by the surveillance of HIV infections as HIV antibody testing became available in 1985.(72) By 1985, through reports received by the Public Health Laboratory Service (PHLS), there had been 2,935 HIV diagnoses.(11) The number of AIDS diagnoses and AIDS-related death reports following increased and peaked shortly before the introduction of ART in 1995 to 1,872 AIDS diagnoses in 1994 and 1,723 AIDS-related deaths in 1995.(11) In the ART era, the annual number of reported AIDS cases and deaths declined to less than 1000 per year and has remained stable since 1998. In contrast, the number of HIV diagnoses increased year on year from this point forward and peaked in 2005 with 7,871 new diagnoses, (Figure 1.) after which there was a steady decline until 2015 when a big drop was noted.(1) Examining the rates of new diagnoses by subpopulations revealed the early increase in new diagnoses was predominantly due to an increase in diagnoses in gay men, which was followed by an increase in heterosexuals, likely to have been due to an

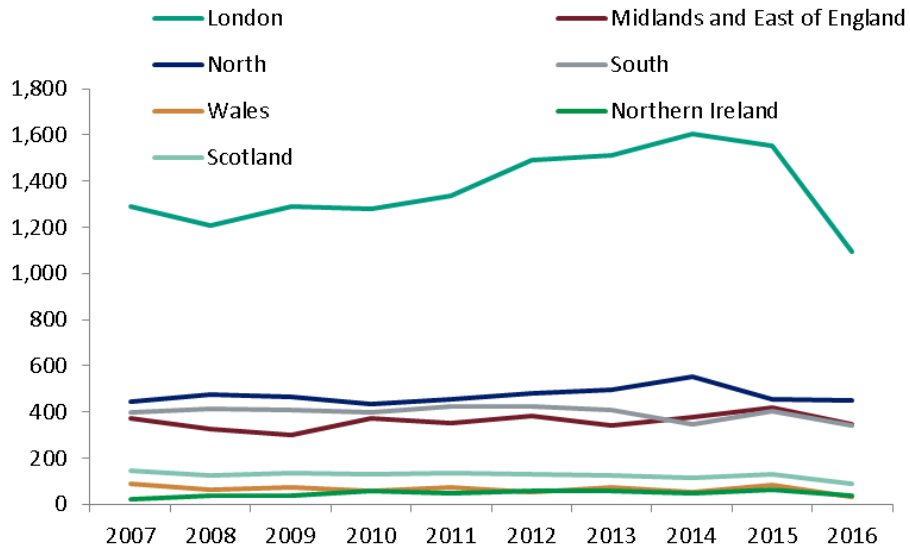
increase in diagnoses in heterosexuals who had acquired their infection abroad, in particular in Sub-Saharan Africa.(5, 11-13, 73) As such, the two key population groups affected by the epidemic in the UK were MSM and black African heterosexuals. The annual increase in new HIV diagnoses in heterosexuals was sustained until 2005, after which there was a steady decline. The changes have again largely been explained by changes in migration patterns from Sub-Saharan African countries. The large drop in new diagnoses from 2015 was observed in MSM, particularly in London (Figure 2). This was the first decline in new diagnoses in gay men since the start of the epidemic, reducing from 3,570 in 2015 to 2,810 in 2016. This decline is thought to be due to reduced transmission brought about by increased levels of testing and accelerated initiation of ART at diagnosis.(1, 4)

Figure 1 Number of people diagnosed with HIV and AIDS, and all-cause deaths among people with HIV in the ART era: UK 1997-2016



Source: Towards elimination of HIV transmission, AIDS and HIV-related deaths in the UK, November 2017, *Public Health England*(1)

Figure 2 Geographical trends of new HIV diagnoses among gay and bisexual men: UK 2007-2016



Source: Towards elimination of HIV transmission, AIDS and HIV-related deaths in the UK, November 2017, *Public Health England*(1)

Overall the UK has made excellent progress towards the UNAIDS 90-90-90 targets; in 2017, these were met with 92% of the estimated 101,600 people living with HIV diagnosed, 98% of diagnosed people receiving treatment and 97% of people receiving treatment virally supressed.(74) This translates in overall 87% of people living with HIV in the UK having an undetectable viral load, likely contributing greatly to the decline in diagnoses observed in recent years. The total number of undiagnosed cases has been declining over the previous decade from an estimated 22,200 in 2009 (75) to 7800 (Crl 5600-12,600) in 2017(76).The highest number of undiagnosed infections in 2017 remained in MSM, with 4,200 cases of an estimated total of 48,900.(76) To note is during the period of study in this thesis (2009-2013) the British HIV Association (BHIVA) guidelines were to initiate patients on ARVs once CD4 cell counts were below 350 cells/mm^3.(77) This was updated in 2012 to start ARVs once CD4 counts dropped below 500 cells/mm^3 (78) and only in 2015 were the guidelines changed to start everyone on treatment after diagnosis.(79) In 2013, although not published

as such in PHE's HIV annual report, data from the report show that the treatment cascade was such that there were an estimated 98,400 people living with HIV of which 77% were diagnosed (76, 500).(80) Among those with a CD4 count <350 cells/mm^3, ART coverage was high at 89%. Overall, it was estimated that 48% of the population living with HIV had an undetectable viral load.

2.3 Estimating HIV incidence

Despite the recent reduction in the number of new HIV diagnoses in the UK, a major challenge remains understanding the epidemic in real-time with respect to the number of new infections, the most valuable measure for describing the current state of the epidemic and for understanding the impact of preventive interventions. Important is the difference between prevalence and incidence how and how these relate to each other with regards to HIV. Prevalence is the proportion of the population found to have a particular condition, or in this case HIV infection.(81) It is used to describe the burden of infection and inform the level of HIV care needed. Incidence represents the number of new cases developing over a set period of time and indicates the level of risk within a population.(81) HIV prevalence and incidence are related to each other in that the higher the prevalence within a population, the higher the risk of new cases being generated in the absence of any interventions. Differences between prevalence estimates can be used to estimate HIV incidence, which I describe later in this section.

Another important concept for disease transmission is the basic reproduction number R0 which denotes the number of secondary infections generated from a primary infection.(82) If R0 < 1each individual produces on average less than one new infected individual. If R0>1 then each individual produces more than one new infection and the infection spreads within the susceptible population. Estimating R0 for HIV is challenging due to the different levels of infectiousness at various stages of infection; for example primary and late-stage infection

have been estimated to be 27 and 7 times more infectious than asymptomatic infection.(83) The primary infection was estimated to last 3 months post after seroconversion and the late stage infection between 19 and 10 months before death. In the absence of any intervention, the asymptomatic stage of infection would contribute the most number of new infections due to the length of this period (up to 10 years). Widespread use of ARVs and implementation of test and treat policies have further implications for R0 by reducing infectivity and the size of the susceptible population and point towards those with undiagnosed primary infection having a larger role in sustaining the epidemic and contributing to new infections.(84)

Importantly, HIV incidence is not to be confused with HIV diagnoses as people newly diagnosed may have been infected for a number of years. Interpreting the number of new diagnoses is difficult against a backdrop of differing testing frequencies within population subgroups and unknown durations of infection at the time of diagnosis. A variety of methodological approaches to estimate HIV incidence have been and are continuing to be developed with the availability of new data sources. These include cohort studies, mathematical modelling methods, particularly those using serial prevalence survey data, back calculation methods, dynamic models, molecular genotyping methods, and laboratory-based testing algorithms. The following sections provide a brief description of each of these, highlighting some of their strengths and limitations.

2.3.1 Prospective cohort studies – the "gold standard"

Prospective cohort studies, also referred to as longitudinal studies, have historically been regarded as the 'gold standard' for determining the HIV incidence. They are a direct measurement of the rate of new infections involving regular follow up of a group of susceptible people over time to measure the rate of infection acquisition in this closely defined population. The timing of new infections is usually estimated as the midpoint of the last negative and first positive HIV test, which are conducted at regular intervals, with

incidence measured by dividing the number of new infections by the number of person years (pys) followed up. With follow up over time, this method enables the measurement of risk factors for infection. For this approach to be feasible and affordable, a large number of expected new infections is required. This may be the case in countries with generalised epidemics (defined as a prevalence consistently over 5% in at least one sub-population and over 1% in pregnant women in urban areas(85)).(86-88) As most western countries have low level or concentrated epidemics (where the prevalence of infection has not consistently exceeded 1% in the general population nationally or 5% in any subpopulation), prospective cohort studies are inappropriate due to the large sample sizes required to obtain meaningful, robust estimates, which would be costly and require vast amounts of time and resources. Often, even with large sample sizes, these kinds of studies have limited generalisability as participants are unlikely to be representative of the population of interest. In addition, for ethical reasons, participants are usually enrolled in counselling sessions for HIV prevention and risk reduction which can result in behaviour change, thereby further undermining the validity of such a study.

2.3.2 Mathematical modelling

Attempts have been made to indirectly estimate HIV incidence using a range of mathematical modelling techniques. For some of these models, tools have been made available for countries to use.(89-91) These methods are usually based on data originally collected for other purposes and are therefore a lot less costly. Some methods, such as those using serial prevalence surveys, are based on data from country-wide, cross-sectional surveys more commonly conducted in Sub-Saharan African countries.(92-94) Others are based on case-based surveillance data, also referred to as case-reporting data (reports of new HIV diagnoses)(95-99); the WHO Working Group on HIV Incidence Assays has recently collated and published current available HIV incidence estimation methods, including the

data requirements, assumptions and existing tools and outputs.(100) The following section provides a brief description of the model types and the data used.

Estimating incidence from prevalence

HIV incidence can be estimated indirectly from serial, cross-sectional, HIV prevalence surveys. This is also more commonly used in countries with generalised epidemics as these types of surveys are often only conducted in such settings (93, 94, 101). The basic principles of this approach is to examine the difference in prevalence between surveys and assume that any observed difference will be due to the number of new infections acquired in the between period.(93, 102) This methodology requires data available on rates of migration and deaths in the population infected with HIV.

The changes in the prevalence from one survey to the next can be described by the following equation (103):

(1) $$P_2 = P_1 + I - d + r - s$$

where

P_1 is the prevalence at time 1

P_2 is the prevalence at time 2,

I is the number of incident infections,

d is the number of deaths,

r is the number of people migrating into the population, and

s the number of people leaving.

Therefore estimating incidence from two prevalence surveys can be expressed as:

(2) $$I = P_2 - P_1 + d - r + s$$

However, there are circumstances when changes or the absence of changes in prevalence are not reflective of any changes in incidence; for example if the prevalence remains stable during two time points due to higher death or emigration rates rather than incidence. Methods developed by Hallett et al. for estimating incidence from prevalence surveys account for changes in survival rates among those with an infection, and changes in mortality rates both in those infected and those not.(93) They estimated the contributions to prevalence made by i.) deaths from AIDS and other causes and ii.) survival rates post infection, and were able to accurately estimate age-specific HIV incidence in areas where ART was less common. However, with the current WHO-recommended test and treat strategy, such settings are diminishing, limiting the applicability of this method. In addition, as with cohort studies, this method also rarely allows for timely estimates as serial population-based prevalence surveys are usually carried out with wide time intervals, e.g. every 5 years.

UNAIDS supported software, Spectrum (Avenir Health, Glastonbury, CT, USA) and the Estimates Projection Package (EPP) (East-West Centre) is used by national programmes, UNAIDS and the WHO to generate key HIV indicators for over 160 countries including HIV incidence.(89-91) The EPP model estimates incidence from prevalence trends and is able to use a combination of case-based surveillance and national prevalence survey data.(89, 90) Prevalence data can be inserted into the model which uses maximum likelihood and Bayesian techniques to estimate incidence and the level of uncertainty around the estimate. An epidemic curve is subsequently fitted to the prevalence data applying the structure of the age and sex distribution in the population and mortality rates to these estimates alongside other assumptions on the effects of HIV on fertility and rates of mother-to-child-transmission (MTCT). The parameters taken into account for the fitting include the proportion of the population at risk of infection at the outset, the rate of epidemic growth and the year the epidemic began in the country of study.(104) The model is updated regularly; some of the latest features are being able to take into account the number of people receiving ART.(105)

This is done by incorporating information from reference groups, allowing consideration for the number of people eligible and receiving treatment and a modelled effect on survival and new infections. Furthermore, information on serological HIV incidence assays can be incorporated; as different incidence patterns are able to generate similar prevalence patterns over the course of an epidemic, these data can refine the likely incidence pattern.(91, 106)

In addition to serial cross-sectional prevalence surveys, it is possible to estimate HIV incidence from a single age-specific cross-sectional survey. The basic principle of this is based on examining the prevalence of HIV in the youngest age group where the duration of risk exposure and the rate of deaths are lowest.(107) In this age group, prevalence is assumed to be equivalent to incidence.

Another approach uses the mode of transmission (MOT) model.(108, 109) This model is based on information on the patterns of risk behaviours within defined population groups, for example the number of sexual partners and the level of condom use, and combines it with information on the sizes of the populations at risk and the current HIV prevalence within the group. The combined information is used to determine an expected number of new infections over a defined period (usually a year) by using probabilities of HIV transmission per exposure act and considering factors that may affect these probabilities such as co-infections and sero-positioning. This method has many limitations with a major one the assumption that HIV acquisition risk within the subpopulation of study is the same for all individuals. In addition, the robustness of the estimates for the HIV transmission probabilities of various acts may be questionable as these are likely to vary over time and in different settings.

Lastly, simulation models can be used; Phillips et al. employed a dynamic, individual-based stochastic computer simulation model reconstructing sexual behaviour, HIV transmission, HIV progression and the effect of ART for UK MSM over 30 years between 1980 and

2010.(96, 110) Like a MOT model, this relied on numerous assumptions on trends in sexual behaviours and the probability of HIV transmission with each risk act. For example, Phillips et al. assumed all transmission stemmed from unprotected anal intercourse (UAI) and modelled risk behaviour based on the number of short and long term partners taking into account age, partner mixing, HIV prevalence and changes over time. Multiple data sources were used for this model including PHE's HIV surveillance data, data from the National Survey of Sexual Attitudes and Lifestyles (NATSAL) and other behavioural studies in UK MSM.

Back-calculation methods

Countries with strong case-based surveillance systems also often do not undertake national prevalence surveys. In these settings, approaches to estimate HIV incidence have more commonly been based on data routinely collected with diagnosis reports. Examples are back-calculation models using any available information on the disease stage at the time of diagnosis to reconstruct trends in HIV infections during previous years. In the pre-ART period, these were based on the incidence of AIDS using the AIDS incubation period assuming that the incidence of AIDS reflected the incidence of HIV approximately a decade earlier.(99, 103, 111-114) As ART became more prevalent, uncertainty around the time from infection to disease increased and these models became less relevant. Consequently information on new HIV diagnoses was used.(115, 116) For example Ndawinz et al. used data on symptoms of primary (early) HIV infection (PHI) and symptoms of AIDS.(97) By exposure category, in his case non-French heterosexual men and women and French heterosexual men and women, individuals diagnosed with a PHI and with an AIDS-defining illness, and the remaining were grouped separately. Infection duration was assumed for each group: three months for those with PHI, 10 years for those with AIDS and for all in-between maximum likelihood techniques were used to estimate the distribution of both pre-AIDS testing and the number of undiagnosed infections. With the group specific estimates for the distribution of time since infection and the number of new infections, the overall

distribution of time since infection was calculated and HIV incidence estimated by dividing the number of infections in a given period by the number individuals at risk. Whilst this method is able to account for changes in test seeking behaviours overtime, it assumes all infections to have been acquired within the country, likely inflating national estimates.

The back calculation method most recently applied in the UK is based on CD4 cell count at diagnosis(1, 5, 95), which in the absence of treatment gradually declines over time to very low levels reflecting deterioration of the immune system.(117-121) The model is based on data from people newly diagnosed with HIV and uses information on the level of CD4 at diagnosis and the rates of progression between CD4 stages. These data (the rates of progression between disease stages) are from the Concerted Action on SeroConversion to AIDS and Deaths in Europe (CASCADE) cohort(122)). The probabilities of a diagnosis at each of these stages is allowed to change due to immune system decline and the likelihood of testing over time increasing. This method has also been applied in other countries. (123, 124) In fact the European Centre for Disease Control (ECDC) has recently made available a free tool which countries can use based on this method.(125)

Whilst this method is considered robust for estimating incidence in the MSM population in the UK(1), to date, it has not been used for any other population groups, because, like Ndawinz's and other back calculation models, it cannot account for infections acquired abroad. In the UK, MSM are believed to have lower rates of migration than other key risk groups.

Other similar back calculation models currently in use are the Bayesian-based hierarchical model and the CD4 depletion-based model in the US,(100, 124) and the Ottawa/Sydney model in Australia and Canada (126, 127). Whilst these models are continuously being developed and improved, with the incorporation of additional data sources, a major limitation remains in that the variance around estimates for the most recent years tend to be wide, hindering the ability to observe any change in incidence in a timely manner.

2.3.3 Molecular and gene sequencing methods

Molecular and gene sequencing techniques have been explored as an alternative approach to estimate the time from HIV infection to diagnosis and thus incidence. In general, the genetic diversity of the virus is used as an indicator for the length of infection, with increasing diversification over time.(128-130) Sanger sequencing methods have been used to study the fraction of polymorphic nucleotides in partial HIV-1 pol genes and this has further been developed into a range of methods to measure this diversity such as Hamming Distance(128) and high-resolution melting (HRM)(129). More recently, next-generation sequencing (NGS) has been explored involving whole genome sequencing. This has shown that sequence diversity grows approximately linearly with time during the initial eight years of infection.(131)

These methods are however still in early stages of development and require validation studies to determine the extent of applicability. For example, if multiple founder viruses with high levels of diversification are present, determining time since infection can be problematic as these may erroneously be classified as chronic infections.(128) Misleading results can also be generated from low level virus; these may include elite controllers (people who naturally are able to maintain low (often undetectable) viral loads and high CD4 counts in the absence of ART).(131) To date, the test properties of these methods necessary for population-based incidence estimation haven't been established.(131) These include the mean duration of recent infection (MDRI) and the FRR, explained in detail in the next section on serological incidence assays. Finally, performing these techniques on a large scale is likely to be expensive.

2.3.4 Serological incidence assays

A promising, relatively cheap method, and the central topic of this thesis, is the use of serological incidence assays which have been in development for over two decades.(9) These assays distinguish long-standing from likely recently acquired infections based on the maturation of the HIV-1 antibody response and, depending on the type, measure HIV-specific antibody titres or antibody-antigen bond strengths, both of which increase over time. To achieve the best interpretation of these data, results are considered alongside other clinical markers for disease progression, such as CD4 cell count, viral load, symptoms of an AIDS-defining illness as well as ARV use. The combination of assay results with the clinical information is termed the Recent Infection Testing Algorithm (RITA).(7)

In the past, there was little data on the performance characteristics of these assays. This was with respect to any variation by demographic characteristics such as age, ethnicity, sex, comorbidities and pregnancy status as well as infection characteristics such as HIV subtype and viral load, the latter often an indicator for exposure to ARVs. Variation in assay results can also occur between laboratories for which quality assurance schemes have been developed to enable standardised performance (personal communication Gary Murphy). Consequently, over time, different testing algorithms have been used and different information has been incorporated into the algorithm guided by the best evidence at the time and data available in surveillance systems.(132-137). In some instances, multi-assay algorithms were used, combining the results of two different types of assays.(138, 139) More recently, a Bill and Melinda Gates funded initiative, the Consortium for the Evaluation and Performance of HIV Incidence Assays (CEPHIA) has undertaken an extensive review of a range of assays.(140, 141) CEPHIA is a collaboration of microbiologists and statisticians from PHE, the Blood Systems Research Institute in San Francisco, the University of California, San Francisco and the South African Centre for Epidemiological Modelling and Analysis. This group collated a repository of 2,500 well characterised, diverse specimens

from many parts of the world to evaluate the variation in key parameters of the assay. With better data on these parameters and RITA algorithms, it is possible to apply a RITA to new diagnoses of HIV to determine the proportion with likely recent infection. Further, incorporating these results into mathematical models enables estimating population-based HIV incidence in real time.

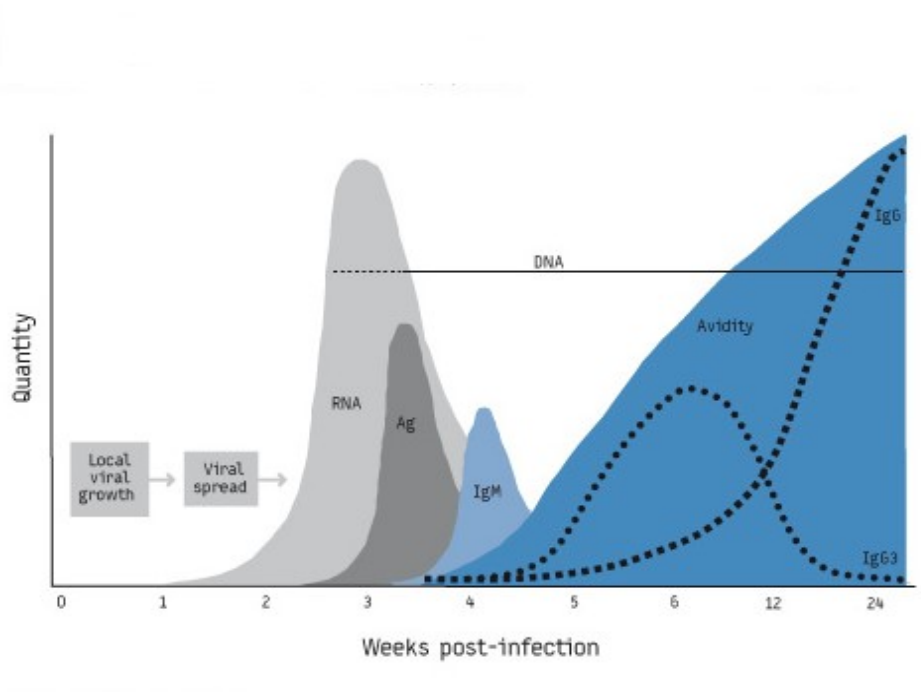
Initially, RITA was commonly applied to new HIV diagnoses identified through cross-sectional surveys which are based on a representative sample of people selected from the population of study at a specified time point, and include both HIV positive and negative individuals.(7, 138, 142-144) More recently, RITA has been applied to case-based HIV surveillance data, where recent infection cases are treated as a sample of incident infections and weighted, using methods developed by Karon et al. to estimate overall HIV incidence.(145, 146) Detailed guidance has been developed by the UNAIDS/WHO Working Group on Global HIV/AIDS and STI Surveillance on how to apply RITA to cross-sectional survey data, particularly those collected routinely in developing countries such as household surveys.(7) I describe Karon et al.'s method in detail in Chapter 3, which in addition to weighting accounts for missing data and differences in HIV testing patterns in the population, using this to determine the likelihood of persons being diagnosed with recent infection.

An additional potential benefit of using RITAs is, unlike with back-calculation methods, that incident infections are identified at the individual level using a single sample. This information could be extremely valuable in identifying populations at highest risk of infection enabling a more targeted approach for intervention efforts. There may also be a role for these data in the clinical setting in prioritising contact tracing efforts in those with a shorter period of infection and better recall of exposed partners.(147)

2.3.4.1 Laboratory aspects

Murphy et al. has summarised the key virological and serological events following a HIV infection.(148) In the first two to three weeks of infection, a high titre of viraemia is produced through replication of the virus. (Figure 3). Viral ribonucleic acid (RNA) is present before detectable HIV antibodies. This can be used as a marker for very recent, acute HIV infection, however it only provides a short window of opportunity for detection.

Figure 3 Key viral and serological markers following infection with HIV-1*,**



*Viral markers: RNA, Ribonucleic acid; DNA, deoxyribonucleic acid: Ag, Antigen. Immunological markers: IgM/IgG, Immunoglobin M/G antibodies. **Source: Murphy et al. *Eurosurveillance* 2008 (148)

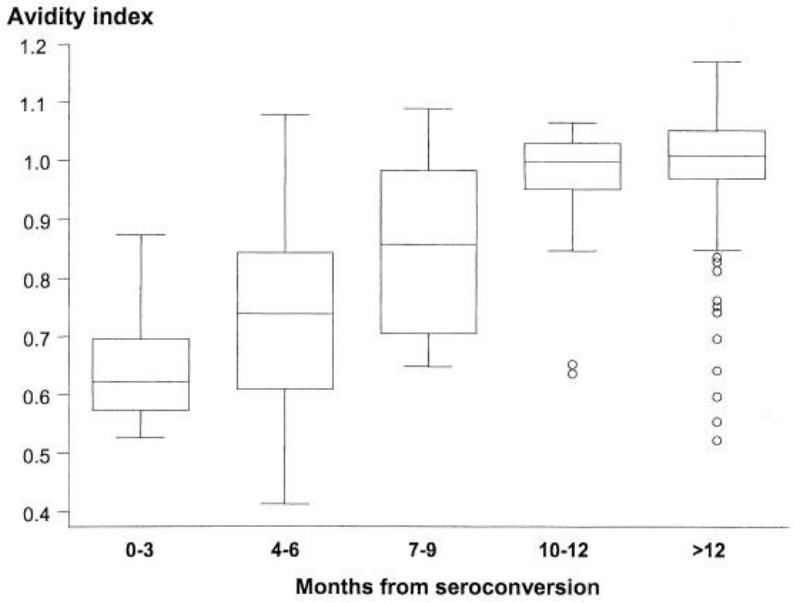
With the initiation of an immune response and the production of HIV antibody, the amount of viraemia and antigen (a surface protein of the virus) reduces. HIV antibody titre increases; this measure was used for the 'detuned' and 'BED' assays.(148) (Detuned assays were modified commercial assays with the base assay withdrawn in 2003. The BED capture enzyme immunoassay (BED-CEIA) was used in the US and a number of other countries until recently.) Avidity-based assays measure the avidity of antibodies (the strength of the antibody antigen binding) which is lower during the initial stages of infection (used in the UK;

Abbott AxSym HIV 1/2 from 2009-2013, Limiting Antigen (SEDIA) from 2013 onwards). Specifically, it is a measure of the strength of binding between immunoglobulin G antibodies and the corresponding antigen.(149) In France, IDE-V3 EIA was used which is an in-house developed assay, based on the presence of two glycol-proteins that induce antibody responses (gp41 &gp120).(148, 150). Similarly the antibody response to other specific antigens can be measured such as the IgG3 Isotype assay and the INNO-LIA HIV I/II score.(151)

To classify recent infection, dependant on the biological marker, an optical threshold is derived referred to as the Optical Density (OD) where results below this threshold are recent infections. This is based on the biomarkers and the immune response, denoting the point at which an individual is no longer recently infected.(148) As the antibody response varies between individuals, the rate at which people cross this threshold also varies considerably. The average duration an individual remains below the threshold is termed the mean window period or MDRI (used interchangeably).

For the AxSym avidity assay, which is based on measuring the strength of the HIV antibody-antigen bond, a sample is treated with a chaotropic agent (e.g. Guanidine) to disrupt the hydrogen bonds and consequently obstruct the antigen-antibody bonds. The calculation of the avidity index is used to denote the threshold for recent versus a longstanding infection. The avidity index is a ratio of the signal cut offs (S/CO) of the Guanidine and phosphate buffered saline aliquots. The avidity index was studied by Suligoi et al. who showed the relation between avidity index scores with time since infection among 216 specimens from 46 HIV positive people with known seroconversion dates (Figure 4).(152)

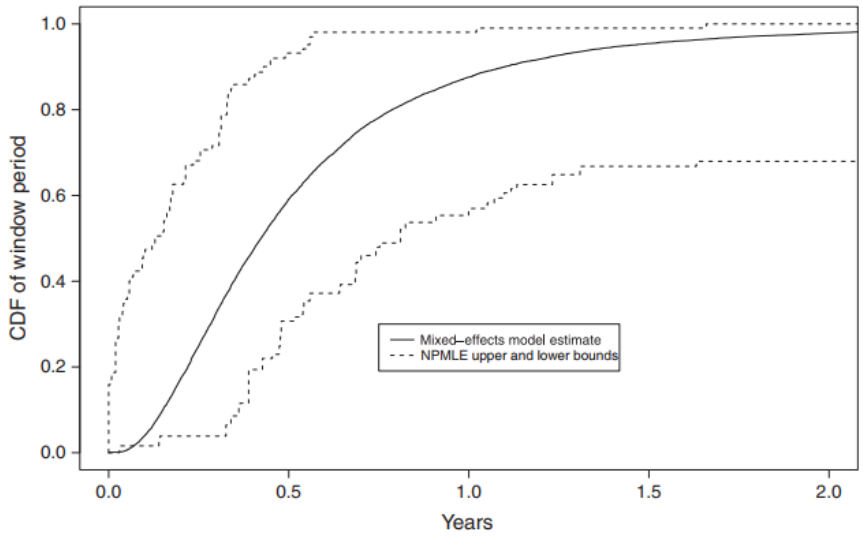
Figure 4 Avidity index score by time since seroconversion*



*Source: Suligoi et al. *Journal of Clinical Microbiology* 2002(152)

The box and whisker plots (denoting the median and interquartile range (IQR)) showed that in the first year, there was a clear increase in the avidity index which levelled off at 12 months. Sweeting el al. estimated the distribution of the window period of the AxSym avidity assay among a cohort of seroconverters in addition to the MDRI.(153) This was based on 103 people who seroconverted with known seroconversion dates and more than one avidity index result available. Figure 5 illustrates the cumulative distribution of the window period for with an avidity index score<80%.

Figure 5 Cumulative distribution function of window period for the AxSym avidity assay for an avidity index threshold of 0.8*



* Source: Sweeting et al. *Statistics in Medicine* 2010 (153)

It is worth noting that all assays have been shown to be sensitive to i) severe immune suppression from advanced disease, ii) ARV use, iii) elite controllers with naturally highly suppressed viral load, iv) co-infections, v) HIV subtype and vi) possibly pregnancy, potentially indicating a recent infection result for established, chronic infections. The CEPHIA group published their first assessment of five assays in 2014 which included the BED assay, Limiting Antigen (LAg) Avidity, Less-sensitive Vitros, Vitros Avidity and BioRad Avidity.(141) This review examined in particular the the MDRI and the FRR. The MDRI was defined as "*the average time spent alive and recently infected, while infected for less than some time cut-off, T*." The FRR was defined as "*the probability that a randomly chosen patient, infected for longer than T, will produce a recent result.*"(141) A Target Product Profile was defined with ideal assay characteristics specified to be an MDRI of one year and the FRR <2%. (7, 141) They found the LAg (Sedia Biosciences Corporation, Portland, Oregon, USA) to have an estimated MDRI of 188 days (95% C.I. 165-211) and the remaining assays between 258-333 days. The FRR ranged between 1.3% (95% C.I. 0.3-3.2) for the LAg and 9.7% (95%C.I. 6.6%-13.5%) for the LS-Vitros Assay and reduced with time since infection. The FRR for elite controllers ranged between 12.9% (95% C.I 3.6 -29.8) for the LAg and BioRad

Avidity and 48.4% (95% C.I. 30.2-66.9) for the LS-Vitros Assay. Extremely high FRR results were observed for ARV-treated patients for all assays ranging from 50.0% (95% C.I. 40.4-59.6) for the BioRad Assay to 76.1% (95% C.I.67.2-83.6) for the LS-Vitros. The assays were also sensitive to low viral load as it evokes a lesser immune response and the production of fewer antibodies, with the FRR having ranged between 40.6% to 68.5%. This was however not the case for low CD4 cell count defined as CD4 cell count<200cells/mm^3, where the FRR was 0.0% for the LAg and Vitros Avidity assay. Since then, some of these estimates have been recalibrated recommending the use of an normalised OD (ODn) of 1.5 for the LAg with a corresponding MDRI of 130 days (95% C.I.118-142).(154) Unfortunately, the assay used at PHE from 2009-2013, the AxSym avidity assay, was not reviewed by CEPHIA as it was due to be no longer commercially available. Therefore, the key characteristics (MDRI and FRR) have been examined as part of this thesis (see section 4.4). From the literature, FRRs were estimated to be between 3-10% in some settings depending on the population.(132, 155)

2.3.4.2 Epidemiological and logistical considerations

In countries with sophisticated HIV case reporting systems that routinely collect data from a range of settings e.g. GUM clinics, HIV clinics, primary care facilities and hospitals, it is desirable to apply RITA to these already available data. Higher risk individuals are more likely to be engaged in healthcare and frequent specialised services and therefore generate a higher number of reports from these settings, whereas the generalised services are more likely to report cases from individuals not or before accessing specialised care, and therefore more likely to include diagnoses of advanced stage disease and symptomatic cases.
Applying RITA to case-based surveillance data has the advantages of:

- data being collected at national level which can be analysed to regional and local levels
- big sample sizes

- linkage to other routinely collected epidemiological data
- real- time, ongoing data collection
- cost-effectiveness (as no additional data need to be collected)

Data requirements, other than the information for the RITA algorithm (CD4 count, treatment status, information on an AIDS defining illness and viral load), include the number of new HIV diagnoses reported per year stratified by risk group, and individual level information on HIV testing history. Other useful data are information on HIV subtype, symptoms of seroconversion (which could aid in validating assay results) and reason or motivation for testing, (which could assist in calibrating incidence estimates at a later stage as people who test due to symptoms or a high risk exposure are more likely to be diagnosed with a recent infection, potentially inflating incidence estimates).(156)

A number of research studies in the UK are able to provide further epidemiological context to findings on HIV incidence based on surveillance data. Since 1990, approximately every 10 years, NATSAL has been conducted which is a probability sample survey of the general population in Britain on sexual behaviours.(157-161) It included 2,110 adults aged 16-44 years in 2000 and 15,000 adults aged 16-74 years in 2010. The survey also collected biological samples (urine and saliva) among a subset and thus has population-based estimates for the prevalence of range of sexually transmitted infections (STIs) including *Chlamydia trachomatis*, Human Papillomavirus, *Neisseria gonorrhoeae*, *Mycoplasma genitalium* and HIV.(158) Importantly, the survey is the largest in the UK that collects data on sexual orientation enabling estimating the size of the MSM population. Another source for country demographic data including information on gender and age which will allow determining population-based incidence rates, is the Office for National Statistics (ONS) which conducts a census every ten years.(162) In addition, there are a number of smaller community surveys that concentrate on key populations and report data on sexual behaviours and HIV testing patterns.(163-167)

Crucial for the application of RITA to case-based surveillance data for HIV incidence estimation is that the surveillance data are complete and represent the diagnosed population. In the UK, HIV reporting is voluntary. Incomplete data can stem from underreporting, reporting delays and substandard data quality. Often, where it is apparent that data are missing, particularly concerning key variables, attempts are made by the HIV and AIDS Reporting Section at PHE to obtain these through follow up. However, with the availability of multiple, distinct monitoring systems, and observing trends in data submissions over time, any underreporting of new diagnoses is likely to be negligible.

Where numerous surveillance systems need to be linked to obtain the required variables, ethical aspects of linking must be considered. Caution is needed not to potentially generate patient identifiable data through deductive disclosure. PHE's HIV surveillance systems collect patient level data although all reports are anonymised. Variables collected include information on age, ethnicity, sexual orientation, date of diagnosis, place of diagnosis, test results and treatment type (see section 3.1 for more detail on datasets). Data are pseudo-anonymised using a soundex code which comprises of the initial of the surname and three numbers.(168) This information is used to carefully link across datasets from different systems ensuring no possible deductive disclosure. It is recommended not to publish information on events with counts where the numerator is less than 3 depending on which other demographic data are presented.(169)

Incidence estimates and the variance around the estimates are affected by the sample size. The use of case-based surveillance data will restrict the sample size to the number of diagnosis reports for a given period. For cross-sectional studies the CEPHIA group have provided tools for countries to use to determine necessary sample sizes to observe a change in incidence of a specified magnitude to a selected level of power, and reversely, the magnitude of the change in incidence required to determine a statistically significant

difference over two time points.(170) For the survey sample approach, the CDC have provided guidance on the minimum number of new HIV and recent infection diagnoses needed to obtain stable incidence estimates for a population (see section 3.6). These must be considered in particular when creating strata for estimates in sub-populations.

2.4 Controlling HIV transmission: using RITA for active case finding

Aside from estimating HIV incidence, as RITA is able to identify incident HIV infections at the individual level, conventional outbreak control methods such as active case finding could become applicable to HIV. There may be an opportunity to determine clusters of new infection which could highlight new risk behaviours and better inform better targeting of interventions to prevent onward transmission. Thus, I review how outbreak investigations and case finding activities including partner notification (PN) for HIV have been conducted to date, and the potential value RITA information may add.

2.4.1 Outbreak investigations for HIV

The strict definition of an infectious disease cluster is the identification of two or more cases which are linked in time and place.(171) A cluster may be referred to as an outbreak if it is sufficiently large and or above expected numbers. ‘Outbreaks’ for HIV as such have historically not been identifiable, at least not in a timely manner due to the asymptomatic nature of infection, wide and irregular testing intervals among people affected and lacking laboratory technologies. Approaches for determining HIV infection clusters to date have mainly been based on the application of gene sequencing technologies and phylogentics (the study of relationships between groups of genes among different virus strains to determine their evolution(172)) in often among smaller, tightly networked communities.(173) An example of such a study is one by Mascolini et al., who conducted a phylogenetic analysis of samples from black MSM aged 16-29 years in Chicago recruited to a longitudinal

study which examined which men had high connectivity to transmission clusters.(174) They analysed the HIV-1 pol sequences from viral samples and defined transmission between men to be sequences that were less than 1.5% genetically distant from another. They also explored risk factors associated with being in a cluster and found these to be being bisexual (versus gay) identity, suffering from depression and use of marijuana. Another such study in Glasgow used a phylogenetic analysis to investigate whether a surge in HIV diagnoses among PWIDs in 2015 were linked.(175) They found the outbreak divided into three subclusters, two of which illustrated rapid and recent transmission events. A study in the US reported on how the use of phylogenetics led to active case finding and the implementation of control measures; in Indiana between November 2014 and November 2015, among 181 newly diagnosed HIV patients, 157 had HIV type 1 pol gene sequences which were highly related.(176) The majority of these patients had reported injecting opioid oxymorphone and over 90% were infected with hepatitis C. Contact tracing in these patients led to 486 of 536 contacts having been followed up and tested for HIV. In response to this investigation, a public health emergency was declared and a needle-syringe exchange programme introduced.

Phylogentic analyses in general are driving forward the concept of monitoring transmission dynamics in real time.(177) The first application of an automated phylogenetic system monitoring a clinical database to detect an HIV outbreak was implemented in British Columbia in 2014.(178) This entailed the daily addition of new HIV genotypes to a drug treatment database which automatically conducted reanalyses of the entire database. The system detected the expansion of a cluster of cases with transmitted drug resistance which was followed up; all had already been linked to care and five had started treatment.

There are many limitations of using phylogenetics most of which have been described in section 2.3.3. In the last example, the outbreak was only identified due to transmission of

drug resistant strains. Further, scalability and cost may be barriers for a wider application of this method.

Historically, infectious disease outbreaks have more often been described for STIs such as Lymphogranuloma Venereum (LGV) (a bacterial infection caused by serovars of *Chlamydia trachomatis*).(179) Increasing numbers and clusters of LGV cases have been reported in Europe since 2003, which were described as outbreaks.(180, 181). In response to outbreaks in the UK, PHE introduced enhanced surveillance of LGV (182, 183), whereby laboratory testing referrals and outbreak investigation questionnaires were implemented. Outcomes of these activities included the revelation that the majority of diagnosed cases were acquired at sex parties among HIV positive people, often co-infected with hepatitis C. This information led to the development of health promotion interventions in gay venues and clinics by public health professionals and the Terrence Higgins Trust (THT).(184, 185) Similarly, gonorrhoea outbreaks have been reported in the UK, particularly among teenagers.(186) Clusters of infection were identified, ranging from two to 13, using network analysis with additional information obtained through the enhanced surveillance activities. In response to this, public health action was carried out with awareness and testing campaigns targeted towards this population, increasing testing outside sexual health clinic settings and dual chlamydia and gonorrhoea testing. More recently, these outbreaks have been of high level azithromycin resistant gonorrhoea; in 2016, 17 cases were diagnosed compared to 15 the year before.(187) Investigations showed initial outbreak cases were in Leeds among heterosexuals under 20 years of age, however more recently the cases have been mixed in terms of age and sexual orientation. The first documented case of treatment failure to both antibiotics indicated for gonorrhoea was reported in 2016. PHE's response was to create a Level 2 Incident Control Team to monitor and control further outbreaks.(187)

2.4.2 RITA as a tool to facilitate case finding

There may to be a role for RITA in the active case finding for HIV in both an outbreak situation and for accelerated or prioritising PN. Outbreak control activities will include HIV testing or screening, and thus being able to distinguish a new from an established infection inexpensively and most importantly, timely, is crucial. Triangulating these data with available epidemiological, clinical and phylogenetic data is essential to undertake a network analysis and identify people at risk.

Traditional PN for HIV is a strong tool for active case finding reaching individuals with previously undiagnosed infection, for which the effectiveness has been demonstrated.(147) Studies in the UK(147), Europe(188) and the US(189) show high HIV diagnosis rates are achievable through PN. Among a range of clinics throughout the UK, HIV diagnosis rates through PN have ranged from 10-37% with an average of 27%.(147, 190) This compares to 1.7% positivity among MSM in sexual health services in 2016.(191) Since 2012, PHE have published rates on diagnoses through PN for HIV and other STIs in sexual health clinics in England which show that in 2012, 8% of PN contacts reported were diagnosed with HIV.(192) This decreased over the years to 3% in 2016, however likely due to a higher number of overall contacts reported, potentially including people at lower risk. Prioritising PN among people diagnosed with incident infection could further increase diagnosis rates, as the infectious period of the index case is known and requires a shorter recall period. Importantly, those with recent infections are likely to be more infectious due to higher viral loads at the outset. Studies have shown that a large fraction of infections are likely to stem from individuals undiagnosed with new infections.(173, 193). Research examining PN outcomes by duration of infection by the European Partner Notification Outcomes Group found a diagnosis rate of 37% versus 27% among seroconverters compared to individuals with longstanding infections.(188) Ahrens et al. found higher rates among those diagnosed in acute and non-acute conditions compared to those with longstanding infections (7%

among acute, versus 5% non-acute and 1% among long-standing).(189) In the UK, Millard et al. showed 53% of partners of those with a recent infection were diagnosed with HIV compared to 21% among individuals with established infections.(194) However, on the contrary, an audit undertaken in 2013 (after the start of this thesis) showed that whilst the number of contacts per index patient was higher among those recently infected compared to those not (0.76 vs. 0.71), the number of contacts at risk (of having undiagnosed HIV) was lower among the recently infected (0.50 vs 0.54).(195)

With RITA enabling the identification of incident infections in real time, infectious disease control models such as those for LGV and gonorrhoea in the UK could be applied to HIV, in particular with respect to the implementation of enhanced surveillance. The role of RITA prioritising PN efforts, however, needs further exploration.

2.5 Summary

Serological assays for recent infections may have significant public health utility in the UK setting both at population and local level. Whilst the development of models to determine HIV incidence are ongoing, there remains a gap in obtaining incidence estimates in real-time for all population groups which the application of serological assays may be able to fill. In addition, these data could enable more traditional infectious disease control interventions for HIV, such as those currently in place for LGV and gonorrhoea in England. Initial steps may be the implementation of enhanced surveillance among the newly identifiable affected population. Subsequent chapters of this thesis will go on to explore the application of RITA in both the aforementioned areas.

3 Methods

In this chapter I describe PHE's national HIV surveillances systems which I use to examine the coverage of PHE's serological HIV incidence testing programme and estimate predictors for a recent HIV infection diagnosis (Chapter 5) and determine HIV incidence in sexual health clinic attendees (Chapter 6) and in the population as a whole (in Chapter 7). I detail the statistical methods applied for these analyses and further present the objective and methods of data collection for the pilot survey of enhanced surveillance in MSM with incident HIV infection.

3.1 UK HIV surveillance systems and datasets

The UK HIV surveillance datasets which I use for my analyses throughout the thesis are created by the HIV and AIDS Reporting Section at PHE of which I have been a member since June 2011. This team creates and manages the below described datasets and each scientist of the team may conduct distinct analyses on data for specific projects. All members of the team are all involved in creating the routine outputs including the official statistics which consist of the national HIV tables published annually on the PHE website and the annual HIV reports.(5, 11-13, 73) My role within this team (relevant to the thesis) was to lead on the management of the recent HIV infection data; this entailed liaising with the VRD at PHE to obtain the data of recently acquired HIV infections and to clean and link these to the new HIV diagnoses data to create the final dataset and the routine outputs.

Surveillance of new HIV diagnoses AIDS and Deaths (HANDD)

PHE collates national data on all diagnoses of HIV, AIDS and AIDS-related deaths along with demographic and epidemiological information for people aged over 15 years. Clinics and laboratories independently submit HIV diagnosis reports in England, Wales and

Northern Ireland to the HIV team at PHE which are compared against existing data to verify each report as a new diagnosis. Diagnoses made in Scotland and in those aged less than 15 years are collated separately and forwarded by Health Protection Scotland and the Institute of Child Health (the National Study of HIV in Pregnancy and Childhood (NSHPC), respectively. Final numbers are adjusted to account for underreporting and a reporting delay. The surveillance system collects, amongst other variables, information on sexual orientation, age, gender, ethnicity, country of birth, probable country of infection, diagnosis site, diagnosis date and HIV type.(196)

Survey of Prevalent HIV Infections Diagnosed (SOPHID) (now superseded by HARS)

Each year (up until 2014), a cross-sectional survey of people accessing HIV-related care in healthcare settings across England, Wales and Northern Ireland is undertaken which provides comprehensive information on people accessing care and the care provided. As with the surveillance of new HIV diagnoses, data from Scotland are provided by Health Protection Scotland, and data on children are collected by the Institute of Child Health and the Medical Research Council (Collaborative HIV Paediatric Study (CHIPS)). This surveillance system collects demographic and clinical information including residence data, CD4 T-lymphocyte count, viral load and date and type of ART prescribed.(196) The data are primarily used to inform estimates of HIV prevalence and the commissioning and planning of HIV services. In 2014 this system was superseded by the new HIV and AIDS Reporting System (HARS). The HARS database collects disaggregate information on every consultation from all outpatient HIV service providers on a quarterly basis and is based on the NHS data dictionary. All data elements of SOPHID system are now included in HARS.

The CD4 cell count surveillance scheme

In 2003, PHE extended its surveillance of HIV to include the collection of CD4 T-lymphocyte count data directly from laboratories. The purpose of this is to monitor national trends and the

population effect of immunosuppression in people living with HIV, and importantly to establish the proportion of late diagnoses (those diagnosed with a CD4 count<350 cells/mm^3).(5, 196) These data are linked to the HANDD and SOPHID datasets annually.

The Genitourinary Medicine Clinic Activity Dataset version 2 (*GUMCADv2)*

In 2008, the Genitourinary Medicine Clinic Activity Dataset (GUMCAD) was implemented by PHE collecting information from all sexual health clinics and other sexual health services providers in England.(197) Data are submitted quarterly on all attendances and services delivered at the attendance, providing epidemiological data of STIs and testing patterns. These are used to inform and improve the commissioning and planning of services, to develop recommendations with regards to testing and treatment, and to detect outbreaks for example of LGV. Variables in this surveillance system include age, gender, sexual orientation, country of birth, area of residence, ethnicity and HIV and STI tests and diagnoses and number of partners contacted and diagnosed. In 2017, this surveillance system was expanded to include variables for the use of PrEP both within and outside of the ongoing PrEP Impact trial.(198)

Surveillance of recently acquired HIV infections

Since 2009 laboratories and clinics in England, Wales and Northern Ireland send blood specimens from people newly diagnosed with HIV to VRD at PHE for testing using a serological incidence assay. Laboratories were asked to complete a Memorandum of Understanding detailing the collaboration on the programme of work to monitor the number of recently acquired infections and invited to submit specimens as and when it was convenient for them. Not all clinics and/or laboratories took part consistently and this varied over the years. The assay in use between January 2009 and September 2013 was the AxSym avidity assay HIV 1/2gO (Abbott, United States), on which the analyses in this thesis are based. Results are linked to corresponding new HIV diagnosis reports (in the HANDD

database). HIV diagnoses linked to a result with an avidity index <80% are classified as recently acquired infections unless other available clinical information, which form part of the algorithm, indicate a potential longstanding infection (e.g. low CD4 count, or the report of an AIDs defining illness. See section 4.1.2). In addition, cases may be reclassified if ARV treatment was given before or at the time the sample was taken, indicated by either a treatment start date or a low viral load reading. The ARV and viral load data were taken from the SOPHID system, CD4 cell counts from the CD4 surveillance scheme and AIDS diagnoses and other epidemiological information are from the HANDD surveillance system.

Data linkage

The HANDD, SOPHID, CD4 surveillance and RITA datasets are linked annually by the HIV and AIDS reporting team using information on any available identifiers, such as soundex (see description on p42) and clinic identification number, and any demographic information such as gender, date of birth, diagnosis site and diagnosis date. I am a member of this team and I linked the RITA data to reports of new HIV diagnoses (HANDD) and extracted the ARV and CD4 data from the other surveillance datasets.

3.2 Laboratory testing for recent HIV infection

Testing for recent infection was carried out by members of VRD using the AxSYM assay HIV 1/2gO (Abbott, United States) modified to determine antibody avidity.(148, 199) As described previously, this assay indirectly measured the HIV antibody-antigen bond strength or 'avidity', which is typically weaker during the initial stages of infection (see Chapter 2, Section 2.3.4). Test results were reported as an avidity index; 80% was used as a cut-off value with lower values indicating recent infection). Samples giving results between 75% and 85% were retested with the mean of the two values used as the final result. The MDRI associated with the 80% cut off was 181 days (standard deviation (SD) 8 days) as estimated

by Sweeting et al. (personal communication Daniela De Angelis). This MDRI is based on only the assay (not the whole RITA). No estimates for the MDRI of the AxSym avidity assay currently exist for a RITA.

3.3 Data management and statistical software

All the data were managed and analysed in Microsoft Access 2007 and Stata 13.0 (Stata Statistical Software: Release 13, United States). Do-files were created for all analyses to ensure reproducibility and for use of future iterations. Data for the years 2009-2013 were used for all analyses. Two-sided tests at the 95% significance level were used for the interpretation of statistical tests.

3.4 Statistical methods for descriptive analyses of the RITA programme[1]

I examined the demographic characteristics of people with recent infection stratified by HIV transmission group (MSM, heterosexual men and women and other), as these groups were assumed to be homogenous in terms of risk for the purposes of this analysis. I determined associated factors with uni-and multivariable analyses using logistic regression, including any variables in the final model where a hypothesis test on the regression parameters resulted in $p<0.2$. A multivariable model was used to minimise confounding which is when the effect of an exposure is over or underestimated due to another unmeasured exposure. (A confounding variable must be related to both the dependent and independent variable, hence the exposure and outcome studied.(200)) The RITA result was considered the

[1] The publication accompanying this analysis was on data for the years 2009-2011 which was undertaken in late 2012 at the outset of the thesis and published in 2014.(145) This was subsequently updated for the thesis to include data for the years 2012 and 2013 so that the period of study was the same for all Chapters.

outcome variable. All other variables were treated as categorical. I used the standard age group categories used by PHE for the analyses of HIV data, which were 15-24 years, 25-34 years, 35-49 years and 50+ years. For region of diagnosis I compared London to outside London, which was the rest of England, Wales and Northern Ireland. CD4 count data was grouped into the following five categories: <50, >50 to ≤200, >200 to ≤350, >350 to ≤500, >500 to ≤750, >750 to ≤1000 and >1000. (<50 was used as people with a CD4 count < 50 were considered to have AIDS or very longstanding infection, those with a CD4 count <200 to have had a very late diagnosis and those with a CD4 count < 350 a late diagnosis). I calculated the proportion of recent infection as the number of recent cases determined by the algorithm divided by the number of cases tested for recent infection for each strata. For the predictors of recent infection, the FRR was not considered as it was not possible to know which recent cases were falsely recent (this was simply a proportion applied to the whole sample of those recently infected). This may have an impact on the overall results of predictors of recent infection however, as the number of false recent cases are comparatively small, it is thought that any effect is likely to be minor. Confidence intervals (CIs) for the proportion of recent infection were derived using the cii command in Stata which is for variables assumed to have a binominal distribution.

3.5 Statistical methods for determining the false recent rate (FRR)

The misclassification rate, referred to as the FRR, had not been evaluated for the AxSYM avidity assay which is now no longer commercially available. Guidance by the WHO Technical Working Group on HIV incidence assays suggests this should be estimated for the population of study where possible among cases known to be longstanding using the following relationship(7):

(3.) $$\in = \frac{R}{L}$$

where

$\in$ = FRR of the algorithm

R = number of cases appearing recent and

L = number of longstanding cases

The FRR was calculated among people tested for recent infection but diagnosed >1 year before the avidity test. These data were from patients who had transferred their care to other sites and were diagnosed for a second time (the notification of which was de-duplicated at PHE). Confidence intervals for the FRR were derived using the cii command in Stata.

3.6 Statistical methods for cross-sectional HIV incidence analyses in sexual health clinics in England

The analysis for cross-sectional HIV incidence estimation required a population for which information on both the number of HIV negative and positive people was available. I used the population of sexual health clinics attendees based on the GUMCAD dataset. Guidance provided by the WHO Technical Working Group on statistical methods for conducting HIV incidence analyses on cross-sectional data using RITAs recommends using the following relationships:

(4) $$lr = \frac{\mathrm{R} - \in \mathrm{P}_R}{(1 - \in)\mathrm{wN}}$$

where

lr = annual rate

R = number of recent infection cases

$\in$ = the FRR

P_R = the number of HIV positive people tested for recent infection

W = the mean window period/MDRI

N = the number of people that tested negative for HIV

The GUMCAD dataset was treated as a cross-sectional survey of people attending sexual health clinics in England over the period of a year for each of the years 2009-September 2013. This provided the denominator for the above expression regarding the number of people that had had a negative HIV test. The number of recent HIV infection cases, the numerator, was taken from the surveillance of recently acquired HIV infection data.

As the GUMCAD and RITA datasets used different codes to identify clinics, to align the datasets, I used the clinic code variable in combination with the postcode to generate a 'look-up' table to map the clinics in GUMCAD to a clinic in the RITA dataset. This had been done previously by the HIV and AIDS Reporting team for other analyses; however I renewed this as each year sites merged, split or ceased to exist.

As not all sites submitted specimens for recent infection testing and even within sites that did, not all new HIV diagnoses were tested, I adjusted the denominator (the number of people that tested negative) to correspond to the numerator (the number of people tested positive for recent infection). For each site (to account for variation in the types of populations clinics served), I calculated the number of HIV tests per diagnosis (the number of tests divided by the number of diagnoses in the GUMCAD data) and applied this ratio to the observed number of recent infections as follows:

(5) $$T_R = P_R \left(\frac{T_G}{P_G}\right)$$

where:

T_R = the number of people that tested for HIV (corresponding to P_R)

P_R = the number of people diagnosed positive with recent infection

T_G = the number of people that tested for HIV in GUMCAD

P_G = the number of HIV positive people observed in GUMCAD

This allowed presentation of HIV incidence by geographical area, as for example, in a low prevalence area, the 'test per diagnosis' rate was higher than in a high prevalence area.

Each clinic attendee was considered only once each year (the first test) despite possible multiple attendances and tests. The numbers of new diagnoses were patients diagnosed for the first time at the clinic in the year of analysis and had not been seen for HIV care previously. Patient characteristics were taken from the first attendance in the year apart from sexual orientation; if a patient identified as MSM at any time during the previous years, they were considered MSM in the year of analysis.

The FRR was calculated for this population as outlined in Section 3.5.

Confidence intervals for these estimates were derived using the delta method approximation recommended in the WHO guidance.(7) As outlined in the guidance, the coefficient of variation (a measure for the dispersion of the variation and frequency of variation defined as the ratio of the standard deviation and the mean) was expressed as follows:

(6) $$C_V = \sqrt{\frac{1}{P_R}\left(\frac{N_R+P_R}{N_R} + \frac{(P_R-R)R[1+\varepsilon/(1-\varepsilon)]^2}{R-\varepsilon/(1-\varepsilon)(P_R-R)^2}\right)} + \frac{\sigma_\omega}{\omega^2} + \frac{\sigma_\varepsilon^2 (P_R-R)^2}{(1-\varepsilon)^4[R-\varepsilon/(1-\varepsilon)(P_R-R)]^2}$$

where

σ_ω = the SD of the mean RITA duration (assumed normally distributed), and

σ_ε = the SD of the FRR (assumed normally distributed).

The 95% CI for I_r was then computed as:

(7) $$I_r \pm 1.96 \times I_r C_V$$

I calculated annual incidence estimates separately for black African heterosexuals, heterosexuals overall and MSM, and separately for those attending clinics in London where half of all new HIV infections were diagnosed with the width of CIs indicating any significant trends over time.

3.7 Statistical methods for population-based HIV incidence estimates

The method to determine population-based HIV incidence using RITA and surveillance data was first described by Karon et al.(146) and further modified by Prejean et al.(201). It is referred to as the stratified extrapolation approach treating the number of diagnosed individuals tested for recent infection as a survey sample. Appropriate weights are applied to the number of observed recent infections to account for the bias in the diagnosis process selection. Hence, each person diagnosed as a recent infection in the sample represents a certain number of individuals with incident infection in the population. The weights used are the inverse of the probability of being detected with a recent infection. The estimation of the weights takes into consideration whether individuals have tested for HIV previously, as frequent testers are more likely to be diagnosed with incident infection. Thus the probabilities used for weighting are calculated separately for people with no testing history, diagnosed at their first test as ‘new testers’ and people diagnosed after their first test as ‘repeat testers’. Weights are also determined for a number of strata within each of these two testing groups. As mentioned previously, these strata consist of population sub-groups considered to have homogenous testing patterns, for example grouped by transmission risk, ethnicity and age. HIV incidence is subsequently estimated as the observed number of recent HIV infections in the sample divided by the probability of being detected as recently infected.

Calculation of probabilities used for weighting

The original methods were first published by Karon et al.(146), and subsequently modified by Prejean et al(201) and incorporates information on testing history. For repeat testers, the probability *P* of being detected as a recent infection was estimated using the interval between the last negative and first positive HIV test, assuming the time of infection is uniformly distributed and that the dates of these tests are accurate. The probability in the repeat testing group is the average probability expressed as:

(8) $$P = \frac{1}{n}\sum_{i=1}^{n} P\,i$$

where

n = the number of repeat testers and each P_i has the expression:

(9) $$P_i = \frac{1}{T_i}\int_0^{T_i} P(W > t)dt$$

where

T_i = the interval between the first positive and last negative test and W is the window period (or MDRI) of the assay

Among people diagnosed with recent HIV infection and no previous HIV testing, the probabilities are calculated using a competing risk model. This model considers multiple events possibly causing the outcome. In this case, the competing risk is the time from infection to either being diagnosed with HIV or AIDS. The distribution of time from infection to HIV diagnosis is taken to be exponential with the following scale parameter(146):

(10) $$\lambda = \frac{\beta_A}{q^{\frac{-1}{\alpha}} - 1}$$

where

q = the probability of an AIDS diagnosis within the group at the time of diagnosis, assuming that the testing rate is constant until an AIDS diagnosis.

Prejean et al. derived the probability of being a recent infection in the new testing group as:

(11)
$$P_{new} = \Pr(X < W \text{ and } X < A)$$

$$= \int_0^\infty \Pr(t < W \text{ and } t < A)\, f(t)dt$$

$$= \int_0^\infty \Pr(t < W)\, \Pr(t < A)\, f(t)dt$$

$$= \int_0^\infty S_W(t) S_A(t) \frac{1}{\beta} e^{-t/\beta} dt$$

where

X = the time from infection to first positive test

A = the time from HIV infection to AIDS,

W = the window period/MDRI of the assay, and

A and *W* are independent.

In the final expression,

S_W = the survival function of the window period,

S_A = the survival function for the time from infection to AIDS and

$\frac{1}{\beta} e^{-t/\beta}$ is the density function for the time from infection to first positive test

Prejean et al. used the shape and scale parameters of the incubation period to and AIDS diagnosis to be 2 and 4 respectively however this is based on the definition of AIDS being a CD4 count<200. In the UK the definition is based on the observation of an AIDS-defining illness. I used the European AIDS case definition corresponding to a median of 10 years for the time interval from infection to AIDS. As approximated by Weibull et al. S_A I have

assumed that this incubation period has a gamma distribution with the scale and shape parameter 5.251 (α) and 1.974 (β) (in years).(202)

Calculating HIV incidence

The total number of new infections can be expressed as:

(12) $$I = I\text{new} + I\text{repeat} = (\frac{\text{Rnew}}{\text{Pnew}}) + (\frac{\text{Rrepeat}}{\text{Prepeat}})$$

where

I = the total number of new HIV infections

I_{new} = the number of new HIV infections in new testers

I_{repeat} = the number of new HIV infections in repeat testers

R_{new} = the number of recent infection diagnoses in new testers

R_{rep} = the number of recent infection diagnoses in repeat testers

P_{new} = the probability of being diagnosed as recently infected for new testers, and

P_{rep} = the probability of being diagnosed as recently infected for repeat testers

I presented annual HIV incidence as per 100,000 pys taking into consideration the subpopulation sizes obtained from ONS.(203)

Handling missing data

Serological incidence data were needed for the complete sample of new HIV diagnoses to obtain population-based incidence estimates and these data were not available for the total population. I used multiple imputation (MI) to account for missing test data by substituting each missing value with a range of likely values, accounting for the uncertainty around the missing values. This process creates and combines multiple datasets to estimate missing values. An assumption for MI is that the data are missing at random (MAR). If there is no

association between the missing data and covariates the data are likely MAR.(204, 205) I reviewed the distribution of the missing data to explore if the data were likely to be MAR. I used a logistic regression model by chained equations to impute the missing transmission risk and serological incidence data based on age group, sex and year of diagnosis. I chose this approach to handle missing data as it provided flexibility in imputing various types of variables at the same time. The minimum number of imputations considered to produce stable and valid results is 5. I chose 20 for improved estimates.

Calculating the variance

The variance around these estimates was calculated using the delta method, as described by Karon el al. and modified by Rick Song (Mathematical Statistician, CDC Atlanta, personal communication, provided derivation) and includes the variance associated with the multiple imputation.(146) The variance of the final incidence estimates are derived as follows:

Using the relationship:

(13) $$I = \frac{R}{P}$$

From the delta method:

(14) $$var(I) = var\left(\frac{R}{P}\right) = \frac{var(R)}{E(P^2)} - 2\frac{E(R)}{E(P^3)}\ cov(R,P) + \frac{E(R^2)}{E\ (P^4)}var(P)$$

Where the variance *var* and expectation *E* are with respect to the sampling distribution of each statistic. Assuming R and P to be independent (so the covariance is 0) and replacing the expected values $E(P^2)$ and $E\ (P^4)$ with the observed values P^2 and P^4 the variance of I can be further approximated as follows:

(15) $$var(I) = I^2(\frac{var(R)}{R^2} + \frac{var(P)}{P^2})$$

For each group of testers (new and repeat) the components of the above expression are calculated as follows:

For new testers:

(16) $$var(R_{new}) \approx R$$

As the observed number of recently infected individuals follows a Poisson distribution with a mean of R, the actual number of recently infected individuals can be estimated by R (var(R)=E(R)=R)).

(17) $$var(P_{new}) \approx P_{1new}P_w$$

As in Karon et al.

(18) $$P_w = \frac{var\ (P_{new})}{P_{new}^2} = \frac{var(P_{1new})}{P_{1new}^2}$$

The estimate of $P_{1\ new}$ is a function of λ (see earlier).

Hence

(19) $$var(P_{1new}) = [\exp\left(-\frac{2}{\lambda}\right)](1-q)/(N_0\alpha\beta q)^2$$

where

N_0 = the number of people classified as a new tester (by strata)

λ = as above

α & β = as previously (5.251 & 1.974)

The estimate of the variance of the incidence for the new testing group can be expressed as follows:

(20) $$var(I_{new}) = I_{new}\ \frac{var(R_{new})}{R_{new}^2} + \frac{var(P_{new})}{P_{new}^2} = I_{new}(\frac{R_{new}}{R_{new}^2} + \frac{var(P_{1new})*P_w^2}{P_{new}^2})$$

For repeat testers, similarly:

(21) $$var(I_{rep}) = I_{new}^2(\frac{var(R_{rep})}{R_{rep}^2} + \frac{var(P_{rep})}{P_{rep}^2})$$

I also took into account the MI in the variance around the incidence estimate. The variance of the MI was calculated in the following manner (taken from Rubin et al.)(204); for every imputation and incidence a variance estimate around the incidence estimate is obtained. Combined, the estimate is

(22) $$\bar{\mathrm{I}} = \frac{1}{m}\sum_{i=1}^{m}\hat{\mathrm{I}}$$

The variance within each imputation, the intra-base variance estimate is expressed as follows:

(23) $$\hat{\mathrm{W}} = \frac{1}{m}\sum_{i=1}^{m}\hat{V}i$$

The variance between each imputation, the inter-base variances estimated as:

(24) $$\mathrm{B} = \frac{1}{m-1}\sum_{i=1}^{m}(\hat{\mathrm{I}}_i - \bar{\mathrm{I}})^2$$

Finally, the total variance is calculated as:

(25) $$\hat{V} = \widehat{W} + (1 + \frac{1}{m})\hat{B}$$

The confidence intervals were consequently calculated using the following:

(26) $$\bar{\mathrm{I}} \pm 1.96\sqrt{V}$$

3.8 Design and data collection for the pilot of enhanced surveillance in MSM with recent HIV infection

Objective

The objective of this survey was to explore the feasibility and utility of using RITA information for enhanced behavioural surveillance of MSM with incident HIV infection, specifically, by

collecting risk behaviour data (including time/place/person details potentially needed for an outbreak investigation) from patients in real-time.

Research topic areas

In consultation with Dean Street Clinic in central London, a short questionnaire was devised covering topics considered to be most relevant for an HIV enhanced surveillance data collection tool (Box 1.) Dean Street clinic was the clinic with the highest number of new HIV diagnoses in MSM in the year of questionnaire development (2013) and a number of years prior. My questionnaire was shared with the lead clinician at Dean Street, other lead clinicians in the recruitment sites and sexual behavioural experts.

Table 1 Topics areas and rationale for the pilot enhanced behavioural surveillance questionnaire

Questionnaire topics	**Rationale**
HIV testing and reason for testing at the time of diagnosis:	To establish whether participants had been prompted by a recent risk exposure or if they were frequent testers or it was their first test, and, if they had experienced symptoms or were asked by either a health professional or their partner to obtain a test.
Experience of a biomedical intervention which may have failed, such as PEP or PrEP:	To establish if the infection was the consequence of a failed intervention.
Recent history of a STI including Hepatitis C (HCV):	To indicate risk behaviour in the preceding 6 months.
Number of sexual and UAI partners and their infection status (if known) in the 6 months prior to diagnosis:	To indicate the participant's risk of infection and how many partners may have been at risk of transmission.

Questionnaire topics	Rationale
Types of sexual partner meeting venues including the names of the venues and internet sites visited:	To explore whether infection clusters can be identified which may have the potential inform an outbreak investigation and prevention initiatives.
Types of sexual activities other than UAI:	To explore the prevalence of other risk behaviours which led to infection (e.g. rimming, group sex or the sharing of sex toys).
Use of any recreational drugs before or during sex:	To establish the proportion of men who were chemsex users (defined as the use of crystal meth, G (including GHB and GBL), or mephedrone) and may therefore have had increased risk of infection either through drug-induced disinhibition or the sharing of injecting equipment.
Other information relevant for active case finding, such as PN activities including the number of contactable partners, the number of partners contacted, and preferences for contacting partners:	To explore the potential for active case finding in this sample of MSM.

In addition, I attempted to collect information from participants that was not guided and/or restricted by a set number of possible responses on how they believed they acquired HIV. I used an open-ended question prompting participants to describe the circumstances of the believed exposure event. The aim of this question was to establish whether, firstly, a recent risk event had been identified, secondly, if the risk event was the likely transmission event compared to other risks indicated in the questionnaire and, thirdly, to explore if the participant had undertaken any preventative measures that may have failed. (Questionnaire in Appendix 1).

Selected sites

Seven HIV clinics were selected based on having had a high number of MSM attend and diagnosed with HIV each year. Two further sites (St Mary's London and Brighton Sussex) were approached but could not take part due to another similar study being conducted at the time. At these sites, a high proportion of men tested for recent infection. In 2013, when the study was conceived, the most recent surveillance data from 2012 indicated the following number of MSM diagnosed with HIV and tested for recent infection in these sites (Table 2).

Table 2 Number of MSM diagnosed with HIV, tested for recent infection and classified as having likely recently acquired HIV in 2012 in the seven selected pilot sites for enhanced behavioural surveillance

Clinic	n MSM diagnosed	% (n) with avidity tests (linked)	% (n) classified with recently acquired HIV
Dean Street	404	74% (299)	41% (121)
Homerton	40	80% (32)	25% (8)
St Thomas	131	94% (123)	33% (40)
Barts and the London	16	81% (13)	23% (3)
Manchester	54	70% (38)	13% (5)
Liverpool	31	32% (10)	20% (2)
Sheffield	24	54% (13)	31% (4)
Total	703	75% (528)	35% (183)

These seven clinics represented 21.6% of the 3,250 MSM diagnosed that year and 34.8% of 1,516 tested for recent infection. As this pilot was a feasibility study to review both the practicality of collecting these data and the value of the data collected, no sample size calculations were conducted.

The number of MSM diagnosed and classified as recently infected recorded in the clinics are likely to have been higher than shown here. This is due to firstly not all tests for recent infection with HIV having linked to a new HIV diagnosis report due to insufficient or wrong patient information submitted with the sample tested at PHE (e.g. date of birth, soundex or

clinic id); secondly, at the national level, all reports of new HIV diagnoses are de-duplicated. As patients may attend multiple clinics and be diagnosed more than once, individual clinics may count more new HIV and recent infection diagnoses than presented in PHE's final figures.

In preparation for the study, I visited each of the London clinics and the clinic in Manchester to present the pilot to the local clinical study leads and health advisors. For the Sheffield and Liverpool clinics, I presented the study via a conference call and posted all study materials (see Appendix 2).

Inclusion criteria

Individuals were eligible to participate if

i. They had a confirmed HIV diagnosis
ii. Were over 18 years of age
iii. Were able to read, write and speak English
iv. Their transmission risk was MSM and they had evidence of recent infection with HIV including
    - RITA indicating recent HIV infection, and/or
    - a negative HIV test within the last 12 months, and/or
    - a p24 antigen positive and HIV antibody negative test result (indicating very recent infection, see section 2.3.4)

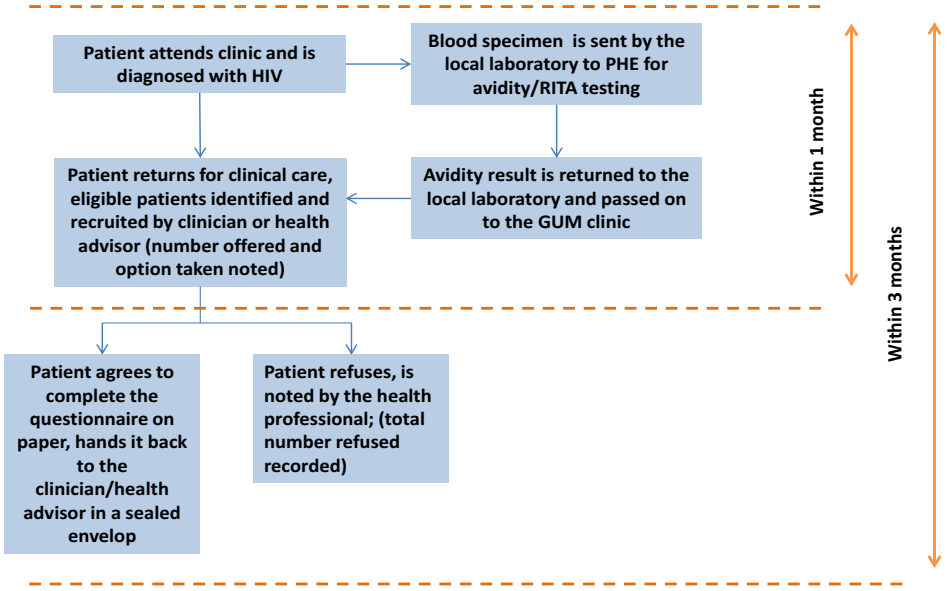
Recruitment methods

To ensure minimal recall bias, the questionnaires were to be completed shortly after diagnosis with recent HIV infection. Clinicians and health advisors invited patients meeting the selection criteria during their second consultation to the pilot, usually within 3 months of HIV diagnosis (Figure 6.). The first consultation was considered inappropriate and unfeasible

due to lack of time and sensitivity around receiving an HIV diagnosis. In addition, it was unlikely that the RITA test result would have been be available at the first consultation (although recent infection could be diagnosed for patients with a recent negative HIV test). Recruiting staff explained the aim of the study and provided an information leaflet (see Appendix 2) describing the purpose of the pilot and contact information of the clinic and PHE survey coordinator (myself). Patients agreeing to participate were asked to complete the confidential, anonymous paper questionnaire, place it in a sealed envelope and return it to recruiting staff at the clinic. To prevent recruiting an individual twice, a note was added to the patient's records. If the patient refused, an uncompleted questionnaire was placed in an envelope and marked with 'REFUSED' enabling calculation of response rates. The questionnaire took approximately 10 minutes to complete. Where possible, questions had been drawn from other surveys and studies (with permission) as these were tested and validated (e.g. Gay Men's Sexual Health Survey (University College London, (UCL)), Behavioural survey of negative MSM attending sexual health clinics in London (PHE, UCL, Dr Sarika Desai), the Gym Survey (City University, Dr Jonathan Elford). Prior to recruitment, the questionnaire was tested with 10 men at Dean Street Clinic. The decision was made not to collect any patient identifiable information to encourage participants to answer questions truthfully. Thus, the responses could not be linked to any epidemiological surveillance records.

Patients were recruited to the pilot for just over a year, starting in January 2014 and ending in February 2015.

Figure 6 Data flow of pilot survey participants



Data management and storage

Completed questionnaires were either collected from the clinic by myself or posted to PHE at regular intervals using pre-paid envelopes provided by PHE. The questionnaires were double entered onto an Access database and stored securely on the HIV & STI department drives on a PHE server in accordance with the Caldicott guidelines. Data were cleaned, validated and analysed using STATA v.13. Where inconsistencies in participant responses were discovered, data were recoded; e.g. if a participant reported a total of 10 anal intercourse (AI) partners but 11 receptive UAI partners, the total of 10 AI partners was recoded to 11.

Ethical approval and consent

This initiative was conducted as enhanced surveillance thereby deemed to not require ethical approval (see Appendix 3 for a letter from PHE's Associate Caldicott Guardian at the time). The study was considered a response to an ongoing public health problem and the pilot of an extension to ongoing surveillance activities. Reviewing the information provided by

the National Research Ethics Service (NRES), the project was categorised as 'usual public health practice/surveillance' (http://www.hra.nhs.uk/research-community/before-you-apply/determine-whether-your-study-is-research/). In addition, most of the questions in the survey were asked during clinical consultation as part of standard practice.

Questionnaire data analysis

The methods used to analyse the behavioural surveillance data were of a descriptive nature only as it was primarily a feasibility study and based on a small sample. I explored the demographic and behavioural attributes of participants and compared these broadly with other data in the literature on newly diagnosed MSM.

For the open-ended question '*How do you think you acquired HIV*' I conducted a thematic analysis, reviewing the responses and analysing these in two parts; firstly by mapping out themes, categorising responses into these themes and secondly by repeating this process a few times for further iterations and refining of the categories and groupings.(206) I subsequently asked a colleague to review these themes and categories and to also assign the responses to the suggested categories for comparison, and or suggest new categories if these were perceived to be inappropriate. In addition, to give context to the described HIV risk event, I reviewed the responses to previous questions in the questionnaire relating to a risk exposure, examining if the described risk was the only risk event in the relevant period or one of many.

Quantitative data were shared with the participating clinics at 6 months primarily to review recruitment progress and response rates. For Dean Street only, data were also presented stratified by drug use (chemsex vs. other or none) as they were particularly interested in whether a large fraction of participants from their clinic were users based on anecdotal evidence at the time.(207)

4 PHE's serological HIV incidence testing programme coverage and review of RITA algorithm

In this chapter I describe the RITA programme data from 2009 to September 2013 after which a new type of serological incidence assay was introduced with different properties. I present the coverage of testing in relation to all people newly diagnosed and examine the representativeness and timeliness of specimens tested. With ongoing discussions on ideal algorithms for serological HIV incidence assays at the time of analysis, I present a range of algorithms possible with PHE data, and their impact on recent infection classification results. I also explore the relationship between assay results and other clinical markers of early infection such as CD4 cell count and viral load, and estimate the misclassification rate of the assay.

4.1 Results

4.1.1 RITA programme coverage and representativeness

Between 2009 and 2013, a total of 27,729 patients were newly diagnosed in England, Wales and Northern Ireland and reported to PHE's HANDD surveillance system with similar numbers diagnosed each year (Table 3.) The annual number of samples submitted for avidity testing increased over time as laboratories gradually enrolled in the programme during this period.

Table 3 Avidity testing of new HIV diagnoses in England, Wales and Northern Ireland, 2009-2013: numbers and coverage by year

	Year					
	2009	2010	2011	2012	2013**	2009-2013 combined
Number of new HIV diagnoses, E, W, NI	6222	5966	5,800	5902	3839	27729
Number of samples submitted for testing	2645	3878	4533	4561	2918	18535
Samples linked to a new HIV diagnosis report (n, % of submitted samples)*	2458 (92.9)	3,650 (94.1)	4019 (88.7)	3,938 (86.3)	2478 (84.9)	16543 (89.3)
Unique patient samples submitted, linked and within 4 months of the 1st diagnosis date (n, % of submitted samples)*	1,461 (55.2)	2,467 (63.6)	3,021 (66.6)	3,003 (65.8)	1,907 (65.4)	11859 (64.0)
Coverage as a % of new diagnoses	23.5	41.4	52.1	50.9	49.7	42.8

* excluding duplicate specimens
**until September 1st 2013; after this date a different assay was used.

Over the five years, a total of 18,535 samples were received for testing of which 16,543 (89%) could be linked to a new diagnosis report. The proportions linked in 2009, 2010, 2011, 2012 and 2013 were 92.9%, 94.1%, 88.7% 86.3% and 82.4%, respectively. Some specimens could not be matched to a new HIV diagnosis report either due to insufficient or mismatching information submitted by clinics and laboratories. In addition, some sites had separate HIV and sexual health clinics and used a different patient number for each clinic. Few matched samples (n=16) were from patients diagnosed outside England, Wales or Northern Ireland for the first time and were therefore excluded from analyses.

Only specimens from people newly diagnosed with HIV were eligible for testing. In some instances, not the first, diagnostic specimen but a subsequent one was submitted likely due to some sites sending a specimen only once the patient had a confirmed diagnosis, using blood specimen taken subsequently to conduct the routine baseline clinical tests such as CD4 cell and viral load count. If a patient had transferred their care to another clinic and had hence been diagnosed previously elsewhere, the date of that specimen may also not have been close to the initial diagnosis date on record. The cut-off period for considering the

recent infection result was chosen to be four months from the earliest recorded diagnosis date due to the decreasing likelihood of the result indicating recent infection.

Overall, I was able to include a total of 11,859 specimens for the study period. The coverage of testing for recent HIV infection (as a proportion of all new HIV diagnoses) increased from 24% in 2009 to 50% in 2012 and 2013 over this time and was broadly similar across subpopulations, aside from slightly higher proportions of people from London and of black ethnicity tested, and lower proportions among PWIDs, although regarding the latter, numbers were small (Table 4). The mean age of participants tested for recent infection was similar to all people newly diagnosed; 37.1 (Standard deviation (SD 11.0) years overall, 35.4 (SD 10.5) years for MSM, 41.8 (SD 10.9) years for heterosexual men and 37.0 (SD 10.6) years for heterosexual women. This compared to 37.6 (SD 11.3) years, 35.9 (SD 10.8) years, 41.6 (SD 11.1) years, and 36.9 (SD10.4) years among all newly diagnosed in these groups, respectively.

Table 4 Proportion of new HIV diagnoses tested for recent infection in England, Wales and Northern Ireland from 2009-2013

Characteristic	% (n/N) proportion tested					
	2009	2010	2011	2012	2013*	2009-2013 combined
Total	23.5 (1461/6222)	41.4 (2467/5966)	52.1 (3021/5,800)	50.9 (3003/5902)	49.7 (1907/3839)	42.8 (11859/27729)
MSM	25.3 (659/2608)	42.5 (1103/2593)	57.7 (1551/2690)	56.2 (1621/2885)	56.3 (1075/1910)	47.4 (6009/12686)
Heterosexual men	21.6 (271/1252)	39.6 (463/1168)	49.1 (578/1177)	46.3 (457/986)	48.0 (301/627)	39.7 (2070/5210)
Heterosexual women	24.0 (434/1873)	42.2 (726/1697)	52.4 (768/1518)	47.7 (745/1465)	46.1 (353/765)	41.4 (3026/7318)
PWID	13.7 (19/139)	36.6 (48/131)	33.3 (38/114)	43.3 (42/97)	39.3 (24/61)	31.5 (171/542)
Other	22.3 (78/350)	33.7 (127/377)	28.6 (86/301)	29.4 (138/469)	32.4 (154/476)	29.5 (583/1973)
Age group (years)						
15-24	23.9 (158/660)	41.4 (264/637)	54.1 (328/606)	54.9 (366/667)	55.4 (263/474)	42.1 (1379/3044)
25-34	23.5 (494/2101)	41.7 (817/1957)	53.3 (1031/1936)	53.9 (993/1841)	50.0 (644/1287)	43.6 (3979/9122)
35-50	23.8 (631/2652)	41.1 (1053/2565)	52.1 (1266/2431)	49.0 (1221/2472)	49.9 (736/1476)	42.3 (4907/11596)
50+	22.0 (178/809)	41.3 (333/807)	47.9 (396/827)	45.9 (423/922)	43.9 (264/602)	40.2 (1594/3967)
Ethnicity						

Characteristic	% (n/N) proportion tested					
	2009	2010	2011	2012	2013*	2009-2013 combined
White	22.4 (692/3091)	40.6 (1189/2926)	53.7 (1661/3095)	54.5 (1721/3157)	52.3 (1075/2054)	44.3 (6338/14323)
Black African	23.0 (481/2089)	41.7 (780/1870)	49.8 (835/1677)	48.2 (735/1524)	45.3 (365/806)	40.1 (3196/7966)
Black Caribbean	32.5 (78/240)	53.3 (105/197)	61.3 (100/163)	57.0 (90/158)	54.4 (62/114)	49.9 (435/872)
Black other	31.3 (40/128)	54.0 (67/124)	54.3 (63/116)	51.7 (62/120)	58.1 (43/74)	48.9 (275/562)
Indian/ Pakistani/ Bangladeshi	25.0 (56/224)	40.5 (106/262)	51.3 (141/275)	49.1 (156/318)	55.2 (116/210)	44.6 (575/1289)
Other	25.3 (114/450)	37.5 (220/587)	46.6 (221/474)	38.2 (239/625)	42.3 (246/581)	38.3 (1040/2717)
Country of birth						
UK	20.5 (488/2386)	42.7 (990/2321)	55.1 (1322/2398)	54.9 (1345/2452)	53.4 (785/1469)	44.7 (4930/11026)
Abroad	25.4 (973/3836)	40.5 (1477/3645)	49.9 (1699/3402)	48.1 (1658/3450)	47.3 (1122/2370)	41.5 (6929/16703)
Country of infection						
UK	28.2 (661/2427)	45.1 (1114/2456)	57.7 (1514/2553)	56.3 (1338/2401)	58.1 (894/1537)	48.5 (5521/11374)
Abroad	21.1 (800/3795)	38.5 (1353/3510)	46.4 (1507/3247)	47.6 (1665/3501)	44.0 (1013/2302)	38.8 (6338/16355)
Region of diagnosis						
London	32.9 (914/2780)	45.5 (1219/2678)	60.5 (1543/2551)	55.5 (1528/2764)	56.0 (1028/1835)	49.5 (6236/12608)
Outside London	15.9 (547/3442)	38.0 (1248/3288)	45.5 (1478/3249)	47.0 (1475/3138)	43.9 (879/2004)	37.2 (5627/15121)
CD4 count at diagnosis*						
<50	23.1 (143/619)	40.6 (230/566)	48.2 (257/533)	51.1 (280/548)	54.1 (145/268)	41.6 (1055/2534)
>50<200	22.9 (233/1019)	42.0 (382/910)	53.3 (474/890)	56.6 (481/850)	53.9 (242/449)	44.0 (1812/4118)
>200 to ≤350	23.5 (259/1157)	44.3 (500/1113)	53.6 (570/1040)	55.5 (527/958)	51.1 (281/550)	44.4 (2137/4818)
>350 to ≤500	25.8 (283/1098)	42.1 (449/1066)	57.9 (616/1063)	57.1 (584/1022)	55.8 (377/676)	46.9 (2309/4925)
>500 to ≤750	25.4 (253/998)	42.7 (431/1009)	57.4 (589/1027)	55.6 (590/1061)	55.2 (396/718)	47.0 (2259/4803)
>750 to ≤1000	26.0 (84/323)	47.6 (156/328)	53.6 (187/349)	56.4 (194/344)	50.0 (124/248)	46.8 (745/1592)
>1000	27.9 (31/111)	43.0 (64/149)	56.5 (65/115)	50.4 (67/133)	56.5 (52/92)	46.5 (279/600)

*until September 1st 2013; after this date a different assay was used.

Few data were available to establish whether those tested for recent infection and linked to a new HIV diagnosis report differed from those tested and not linked. I was able to compare information on gender and the avidity test result which revealed that a much smaller proportion of unlinked specimens had evidence of recent infection (avidity score<80%) than those linked (5.4 % versus 13.6%) but a similar proportion was male. I was unable to

hypothesise how, if these data could have been linked, the results may have affected the proportion of recent infection, as they may have been duplicate specimens or specimens not taken close to the time of diagnosis.

4.1.2 Exploration of RITAs

As presented in the introduction, it is known that serological HIV incidence assays misclassify established, long standing infections in some instances. Misclassification is minimised if results are considered as part of an algorithm including clinical markers for established infection and treatment status. As UK HIV surveillance data include information on CD4 cell count, viral load, treatment status and the diagnosis of an AIDS defining illness, I explored how incorporating different combinations of these into the algorithm impacted final results.

For each year, viral load and/or CD4 cell count data were available for 90% or more of recent cases. Guided by findings of CEPHIA, the most sensitive marker was shown to be viral load (threshold <400 copies), which primarily indicates current or recent ARV exposure.(141) They showed that only approximately 2% of untreated patients had a viral load of <75 copies/mL after being infected for 2 years, and 11% had <1000 copies/mL. In addition, FRRs (calculated in the following section) are considerably lower when people with low viral loads are omitted. CEPHIA have made no recommendations on a particular viral load threshold however, a lower threshold is preferred as it will have a lesser impact on the MDRI, likely shortening it slightly. Originally, a CD4 count threshold of <200 cells/mm^3 was considered, however as CD4 counts can drop during the early stages of infection (208), this would have likely included some seroconverters. A CD4 count <50 is unlikely to occur at such an early stage; I therefore explored the impact of this as a threshold. With an AIDS-defining illness the definition of a chronic infection in itself, and treatment shown to be an important factor, these were both also included in the algorithm.

Table 5 illustrates how the different algorithms affected the final recent infection classifications.

Table 5 Review of RITA algorithms and recent infection reclassifications using AIDS, ARV and varying a CD4 cell count threshold of <200 cells/mm^3, a CD4 cell count threshold of <50 cells/mm^3 and a viral load threshold of <400 copies/ml

	Year				
	2009 (n=1461)	2010 (n=2471)	2011 (n=3023)	2012 (n=3004)	2013* (n=1909)
Specimens avidity index (AI) <80.0 (n, %)	224 (15.3)	390 (15.8)	540 (17.9)	630 (21.0)	460 (24.1)
Proportion CD4 or viral load data available for with avidity<80.0	205 (91.5)	361 (92.6)	501 (92.8)	584 (92.7)	407 (88.5)
Specimens AI<80.0 & on ARV (n, % of total <80.0)	8 (3.6)	26 (6.7)	30 (5.6)	23 (3.7)	19 (4.1)
Specimens AI<80.0 & AIDS within 1 yr (n, % of total <80.0)	5 (2.2)	10 (2.6)	8 (1.5)	11 (1.7)	3 (0.7)
Reclassifications using AIDS, ARV and a CD4 cell count threshold of <200 cells/mm^3					
Specimens AI<80.0 & CD4<200 (n, % of total <80.0)	18 (8.0)	20 (5.1)	23 (4.3)	49 (7.8)	13 (2.8)
Total re-classified	26 (11.6)	44 (11.3)	53 (9.8)	71(11.3)	32 (7.0)
Recent (n, %)	198 (13.5)	346 (14.0)	487 (16.1)	559 (18.6)	428 (22.4)
Reclassifications using AIDS, ARV and a VL count threshold of <400 copies/ml					
Specimens AI<80.0 & vl<400 (n, % of total <80.0)	24 (10.7)	18 (4.6)	35 (6.5)	36 (5.7)	37 (8.0)
Total re-classified	33 (14.7)	48 (12.3)	66 (12.2)	63(10.0)	56 (12.2)
Recent (n, %)	191 (13.1)	342 (13.8)	474 (15.7)	567 (18.9)	404 (21.2)
Reclassifications using AIDS, ARV, a viral load threshold of 400 copies/ml and CD4<50cell/mm^3					
Specimens AI<80.0 & cd4<50 (n, % of total <80.0)	8 (3.6)	9 (2.3)	12 (2.2)	24 (3.8)	5 (1.1)
Total re-classified	37 (16.3)	53 (13.6)	72 (13.3)	79 (12.5)	59 (12.8)
Recent (n, %)	187 (12.8)	337 (13.6)	468 (15.5)	551 (18.3)	401 (21.0)

*until September 1st 2013; after this date a different assay was used.

To take advantage of as much information as possible, I used all available data as components in the final PHE algorithm, which included AIDS, ARV, a viral load threshold of 400 copies/ml and CD4<50cell/mm^3. In this instance, between 5% and 11% of recent specimens were from people with a viral load <400 copies/ml, indicating likely exposure to

ARVs or that they were possibly elite controllers. Information available on ARVs prescribed showed that between 4% and 7% of recent cases were on ARVs before the specimen was taken. Each year, between 3 and 24 cases were reclassified due to a CD4<50 cells/mm^3 (34 in total over the period). Using the PHE algorithm, in total between 13% and 17% of recent cases were reclassified each year, resulting in the proportion of recent infection having been 12.8%, 13.6% 15.5%, 18.3% and 21.0% in 2009, 2010, 2011, 2012 and 2013, respectively.

4.1.3 FRR for the AxSym avidity assay

The FRR for serological assays is related to the MDRI. The MDRI is the area under the curve of a cumulative distribution function up to a specified time point T, which here I chose to be a year. I chose this period to be a year as for my analyses I estimate annual HIV incidence. Any assay results appearing as recent after time T contribute to the FRR. A longer MDRI results in a smaller FRR and therefore more accurate incidence estimations. In my dataset, I identified 2,829 recent HIV infection test results among people that had been diagnosed more than a year prior to testing for recent infection. Of these, only 580 had complete viral load or CD4 data available at the time the specimen was taken (in most cases more than a year after the initial diagnosis). Thirty-eight (6.6%) had an avidity test result <80%. When applying the components of the PHE RITA algorithm, 24 recent cases were reclassified as long-standing due to treatment prior to the specimen date, 2 due to a viral load<400 copies/mL and one additionally due to information of an AIDS-defining illness leaving 11 false recent cases.(Table 6). Using the time period of 1 year, I estimated the FRR to have been 1.9% (95% C.I. 1.0%-3.4%).

As the MDRI of the assay can be longer than a year for some people diagnosed with recent infection, I examined what difference a threshold of two years would have on the FRR, assuming that those diagnosed at least two years prior were truly recent cases. I found that, in this instance, doubling the period over which a specimen may incorrectly appear as recent

(n=447), had little impact on the FRR with 8 FR cases remaining resulting in a FRR of 1.8% (95% C.I 0.8-3.5%). One person had been diagnosed up to 16 years previously. Examining the FR cases in detail showed that all 11 cases were MSM; ages varied with 1<25 years, 6 between 25-34 years, 2 between 35-50 years and 2 aged > 50. Among the 11 cases, viral load readings ranged from 3033-6818839; only four had a CD4 cell count reading recorded at the time the specimen was taken with readings of 79, 342, 520 and 560 respectively.

Table 6 False recent rate (FRR) estimate among people tested with the AxSym avidity assay known to have been infected for more than 1 and 2 years

		Year					
		2009	2010	2011	2012	2013**	TOTAL
Infected >1 year	Total (n)	533	742	570	579	405	2829
	VL or CD4 data complete*(n, %)	79 (14.8)	148 (19.9)	152 (26.7)	137 (23.7)	64 (15.8)	580 (20.5)
	AI<80.0 (n,%)	3 (3.8)	13 (8.8)	12 (7.9)	5 (3.6)	5 (7.8)	38 (6.6)
	AI<80.0 no treatment (n, %)	1 (1.3)	8 (5.4)	3 (2)	2 (1.5)	0 (0)	14 (2.4)
	AI<80.0, no ARV & VL≥400 (n,%)	1 (1.3)	7 (4.7)	2 (1.3)	2 (1.5)	0 (0)	12 (2.1)
	AI<80.0, no ARV & VL≥400 & CD4≥50 (n,%)	1 (1.3)	7 (4.7)	2 (1.3)	2 (1.5)	0 (0)	12 (2.1)
	FRR at 1 yr (AI<80.0, no ARV & VL≥400 & CD4≥50 & no AIDS (n ,%))	1 (1.3)	6 (4.1)	2 (1.3)	2 (1.5)	0 (0)	11 (1.9)
Infected >2 years	Total (n)	451	622	502	518	349	2442
	VL or CD4 data complete* (n ,%)	62 (13.7)	117 (18.8)	119 (23.7)	104 (20.1)	45 (12.9)	447 (18.3)
	AI<80.0 (n ,%)	3 (4.8)	8 (6.8)	11 (9.2)	5 (4.8)	4 (8.9)	31 (6.9)
	FRR at 2 yrs (AI<80.0, no ARV & VL≥400 & CD4≥50 & no AIDS (n ,%))	1 (1.6)	3 (2.6)	2 (1.7)	2 (1.9)	0 (0)	8 (1.8)

**until September 1st 2013; after this date a different assay was used

4.1.4 Correlation of AxSym avidity assay results with CD4 count and viral load

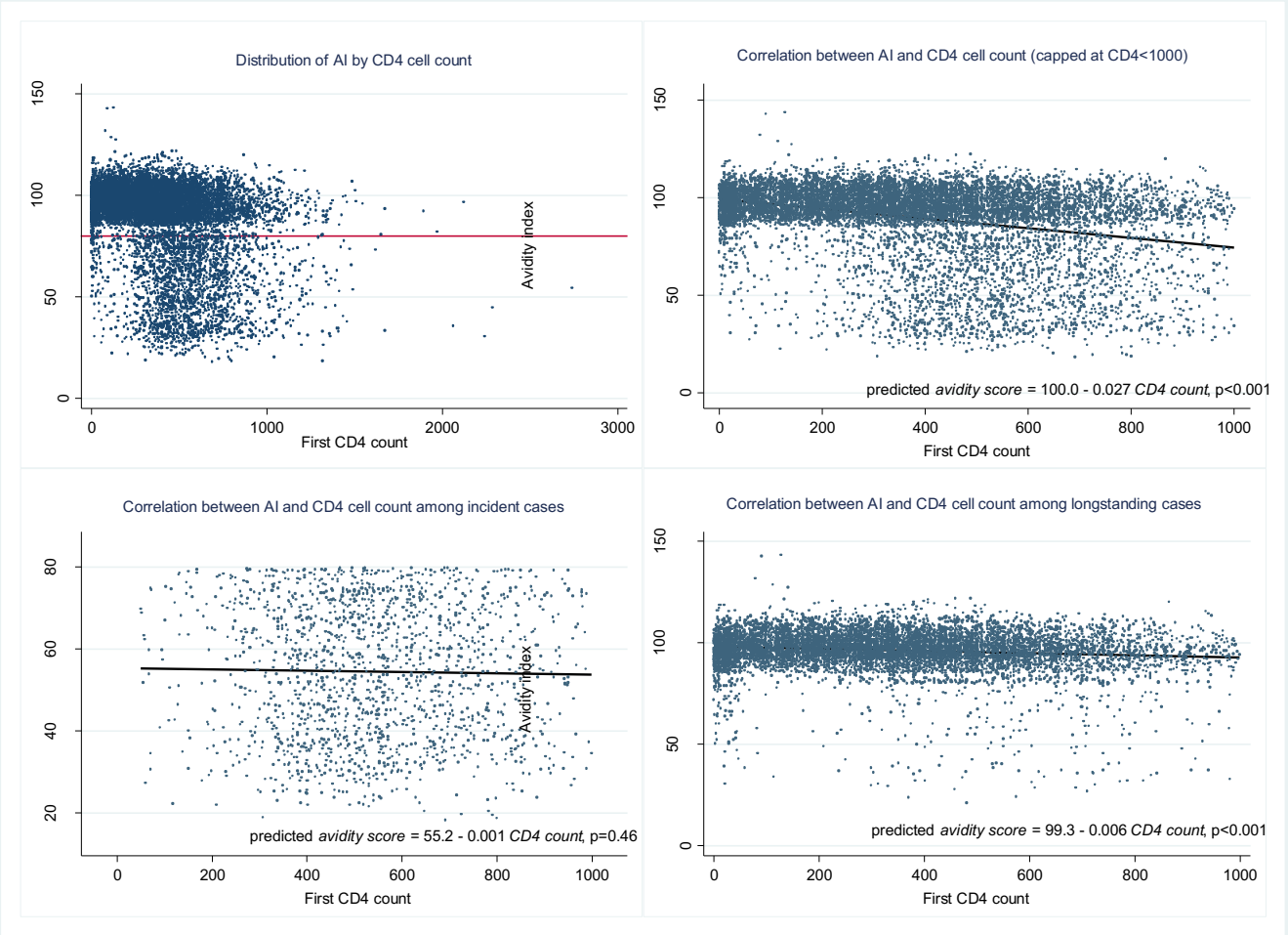
Studies have shown that in the absence of ART, low CD4 cell count is an indicator of late stage disease and conversely, high CD4 counts associated with more recent infection.(209)

Although the CD4 decline rates can vary by age, ethnicity and comorbidities (210), the trend is the same for all. A high viral load can be associated with a new infection or may indicate very late, AIDS stage of infection. With CD4 cell count data available for 90% and viral load data available for 60% of specimens, I examined the correlation between a high CD4 cell count and a low avidity index and high viral load counts and low avidity index.

In the first of the series of graphs I present CD4 cell count by avidity index illustrating little trend regarding any association (Figure 7). I subsequently confined the presentation to CD4 cell counts <1000 copies to omit outliers and zoom in. In the truncated version, a fitted regression line showed a significant relationship between CD4 count and the avidity index ($p<0.001$); the coefficient of determination of the regression model was $R2 = 0.093$, meaning CD4 explained 9% of the variance of the avidity index.

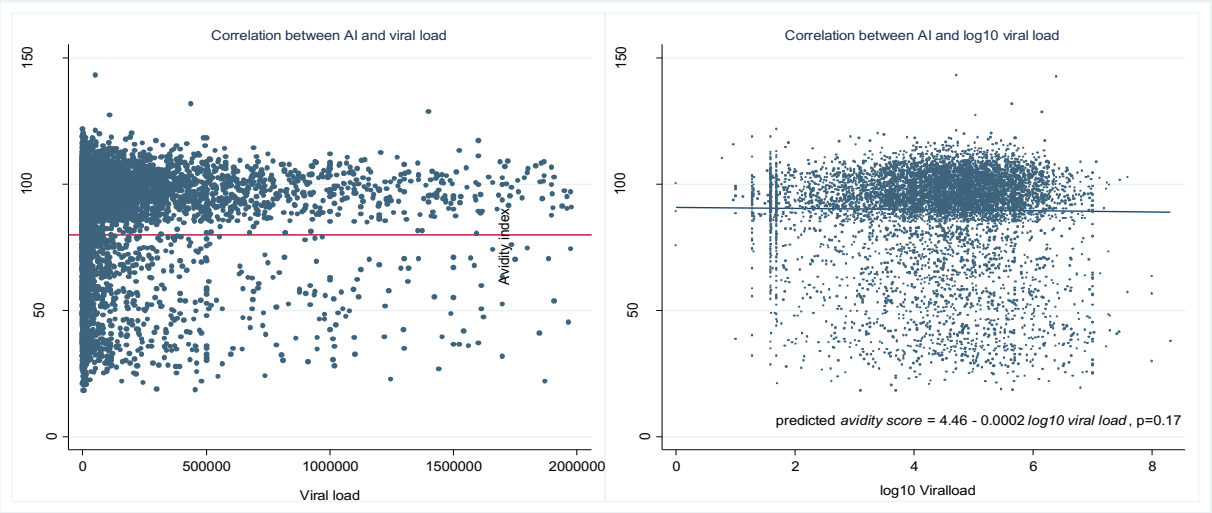
Examining the distribution of values above and below the recent infection classification avidity index cut-off value at 80.0%, showed no correlation for recent infection cases ($p=0.46$) and a small but significant relationship between CD4 count and the avidity index ($p<0.001$); $R2 = 0.02$ for longstanding cases. In this instance, for every additional CD4 cell, the avidity index decreased by 0.006 and predicted an avidity index of 99.3% where the CD4 count was zero (predicted avidity index = 99.3 -0.006(CD4count)).

Figure 7 Correlation between avidity index and CD4 cell count among people tested for recent infection



On examining viral load and avidity index, it was evident that there was even less correlation than with CD4 cell count (Figure 8). As the data showed a nonlinear relationship, I performed a log-transformation. Even with the data transformed by log10, there was only a very slight correlation between viral load and the avidity index (predicted avidity index=4.46-0.0002 viral load, p<0.001).

Figure 8 Correlation between avidity index and viral load among people tested for recent infection



Finally, I created categories of recent versus non-recent infection and avidity index (Figure 9). This showed a difference in the median CD4 counts by recent and longstanding infection and the extent of the overlap of the distribution. Further, it showed a greater disparity between those with an avidity index <20.0 compared to >80.0.

On the contrary, the comparison of median viral load by recent versus non-recent infection status showed little difference (Figure 10). With regards to the avidity index categories, considering the interquartile ranges (IQRs), there was a slight trend in declining viral loads up to an avidity index of <80.

Figure 9 Relationship between avidity index and CD4 cell count, by avidity index categories

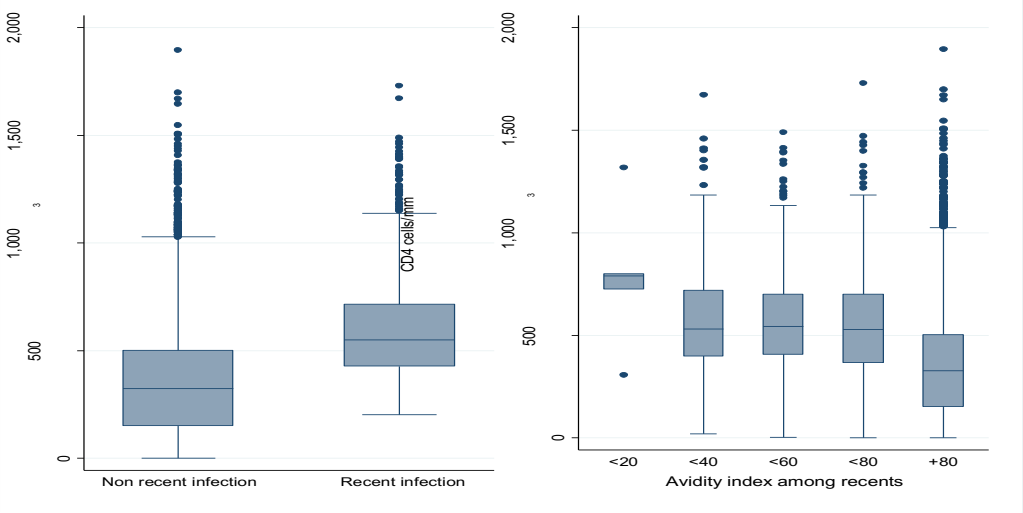
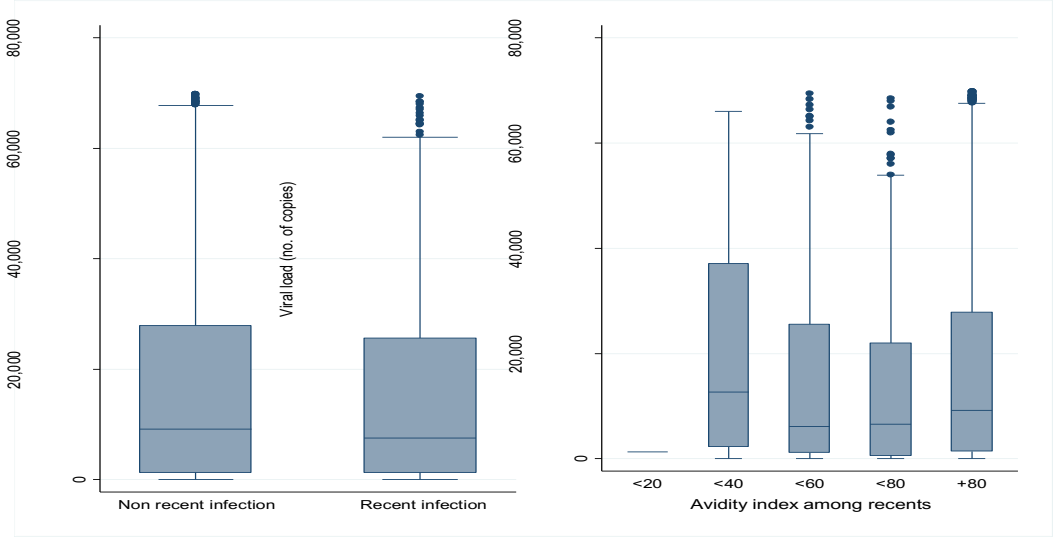


Figure 10 Relationship between avidity index and viral load, by avidity index categories



4.2 Discussion

4.2.1 Principal findings

Between 2009 and 2013, a total of 27,729 patients were newly diagnosed in England, Wales and Northern Ireland of which 11,859 (42.8%) had been tested for recent infection within four months of the diagnosis date and linked to the new HIV diagnosis report. This increased over the years as more sites enrolled to the programme submitting specimens from 24% in 2009 to 50% in 2012 and 2013. Although not all clinics and laboratories submitted specimens for testing over the studied period and overall less than 50% coverage for the years combined, analyses for the demographic variables available showed that these were broadly representative of new HIV diagnoses aside from slightly higher proportions of people from London and of black ethnicity tested, and lower proportions among PWIDs. Bias may have been introduced by the number and characteristics of the clinics/laboratories which chose to submit specimens, but no evidence of such bias was identified on review of the demographic variables available. Guided by findings of the CEPHIA group that evaluated the characteristics of a number of serological incidence assays(141) but not the AxSym avidity assay, a review of the impact of incorporating various components into the algorithm (e.g.

CD4 count, viral load and treatment information) showed that the proportion of recent infection did not vary greatly depending on whether a CD4 count threshold of <200cells/mm^3, or a viral load threshold of < 400copies/ml or a CD4<50cells/mm^3 was used. However, to minimise misclassification due to exposure to ARVs or AIDS, both the CD4<50 and viral load <400 thresholds were used in addition to any information on AIDS or previous treatment in the final algorithm. Among 580 people known to have been infected for more than a year, I estimated a FRR of 1.9% (95% C.I. 1.0%-3.4%) for the algorithm.

A comparison of the correlation between CD4 count and avidity index score showed median CD4 counts to be higher in those with recent infection compared to longstanding, and a slight trend in the relationship between viral load and avidity index score with higher readings in those both with very low and high avidity scores. However, neither the CD4 cell count nor viral load information would independently have been able to predict the avidity score and therefore been able to predict recent infections as classified by the assay.

4.2.2 Comparison with other studies

Alongside the US and France, the UK was one of the first countries to apply a RITA to routine case-based surveillance data. The assays used in the various countries were different, with differing characteristics, hindering the ability to make direct comparisons. During the studied period the BED-CEIA was used in the US and the IDE-V3 EIA in France. Comparison of recent infection testing coverage show much higher rates in France, with 77% reported between 2003 and 2006.(133, 211) Whilst in the US, this was much lower in the earlier years of the programme with 30% coverage.(212) More recent publications report this having increased to 50% for 2009.(201)Variations in testing coverage were likely due in part to the differences in the data collection structures; in France reporting of HIV diagnoses is mandatory (although they estimate approximately 40% under-reporting) to the Institute for

Public Health Surveillance and remnant specimens were tested centrally at the National HIV Reference Centre.(211) In the US, HIV is also a notifiable disease at state level but reporting to CDC is voluntary. Data on diagnoses and remnant specimen were collected at state level, within selected public health surveillance jurisdictions (the number of states varied in different publications, 22 states in 2008(212), 16 states and two cities in 2011(201, 213)), with these used to extrapolate to the whole country. In the US, testing for recent infection is conducted centrally at a national laboratory.(201)

Whilst CEPHIA have now published the characteristics of a range of incidence assays, of interest perhaps is how other countries accounted for misclassification; in France the locally derived FRR was 0.8% (95%C.I 0.0-3.1%) for the EIA. In the US, Prejean et al. did not accommodate a misclassification rate in their calculations.(201) Implications of having a high FRR are overestimating the number of recent infections and thus incidence. In France, AIDs information was considered in the final recent classification, whilst in the US, data on testing history (for repeat testers) was considered as well as AIDS information.

4.2.3 Limitations

On review of the first five years of the RITA programme, one of the main limitations which impacts all subsequent analyses is the coverage of avidity testing with respect to all new HIV diagnoses, potentially introducing sampling bias. This is not only due to potential bias within the individual clinics/laboratories as to which specimens were sent for testing but also bias in which clinics overall chose to submit specimens as the populations they serve may differ in not only demographic characteristics. At the outset of my analyses I reviewed the testing bias by all available variables and found little differences aside from oversampling people of black ethnicity and from London, although the latter was only true for the initial years. The oversampling may have stemmed from clinicians having been inclined to send more specimens from people they suspected were higher risk in addition to people who reported a

recent risk exposure. However, to note is that although the avidity data seemed broadly representative, and recent infection was associated with some demographic characteristics as shown in Chapter 5 and published, similar demographic characteristics may not mean similar risk of HIV.(199) In addition, specimens from people with strong indications of late stage infection may also not have been submitted as it could be that the recent infection test result would not be considered to add any additional insights at the individual level. However, my analyses in terms of coverage of testing by CD4 count showed no such inclination.

A full exploration of recent infection testing algorithms would have required sequential, well characterised specimens from people with known seroconversion dates which were not available at the time of study. In addition, the work undertaken by CEPHIA and added to by the CDC is extensive and covers all commercially assays currently available including that presently in use at PHE (the Limiting Antigen). With a repository of such specimens extremely difficult to collect, and more so now in the era of TasP and PrEP, these kind of specimens are particularly valuable and using them to characterise an assay no longer produced was likely considered wasteful.

While CD4 and viral load data were available for over 90% of cases for all years, they were missing for some implying that a few potential FR cases may not have been reclassified. In addition, other factors which may affect the FRR were not taken into account; e.g. it is known that HIV subtypes or clades may affect the FRR.(141) However, we believe HIV subtype variation is unlikely to have had a huge effect on the estimates as the composition of the population regarding transmission risk was similar to that of the composition of the sample to estimate the FRR (50% MSM, 43% heterosexuals, 6% other e.g. PWIDs). (Subtype B is mostly diagnosed in the UK (40% overall, 89% among MSM) followed by subtype C (34%) which is most common among heterosexuals (51% subtype C heterosexuals and 15% subtype B).(214) Despite having had the opportunity to estimate a local FRR, the population

on which this was based was not randomly selected, but rather an opportunistic sample among whom information was available that a diagnosis had occurred over a year ago. By year, this varied between 64 and 152 specimens. It is unclear how this population compared to the overall population of newly diagnosed cases and numbers for each year were too small for comparison with any differences likely to have been attributed to small numbers. Moving forward, it will be increasingly difficult to obtain a suitable population for estimating the FRR as with the expansion of PrEP an increasing number of people will have been exposed to ARVs.

Of note is that the UK is currently one of the only countries world-wide to provide the option of returning results back to patients.(215) Clinicians using these results in consultations will need to consider the 2% of all HIV positive cases tested that falsely appear recent even after consideration of other clinical data such as ARV use, CD4 cell count and viral load. For clinical, individual level use, using a lower threshold of the avidity index may be more appropriate to have increased certainty that the diagnosis of a recent infection is a true recent infection.

4.2.4 Conclusions

Analyses from this chapter show that the collection of biomarker data indicating recent HIV infection among those newly diagnosed with HIV has been feasible in the UK and may be for other countries with established case-based surveillance systems. The programme data showed that despite only up to half of all new HIV diagnoses having had an avidity test result, the data seem representative of all new HIV diagnoses by the demographic variables available. My calculated FRR was low at 1.9% (95% C.I. 1.0%-3.4%) and will be adjusted for in subsequent analyses.

The weak relationship between avidity and CD4 count is likely to be due to the wide range of possible results and the variations within and between people. Studies have shown, that particularly among individuals with HIV, it is not uncommon for CD4 counts to double or half within 8 weeks of an initial count with an average variation of 25% from the mean over this period.(216)

5 Prevalence and predictors of recent HIV infection diagnoses

Having reviewed the RITA programme coverage and representativeness, defined the algorithm and calculated the FRR, in this chapter I examined the prevalence of recent infection diagnosis by subpopulations and explore trends over time. Secondly, I determined predictors for a recent infection diagnosis. Part of the results of this Chapter have been published in Eurosurveillance (199)and were presented at the 18th Annual Conference of the British HIV Association, Birmingham 2012 (Oral presentation) (see Appendix 4).

5.1 Results

5.1.1 Prevalence of recent infection diagnoses by transmission group

Using available epidemiological data, I examined the rates of recent infection by demographic characteristics and determined associated factors. I present the rates both with and without application of the FRR. Overall, for all years combined, the proportion of recent infection was 16.3% (1932/11,859) (Table 7). After applying the FRR, the proportion recent reduced to 14.4% (1707/11,859). MSM had the highest proportion of recent infection at 24.2 %, (1453/6,009) compared to 7.9% (403/5,096) among heterosexuals and 10.1% (76/754) among others which included all non-MSM and non-heterosexual sex transmission risk groups. Considering the FRR, this reduced to 22.2% (1339/6,009) in MSM compared to 6.0% (306/5,096) in heterosexuals. Annually, the proportion of recent HIV infection increased over time with 12.8% (187/1,461) in 2009 increasing to 20.8% (397/1,907) in 2013, which, after adjusting increased from 10.9% (159/1,461) in 2009 to 19.0% (361/1,907) in 2013. This was the case for all transmission risk groups with increases from 19.1% (126/659) to 28.4% (305/1,075) in MSM (after FRR: 17.1% (113/659) to 26.5% (284/1,075)), 7.5% (53/705) to 11.0% (72/654) (after FRR: 5.7% (40/705) to 9.2% (60/654)) in

heterosexuals and from 8.3% (8/97) to 11.2% (20/178) (after FRR: 6.2% (6/97) to 9.6% (17/178)) among others.

Table 7 Proportion of recent infection by exposure group and year, 2009-2013

	Proportion of recent HIV infection diagnoses					
	Year					
	2009 % (n)	2010 % (n)	2011 % (n)	2012 % (n)	2013* % (n)	All years combined
MSM	19.1 (126/659)	21.5 (237/1103)	22.9 (355/1551)	26.5 (430/1621)	28.4 (305/1075)	24.2 (1453/6009)
after FRR	*17.1 (113/659)*	*19.6 (216/1103)*	*21.0 (326/1551)*	*24.6 (399/1621)*	*26.5 (285/1075)*	*22.3 (1339/6009)*
Heterosexuals	7.5 (53/705)	7.0 (83/1189)	7.5 (101/1346)	7.8 (94/1202)	11.0 (72/654)	7.9 (403/5096)
after FRR	*5.7 (40/705)*	*5.0 (60/1189)*	*5.6 (75/1346)*	*5.9 (71/1202)*	*9.2 (60/654)*	*6.0 (306/5096)*
Other	8.3 (8/97)	6.9 (12/175)	8.9 (11/124)	13.9 (25/180)	11.2 (20/178)	10.1 (76/754)
after FRR	*6.2 (6/97)*	*5.1 (9/175)*	*7.3 (9/124)*	*12.2 (22/180)*	*9.6 (17/178)*	*8.2 (62/754)*
All	12.8 (187/1461)	13.5 (332/2467)	15.5 (467/3021)	18.3 (549/3003)	20.8 (397/1907)	16.3 (1932/11,859)
after FRR	10.9 (159/1461)	11.6 (285/2467)	13.6 (410/3021)	16.4 (492/3003)	19.0 (361/1907)	14.4% (1707/11859)

*until September 1st 2013; after this date a different assay was used

5.1.2 Predictors of recent infection diagnoses in MSM

In MSM, higher proportions of recent infection were observed in younger individuals, with the highest among those aged 15-24 years compared with over 50 (32.4% vs. 14.5%) (Table 8). There was little difference across ethnicities and country of birth. The proportions of recent was slightly lower among MSM reported as having acquired their infection abroad than those reported as having acquired their infection in the UK (20.2% vs. 26.2%) and also slightly higher among men diagnosed in London versus outside London (26.1% vs. 21.8%). Higher proportions of recent infection were diagnosed among men with higher CD4 counts, (42.4% in men with CD4>1000cells/mm^3 vs. 4.9% in men with CD4>50≤200 cells/mm^3). I used a logistic regression model to examine the association between recent infection diagnosis (the outcome variable) and the demographic variables (the predictor variables). All variables in univariate analysis with a $p<0.2$ were included in the multivariable analysis to assess

independent relationships between the outcome and predictor variables and reduce the impact of any potential confounding. CD4 cell count was included in the model as it has been shown that CD4 cell decline is associated with age.(210) In the multivariable model, younger age (15-24 years compared to + 50 years) (adjusted odd ratio (AOR) 2.8 95% C.I 2.2-3.7), the UK as probably country of infection (AOR 1.4 95% C.I 1.2-1.6) and higher CD4 counts (>1000 cells/mm^3 compared to >50≤200 cells/mm^3, AOR: 14.3, 95% C.I. 8.9-22.8) were associated with a likely recent infection diagnosis in MSM.

5.1.3 Predictors of recent infection diagnoses in heterosexuals

In heterosexual men and women, like in MSM, the highest proportions of recent infection were in 15–24 year-olds, 14.2% (57/401) compared to 6.2% (54/872) those over 50. Black African heterosexuals had the lowest proportion of recent infection (4.9%, 141/2,899) compared with those who were white (14.4%, 185/1,289); individuals in the black Caribbean and 'black other' group had higher proportions compared to black Africans with 8.5% and 8.2% respectively. Contrary to MSM, lower proportions were observed in people born abroad (5.8%, 277/3,911 vs. 14.9%, 176/1,185) and those reported to have acquired their infection abroad compared with in the UK (6.0%, 222/3,679 vs 12.8%, 181/1,471). Multivariable analyses showed UK country of birth (AOR: 1.7, 95% C.I. 1.2-2.3) and UK country of infection (AOR: 1.4 95% C.I. 1.1-1.8) to be associated with a recent infection diagnosis.

5.1.4 Predictors of recent infection diagnoses in non MSM, non-heterosexual sex transmission risk groups

The non-MSM, non-heterosexual sex transmission risk group, referred to here as the 'other' group was diverse and included PWID, people who acquired their infection through MTCT or via blood/tissue transfer. The sizes of these individual groups were small so I combined them. However, due to the heterogeneity, interpreting any trends in this group was difficult.

The same trends in the proportions of recent infection could be observed in the different age groups, and among those who probably acquired their infection in the UK or abroad. In a few categories, numbers were small. Of note was that between a third and half of people born in the UK reported their probable country of infection to have been outside the UK (Table 9).

Table 8 Characteristics of people diagnosed with recent infection in England, Wales and Northern Ireland, by transmission risk group, 2009-2013[f]

Characteristic	Proportion tested of all new diagnoses (n/N)	Men who have sex with men			Heterosexual men and women			Other		
		% (n/N) recent[d]	Odds Ratio (95% C.I)	Adjusted Odds Ratio[a, b] (95% C.I)	% (n/N) recent[d]	Odds Ratio (95% C.I)	Adjusted Odds Ratio[a, b] (95% C.I)	% (n/N) recent[d]	Odds Ratio (95% C.I)	Adjusted Odds Ratio[a,b] (95% C.I)[e]
Total	41.2 (10,061/24,424)	24.2 (1453/6009)	--	--	7.9 (403/5096)	--	--	10.1 (76/754)	--	--
Age group (yrs)										
15-24	39.6 (1,139/3272)	32.4 (289/892)	**2.8 (2.2-3.7)**	**1.8 (1.3-2.4)**	14.2 (57/401)	**2.5 (1.7-3.7)**	1.4 (0.9-2.1)	11.6 (10/86)	2.0 (0.8-5.2)	--
25-34	42.5 (3,362/9690)	28.2 (634/2251)	**2.3 (1.8-3.0)**	**1.5 (1.2-2.0)**	9.5 (144/1,511)	**1.6 (1.2-2.2)**	1.4 (1.0-2.0)	14.3 (31/217)	2.5 (1.0-5.6)	--
35-50	41.2 (4,220/12310)	19.5 (444/2272)	**1.4 (1.1-1.8)**	1.0 (0.8-1.4)	6.4 (148/2,312)	1.0 (0.8-1.4)	1.0 (0.71.5)	8.4 (27/323)	1.4 (0.6-3.1)	--
50+	39.5 (1,340 /4296)	14.5 (86/594)	1.0	1.0	6.2 (54/872)	1.0	1.0	6.3 (8/128)	1.0	1.0
Ethnicity										
White	42.3 (5,079/15295)	24.5 (1168/4774)	1.0	1.0	14.4 (185/1289)	1.0	1.0	11.8 (16/136)	1.0	1.0
Asian	46.0 (215/1375)	24.3 (79/325)	1.0 (0.8-1.3)	--	6.4 (14/220)	**0.4 (0.2-0.7)**	0.6 (0.3-1.2)	4.0 (1/25)	0.3 (0.04-2.2)	--
Black African	38.1 (2,731/8347)	20.0 (34/170)	0.8 (0.5-1.1)	--	4.9 (141/2899)	**0.3 (0.2-0.4)**	0.6 (0.4-0.8)	7.6 (9/118)	0.6 (0.3-1.4)	--
Black Caribbean	49.8 (367/936)	19.2 (26/136)	0.7 (0.5-1.1)	--	8.5 (24/283)	**0.6 (0.4-0.9)**	0.7 (0.4-1.2)	9.1 (1/11)	0.6 (0.07-4.4)	--
Black other	48.3 (214/602)	22.0 (21/95)	0.9 (0.5-1.4)	--	8.2 (13/159)	0.5 (0.3-1.0)	0.8 (0.4-1.6)	5.3 (1/19)	0.4 (0.05-3.3)	--
Other	39.7 (1,218/3013)	24.6 (125/509)	1.0 (0.8-1.2)	--	10.6 (26/246)	**0.7 (0.5-1.1)**	1.0 (0.60-1.7)	12.8 (35/274)	1.2 (0.7-2.0)	--
Country of birth										
UK	42.9 (3,757/11682)	24.8 (889/3584	1.1 (1.0-1.2)	--	14.9 (176/1185)	**2.8 (2.3-3.5)**	**1.7 (1.2-2.3)**	10.2 (10/98)	0.9 (0.5-1.6	--
Abroad	40.3 (6,304/17886)	23.3 (564/2425)	1.0	--	5.8 (227/3911)	1.0	1.0	10.9 (53/485)	1.0	1.0
Country of infection										

UK	46.6 (4,489/12146)	26.2 (1042/3976)	**1.4 (1.2-1.6)**	**1.4 (1.2-1.7)**	12.8 (181/1,417)	**2.3 (1.9-2.8)**	**1.4 (1.1-1.8)**	7.4 (5/68)	0.7 (0.4-1.4)	--
Abroad	37.6 (5,572/17422)	20.2 (411/2033)	1.0	1.0	6.0 (222/3679)	1.0	1.0	11.3 (58/515)	1.0	1.0
Region										
London	48.0 (5,289/13466)	26.1 (866/3321)	**1.3 (1.1-1.4)**	1.3 (1.1-1.5)	7.9 (196/2495)	0.9 (0.8-1.2)	--	11.3 (38/337)	1.3 (0.8-2.1)	--
Outer London	35.6 (4,772/16102)	21.8 (587/2688)	1.0	1.0	8.0 (207/2,601)	1.0	--	10.2 (25/246)	1.0	1.0
CD4 count at diagnosis (cells/mm^3)[c]										
<50	39.6 (1055/2664)	0.0 (312)	--	--	0.0 (0/663)	--		0.0 (0/62)	--	
>50 ≤200[d]	41.4 (2,518/6997)	4.9 (31/630)	1.0	1.0	1.8 (19/1,078)	1.0	1.0	5.5 (4/73)	1.0	--
>200 ≤350	43.3 (1,893/5088)	12.9 (134/1041)	**2.9 (1.9-4.3)**	**2.6 (1.7-3.9)**	6.4 (65/1013)	**3.8 (2.3-6.4)**	**3.5 (2.1-6.0)**	5.6 (3/54)	1.3 (0.3-5.2)	1.0
>350≤500	44.7 (1,940/5245)	26.3 (385/1462)	**6.9 (4.7-10.1)**	**6.1 (4.2 -8.9)**	9.6 (74/771)	**5.9 (3.5-9.9)**	**5.0 (3.0-8.4)**	10.0 (5/50)	2.9 (0.9-10.6)	--
>500 ≤750	44.3 (1,879/5163)	35.9 (541/1508)	**10.8 (7.4-15.7)**	**9.6 (6.6-14.0)**	17.1 (117/685)	**11.5 (7.0-18.8)**	**9.5 (5.7-15.7)**	20.0 (7/35)	**6.7 (2.1-21.5)**	--
>750 ≤1000	45.4 (628/1708)	40.8 (200/499)	**12.9 (8.6-19.3)**	**11.5 (7.7-17.3)**	23.6 (52/220)	**17.3 (10.0-29.9)**	**14.2 (8.1-24.8)**	23.5 (4/17)	**4.5 (1.1-19.6)**	--
>1000	41.0 (229/669)	42.4 (73/172)	**14.3 (8.9-22.8)**	**13.0 (8.1-21.0)**	25.5 (25/98)	**19.1 (10.0-36.3)**	**15.9 (7.7-28.6)**	33.3 (2/6)	**13.5 (2.3-69.0)**	--

[a] in bold where p<0.05
[b] Not applicable where '—'.
[c] CD4 data not available for all
[d] reclassified as longstanding according to the algorithm
[e] no multivariable model as only CD4 category significant
f until September 1st 2013; after this date a different assay was used

Table 9 Probable country of infection by transmission risk group and country of birth, for years 2009-2013* combined

Country of birth	Probable country of infection							
	MSM % (n)		Heterosexuals % (n)		Other % (n)		Total % (n)	
	UK	Abroad	UK	Abroad	UK	Abroad	UK	Abroad
UK	71.1 (2,825)	37.3 (759)	51.0 (723)	12.6 (462)	64.1 (82)	12.6 (79)	65.8 (3630)	20.5 (1,300)
Abroad	29.0 (1151)	62.7 (1274)	49.0 (694)	87.4 (3217)	35.9 (46)	87.4 (547)	34.3 (1891	79.5 (5,038)

*until September 1st 2013; after this date a different assay was used

5.2 Discussion

5.2.1 Principal findings

In addition to increasing RITA coverage over the studied period the proportion of recent HIV infection diagnosed rose from 10.9% in 2009 to 19.0% in 2013. There was a wide disparity between risk groups with up to one in three MSM diagnosed with recent infection in the final year of study compared to approximately one in 10 in heterosexuals. For MSM, young age, the UK as country of infection and high CD4 count at diagnosis (>1000 cells/mm^3 compared to >50≤200 cells/mm^3) were associated with recent infection. For heterosexuals, only UK country of birth and UK country of infection were associated with a recent infection. For the remaining, similar trends were observed although numbers were too small for significant results.

5.2.2 Comparison with other studies

Both in France and the US highest rates of recent infection diagnoses were found in MSM; in France this was 40% compared to 28% and 22% in French heterosexual women and men.(211) In the US, figures were only published for incident cases (discussed later). In France the risk of a recent HIV infection diagnosis was studied with infections greater in MSM compared to heterosexual men (AOR 1.9, 95% C.I. 1.6-2.2), those of French

nationality compared to sub-Saharan African (AOR 3.9, 95% C.I. 3.4-4.6), those with a higher socioeconomic status compared to an unknown and non-professional activity (AOR 1.2, 95% C.I. 1.02-1.4), those tested after a HIV risk exposure compared to tested via pregnancy and systematic screening (AOR 1.4, 1.2-1.6) and those who had had three or more HIV tests during their lifetime compared to 1 (AOR 2.5, 95% C.I. 2.16-2.93).(133) Comparison of findings is difficult as I had stratified the analysis by transmission risk group and did not have information on the other factors. Also, as the different assays have different MDRIs, these data are not comparable.

5.2.3 Limitations

Whilst analysing and presenting data on the prevalence of recent HIV infections diagnosed provides insight into the fraction of new HIV diagnoses which were likely new infections, the interpretation of these data is difficult. Firstly the MDRI of the assay is quite short and, as this value is a mean, a number of truly recent cases are likely to be missed. Secondly, diagnoses are influenced by testing patterns with regular testers more likely to be diagnosed during the recent period of infection. It is therefore difficult to disentangle whether a higher proportion of recent infection in a particular group of people may be due to more new infections or more testing. However despite this, analyses on the predictors of recent infection present characteristics one would expect to be associated with new infections, e.g. associations with young age, having acquired the infection in the UK and high CD4 counts.

5.2.4 Conclusions

Findings from this chapter show that, in addition to an increase in the number of avidity tests conducted, an increasing proportion of new HIV diagnoses were being diagnosed as recent infection between 2009 and September 2013. Rates of recent infection diagnoses varied widely between risk groups with highest rates in MSM and lowest in heterosexuals born

abroad. Young age as a factor associated with recent infection is to be expected as people would have had less time to have been infected. The associated factors of UK country of birth and country of infection reflect the infection having been acquired close to the time of diagnosis in the UK. High CD4 counts as a factor is due to the natural history of infection; as explored in the previous Chapter. These data demonstrate the characteristics of a subset of the population with incident HIV infection. To what degree this sample reflects the population affected by incident infection is unknown. However, although this analysis does not reflect HIV incidence, it demonstrates high rates of new infections in key population groups. As such the data are published annually in PHE's HIV report alongside the number of new HIV diagnoses. Comparing these results with the HIV incidence estimates that take into account differences in HIV testing patterns of subgroups will indicate to what extent testing patterns may affect interpretation of the proportions of recent infections observed.

6 HIV incidence in sexual health clinic attendees

As the recent infections determined through RITA in the previous Chapter did not reflect HIV incidence in this Chapter I combined the RITA data with data from sexual health clinics which includes information on HIV testing and diagnoses conducted in these settings throughout England. This was the first attempt to generate HIV incidence estimates using these data. I applied the cross-sectional method using each year of the surveillance data as a cross-sectional survey (see section 3.6 for more on methods). This work has been published in PLoS One (217) and was presented at the annual conference of the British Association for Sexual Health and HIV, 2015 (Oral presentation.)

6.1 Results

6.1.1 Number of people tested for HIV in sexual health clinics

As described in the methods section, using the guidance provided by WHO on how to generate incidence estimates from cross-sectional survey data using RITAs, I combined the recent infection data with HIV testing data from sexual health clinics to obtain corresponding information on the number of people tested for HIV. Due to the fact that these data were taken from two different datasets (RITA and GUMCAD), I needed to ensure they were comparable which I did by aligning the data by clinic. As GUMCAD data are considered complete, and RITA was up to 50% complete in the final year (based on coverage of new HIV diagnoses), I needed to obtain a number of HIV tests that corresponded to the 50% coverage of RITA. Therefore, using the GUMCAD data, for each clinic, each year, I examined the number of HIV tests undertaken and the number of resulting HIV diagnoses thereby calculating the number of tests per diagnosis. I used the number of HIV tests per diagnosis in the GUMCAD dataset to determine the number of HIV tests corresponding to each recent infection diagnosis in the RITA data.

Between 2009 and September 2013, the number of clinics which submitted specimens for recent infection testing was 144, 141, 136, 150 and 125 of a total of 210 in England. A total of 19,008 new diagnoses were reported over this period in the GUMCAD data with similar numbers each year, apart from in 2013, where data were included only until September for that year (Table 10). The number of people tested for each HIV diagnosis increased over the years from 162 in 2009 to 215 in 2013. This increase occurred in all risk groups, however there was significant variation between the groups with a much lower number of tests per diagnosis in MSM (increasing from 26 in 2009 to 41 in 2013) compared to heterosexuals (increasing from 236 in 2009 to 424 in 2013). As described in the methods, each clinic attendee was considered only once each year (the first test) and people may have attended multiple times and have had more than one test. However, in black African heterosexuals, the test per diagnosis rate was similar to that of MSM, increasing from 22.1 in 2009 to 55 in 2013. For 2012, the most recent year for which there was complete data, this equated to a positivity rate of 0.50% for all attendees, 2.7% for MSM, 0.27% among heterosexuals and 2.2% for black Africans. For all risk groups combined, the estimated number of negative tests was 237,395 in 2009 increasing to 534,809 in 2012; in MSM this was 18,080 in 2009 increasing to 53,379 in 2012 and in heterosexuals, 160,036 in 2009 increasing to 389,214 in 2012. In black African heterosexuals, the estimated number of negative tests was 9,298 in 2009 increasing to 25,457 in 2012.

6.1.2 Recent HIV infection rates in sexual health clinic attendees

The proportion of recent HIV infection by risk group here varies slightly from that presented in Chapter 5 as only people diagnosed for the first time in sexual health clinics were included, although the trends are the same. After adjusting for the FRR (1.9%) the proportion of recent infection overall was 9.8% (145/1,478) in 2009, increasing to 16.9% (456/2,700) in 2012 and 19.3% (321/1,665) in 2013. For MSM it was 14.5% (103/715) in 2009 increasing to 25.1% (376/1,497) in 2012 and 27.3% (265/970) in 2013 and for heterosexuals 5.3%

(36/681) in 2009 increasing to 5.8% (61/1,050) in 2012 and 8.4% (46/546) in 2013. In black African heterosexuals the recent infection rates were lowest at 1.7% (8/440) in 2009 increasing to 3.1% (18/585) in 2012 and in 4.4% (11/256) in 2013.

6.1.3 Estimated HIV incidence in sexual health clinic attendees

Using the formula for cross-sectional incidence estimates (see Section 3.6), I estimated overall HIV incidence in sexual health clinics to have changed little from 0.13% (95% C.I 0.10%-0.16%) in 2009 to 0.19% (95%C.I 0.16%-0.21%) in 2012 and 0.20% (95% C.I. 0.17%-0.23%) in 2013. HIV incidence was highest in MSM with also little change over the period with 1.24% (95%C.I. 0.96%-1.52%) in 2009 and 1.52% (95%C.I 1.30-1.75) in 2012 and 1.46% (95% C.I. 1.23%-1.70%) in 2013 (Figure 11). In heterosexuals, there was no change with estimates between 0.03% (95% C.I. 0.02%-0.05%) and 0.05% (95% C.I. 0.03%-0.07%) over the years (Figure 12). In black African heterosexuals, HIV incidence was close to 5 times higher each year than for heterosexuals overall, and it also remained stable over the period between 0.15% (95% C.I 0.05%-0.26%) and 0.19% (95% C.I. 0.05%-0.33%).

As approximately half of new HIV diagnoses in England were in the capital, London, I explored how incidence rates reflected this. I found a similar pattern in incidence with estimates slightly, but not statistically significantly higher, particularly in MSM (Table 11). As the rates were slightly higher in London I conducted further analysis by age which showed the increase in incidence in MSM was in all age groups (Table 12.) with highest rates in those aged 25-34 years followed by 35-50 years, although again, estimates were not significantly different for any of the age groups. There was little difference in incidence by age in heterosexuals; estimates were marginally higher in persons aged 35-50 years, however also not significantly different.

Table 10 Estimated HIV incidence in sexual health clinics in England; by transmission risk group 2009-2013

	Risk group	All attendees					MSM					Heterosexuals All					Heterosexuals Black Africans				
	Year	2009	2010	2011	2012	2013*	2009	2010	2011	2012	2013*	2009	2010	2011	2012	2013*	2009	2010	2011	2012	2013*
GUMCAD	N tests taken[a]	699487	694800	739446	774212	520240	44634	51403	65443	71152	53053	518494	561970	633006	667166	447302	23813	26613	29178	33031	23113
	N Dx[b]	4328	4117	4250	3889	2424	1698	1636	2010	1941	1280	2197	1947	2045	1795	1056	1076	961	953	742	420
	Tests per Dx[c]	161.6	168.8	174	199.1	214.6	26.3	31.4	32.6	36.7	41.4	236	288.6	309.5	371.7	423.6	22.1	27.7	30.6	44.5	55
	N tested[d]	1478	2230	2724	2700	1665	715	997	1428	1497	970	681	1083	1180	1050	546	440	660	671	585	256
RITA	N recent (0.8)[e]	173	286	426	507	353	117	206	327	404	283	49	68	89	81	56	16	28	30	29	16
	% recent[f]	11.7	12.8	15.6	18.8	21.2	16.4	20.7	22.9	27	29.2	7.2	6.3	7.5	7.7	10.3	3.6	4.2	4.5	4.96	6.3
	N recent after FRR applied[g]	144.9	243.6	374.2	455.7	321.4	103.4	187.1	299.9	375.6	264.6	36.1	47.4	66.6	61	45.6	7.7	15.5	17.3	17.9	11.1
	% recent after FRR[h**]	9.8	10.9	13.7	16.9	19.3	14.5	18.7	21.0	25.1	27.3	5.3	4.4	5.6	5.8	8.36	1.7	2.3	2.6	3.1	4.4
Estimated	N tests taken for RITA[i]	238873	376343	473941	537509	357343	18795	31326	46494	54876	40204	160717	312590	365255	390264	231275	9738	18277	20544	26042	14088
	N negative tests[j]	237395	374113	471217	534809	355678	18080	30329	45066	53379	39234	160036	311507	364075	389214	231275	9298	17617	19873	25457	14088
	Estimated incidence[k] (%) (95% C.I)	**0.13** (0.10-0.16)	**0.14** (0.12-0.17)	**0.17** (0.15-0.20)	**0.19** (0.16-0.21)	**0.20** (0.17-0.23)	**1.24** (0.96-1.52	**1.34** (1.10-1.58)	**1.44** (1.22-1.67)	**1.52** (1.30-1.75)	**1.46** (1.23-1.70)	**0.05** (0.03-0.07)	**0.03** (0.02-0.05)	**0.04** (0.03-0.05)	**0.03** (0.02-0.05)	**0.04** (0.03-0.06)	**0.18** (0.03-0.39)	**0.19** (0.04-0.34)	**0.19** (0.05-0.33)	**0.15** (0.05-0.26)	**0.17** (0.05-0.30)

[a] data from GUMCAD, [b] = data from New HIV Surveillance, [c]=a/b, [d,e,f] = data from the recent HIV infection testing programme after applying the RITA algorithm [g]=f/d,[h]=f-(FRR*d),[i]=h/d [j]=c*d, [k]=j-d, [l]applying the WHO formula[24]

*until September 1st 2013; after this date a different assay was used

** False Recent Rate = 1.9%

Table 11 Estimated HIV incidence in sexual health clinics in London; by transmission risk group 2009-2013

	Risk group	Total					MSM					Heterosexuals									
												All					Black Africans				
	Year	2009	2010	2011	2012	2013*	2009	2010	2011	2012	2013*	2009	2010	2011	2012	2013*	2009	2010	2011	2012	2013*
GUMCAD	N tests taken[a]	219614	232398	244252	270491	193875	22651	27206	32694	39143	30016	155256	171222	193291	223185	157864	14015	15667	17484	19833	14067
	N Dx[b]	2048	2019	2204	1940	1286	951	931	1184	1101	759	905	788	925	781	484	454	424	491	367	224
	Tests per Dx[c]	107.2	115.1	110.8	139.4	150.8	23.8	29.2	27.6	35.6	39.5	171.6	217.3	209	285.8	326.2	30.87	37	35.6	54	62.8
	N tested[d]	961	1206	1513	1468	958	492	537	845	859	593	402	592	599	524	277	258	362	361	317	139
RITA	N recent (0.8)[e]	124	156	262	321	231	88	113	205	267	195	30	37	50	36	30	11	17	19	19	8
	% recent[f]	12.9	13	17.3	21.9	24.1	17.9	21.0	24.3	31.1	32.9	7.5	6.3	8.4	6.9	10.8	4.3	4.7	5.3	6.0	5.8
	N recent after FRR applied[g]	105.7	133	233	293.1	212.8	78.7	102.8	188.9	250.7	183.7	22.4	25.8	38.6	26	24.7	6.1	10.1	12.1	13.0	5.4
	% recent after FRR[h**]	11.0%	11.0%	15.4%	20.0%	22.2%	16.0%	19.1%	22.4%	29.2%	31.0%	5.6%	4.4%	6.5%	5.0%	8.9%	2.4%	2.8%	3.4%	4.1%	3.9%
Estimated	N tests taken for RITA[i]	103051	138817	167674	204681	144426	11718	15692	23333	30539	23451	68965	128634	125169	149743	90348	7964	13376	12855	17131	8729
	N negative tests[j]	102090	137611	166161	203213	143468	11226	15155	22488	29680	22858	68563	128042	124570	149219	90071	7706	13014	12494	16814	8591
	Estimated inc-idence[k] (%) (95% C.I)	**0.23** (0.17-0.28)	**0.21** (0.17-0.26)	**0.31** (0.25-0.36)	**0.31** (0.26-0.36)	**0.32** (0.27-0.38)	**1.52** (1.13-1.90)	**1.47** (1.14-1.80)	**1.82** (1.49-2.14)	**1.83** (1.53-2.31)	**1.74** (1.43-2.05)	**0.07** (0.04-0.11)	**0.04** (0.02-0.07)	**0.07** (0.04-0.09)	**0.04** (0.02-0.06)	**0.06** (0.03-0.09)	**0.17** (0.02-0.37)	**0.17** (0.02-0.32)	**0.21** (0.05-0.37)	**0.17** (0.05-0.29)	**0.14** (0.01-0.28)

[a] data from GUMCAD, [b] = data from New HIV Surveillance, [c]=a/b, [d,e,f] = data from the recent HIV infection testing programme after applying the RITA algorithm [g]=f/d,[h]=f-(FRR*d),[i]=h/d [j]=c*d, [k]=j-d, [l]applying the WHO formula[24]

*until September 1st 2013; after this date a different assay was used

** False Recent Rate = 1.9%

Table 12 Estimated HIV incidence in sexual health clinics in London; by transmission risk group and age 2009-2013

			2009		2010		2011		2012		2013*	
		Age group (years)	Estimated incidence[k] (%)	95% C.I	Estimated incidence[k] (%)	95% C.I	Estimated incidence[k] (%)	95% C.I	Estimated incidence[k] (%)	95% C.I	Estimated incidence[k] (%)	95% C.I
ALL		15-24	0.06	0.03-0.08	0.07	0.05-0.09	0.09	0.07-0.11	0.09	0.07-0.11	0.10	0.08-0.13
		25-34	0.15	0.11-0.20	0.18	0.04-0.22	0.19	0.15-0.22	0.21	0.17-0.24	0.22	0.17-0.26
		35-50	0.24	0.15-0.32	0.23	0.17-0.30	0.30	0.23-0.36	0.30	0.24-0.36	0.29	0.22-0.36
		50+	0.18	0.04-0.33	0.12	0.03-0.20	0.21	0.11-0.31	0.26	0.16-0.37	0.26	0.14-0.39
MSM		15-24	0.76	0.35-1.17	1.17	0.77-1.56	1.14	0.84-1.45	1.28	0.95-1.60	1.34	0.97-1.72
		25-34	1.48	1.02-1.93	1.57	1.19-1.95	1.63	1.30-1.97	1.77	1.45-2.10	1.68	1.33-2.03
		35-50	1.40	0.87-1.93	1.39	0.98-1.80	1.65	1.26-2.03	1.64	1.28-2.00	1.32	0.98-1.66
		50+	0.82	0.13-1.51	0.62	0.20-1.04	0.70	0.31-1.10	0.69	0.34-1.04	1.12	0.52-1.73
Hetero-sexuals	All	15-24	0.03	0.01-0.06	0.01	0.00-0.02	0.02	0.01-0.04	0.01	0.00-0.02	0.02	0.00-0.03
		25-34	0.04	0.01-0.07	0.05	0.02-0.07	0.03	0.02-0.05	0.03	0.01-0.04	0.04	0.02-0.07
		35-50	0.09	0.03-0.16	0.06	0.02-0.10	0.07	0.03-0.12	0.06	0.03-0.10	0.08	0.04-0.13
		50+	0.08	0.05-0.22	0.01	0.04-0.06	0.12	0.04-0.21	0.15	0.06-0.25	0.08	0.01-0.17
	Black Africans	15-24	0.22	0.0-0.47	0.01	0.08-1.11	0.21	0.02-0.40	0.11	0.00-0.23	0.09	0.06-0.24
		25-34	0.00	0.23-0.20	0.31	0.06-0.56	0.23	0.04-0.43	0.13	0.01-0.25	0.13	0.05-0.31
		35-50	0.47	0.17-1.11	0.36	0.03-0.75	0.18	0.16-0.52	0.21	0.05-0.47	0.33	0.00-0.67
		50+	0.15	0.23-1.52	0.00	N/A	0.00	N/A	0.27	0.39-0.93	0.35	0.50-1.19

*until September 1st 2013; after this date a different assay was used.
[k] [l]applying the WHO formula[24]

Figure 11 Trends in HIV incidence among MSM sexual health clinic attendees by region and age 2009-2013

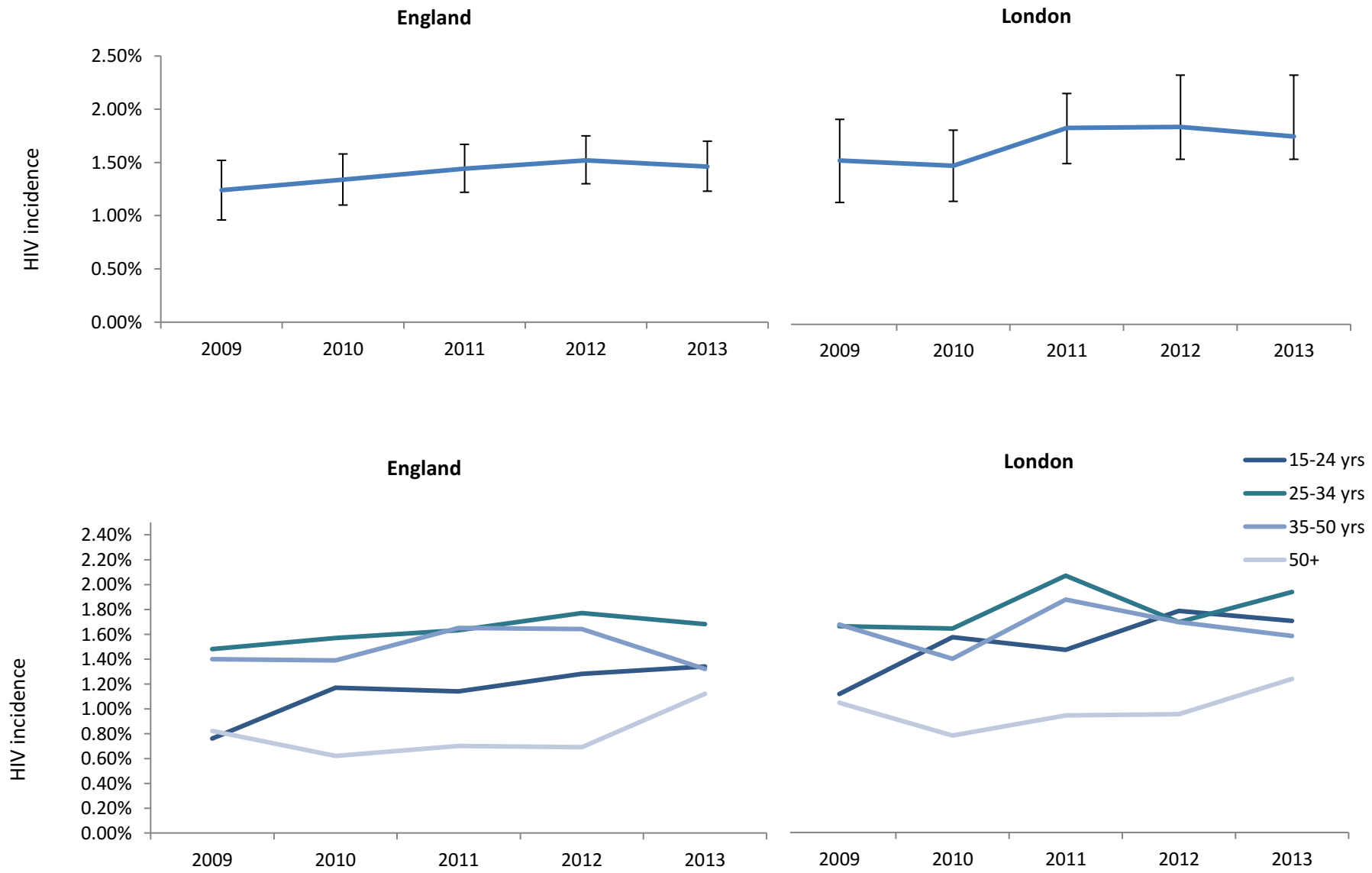
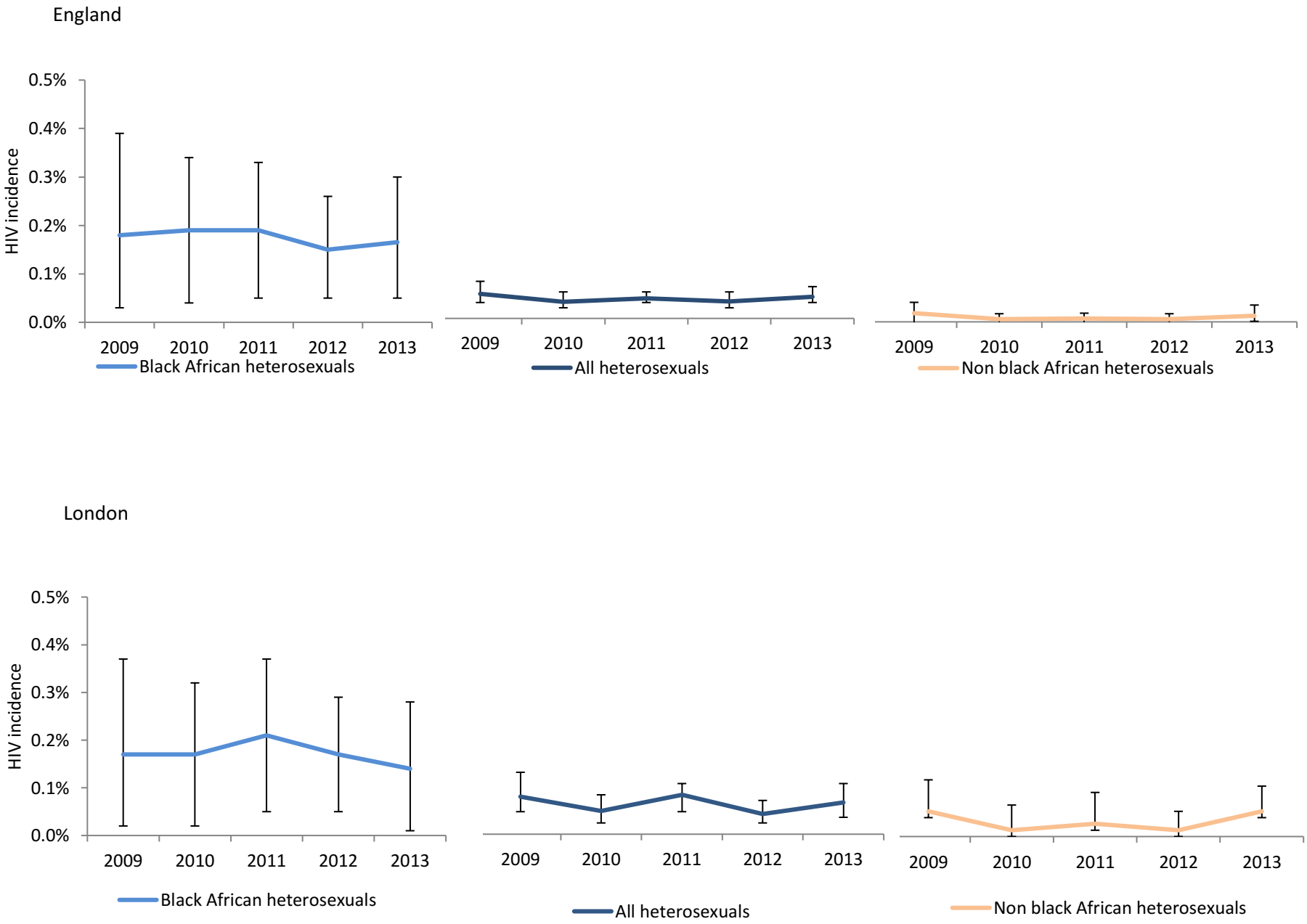


Figure 12 Trends in annual HIV incidence among heterosexual sexual health clinic attendees by year and region



6.1.4 Sensitivity analyses varying the FRR and MDRI

As highlighted in Chapter 2, the estimate for the MDRI for the AxSym avidity assay is based on a study including relatively few people.(153) Similarly, my calculation of the FRR was based only on 580 people (see section 4.4). I therefore explored how sensitive my incidence estimates were to any variation of these parameters. Firstly, I chose to vary the FFR by i.) increasing it by 50% to 2.85% and ii.) doubling it to 3.8%. In Table 13 I illustrate how much this affected the cross-sectional incidence rates and show that even with double the FRR, this had very little impact.

The MDRI can vary depending on the population tested and the population studied here is likely to be different from that the MDRI estimate is based on. For example rapid HIV tests are able to detect infection after approximately 20 days.(100) The window period for a fourth generation antigen/antibody test now commonly used is four weeks. The MDRI was therefore the time since seroconversion rather than the time since infection. Hence, the MDRI may have an additional 20-30 days if it is considered to be the time since infection. I have therefore presented the impact on incidence estimates increasing the MDRI by 20, 30 and 40 days (Table 14). This showed that the incidence estimates were more sensitive to these changes but even a 20% increase in the MDRI did not result in estimates outside of the confidence intervals. Lastly, I conducted estimates for a higher FRR and the MDRI combined; even with a 3.8% FRR and 221 day MDRI, HIV incidence estimates were not significantly different compared to original estimates (Table 15).

Table 13 Sensitivity analyses: HIV incidence estimates in sexual health clinic attendees varying the FRR

	All					MSM					All heterosexuals					Black Africans				
Year	2009	2010	2011	2012	2013*	2009	2010	2011	2012	2013*	2009	2010	2011	2012	2013*	2009	2010	2011	2012	2013*
N tested for RITA[d]	1478	2230	2724	2700	1665	715	997	1428	1497	970	681	1083	1180	1050	546	440	660	671	585	256
N (%) recent (0.8)[e]	173 (11.7)	286 (12.8)	426 (15.6)	507 (18.8)	353 (21.2)	117 (16.4)	206 (20.7)	327 (22.9)	404 (27)	283 (29.2)	49 (7.2)	68 (6.3)	89 (7.5)	81 (7.7)	56 (10.3)	16 (3.6)	28 (4.2)	30 (4.5)	29 (5.0)	16 (6.3)
N (%) recent after FRR applied (1.9%)[g]	144.9 (9.8)	243.6 (10.9)	374.2 (13.7)	455.7 (16.9)	321.4 (19.3)	103.4 (14.5)	187.1 (18.7)	299.9 (21.0)	375.6 (25.1)	264.6 (27.3)	36.1 (5.3)	47.4 (4.4)	66.6 (5.6)	61 (5.8)	45.6 (8.4)	7.7 (1.8)	15.5 (2.3)	17.3 (2.6)	17.9 (3.1)	11.1 (4.3)
Estimated incidence using 1.9% (95% C.I)	0.13 (0.10-0.16)	0.14 (0.12-0.17)	0.17 (0.15-0.20)	0.19 (0.16-0.21)	0.20 (0.17-0.23)	1.24 (0.96-1.52)	1.34 (1.10-1.58)	1.44 (1.22-1.67)	1.52 (1.30-1.75)	1.46 (1.23-1.70)	0.05 (0.03-0.07)	0.03 (0.02-0.05)	0.04 (0.03-0.05)	0.03 (0.02-0.05)	0.04 (0.03-0.06)	0.18 (0.03-0.39)	0.19 (0.04-0.34)	0.19 (0.05-0.33)	0.15 (0.05-0.26)	0.17 (0.05-0.30)
N (%) recent after FRR applied 2.85%	130.8 (8.8)	222.4 (10.0)	348.4 (12.8)	430.0 (15.9)	305.5 (18.3)	96.6 (13.5)	177.6 (17.8)	286.3 (20.0)	361.3 (24.1)	255.4 (26.3)	29.6 (4.3)	37.1 (3.4)	55.4 (4.7)	51.1 (4.9)	40.4 (7.4)	3.5 (0.8)	9.2 (1.4)	10.9 (1.6)	12.3 (2.1)	8.7 (3.4)
Estimated incidence using FRR[k] 2.85% (95% C.I)	0.13 (0.10-0.15)	0.14 (0.11-0.16)	0.17 (0.14-0.20)	0.18 (0.15-0.21)	0.19 (0.16-0.23)	1.21 (0.92-1.50)	1.33 (1.07-1.58)	1.44 (1.20-1.67)	1.52 (1.30-1.76)	1.47 (1.23-1.72)	0.04 (0.02-0.06)	0.03 (0.01-0.04)	0.03 (0.03-0.05)	0.03 (0.02-0.04)	0.04 (0.02-0.05)	0.18 (0.0-0.37)	0.12 (0.0-0.28)	0.12 (0.0-0.27)	0.11 (0.00-0.22)	0.14 (0.01-0.27)
N(%) recent after FRR applied (3.8%)[g]	116.8 (7.9)	201.3 (9.0)	322.5 (11.8)	404.4 (15.0)	289.7 (17.4)	89.8 (12.6)	168.1 (16.9)	272.7 (19.1)	347.1 (23.2)	246.1 (25.4)	23.1 (3.4)	26.8 (2.5)	44.2 (3.7)	41.1 (3.9)	35.2 (6.4)	0 (0.0)	2.9 (0.4)	4.5 (0.7)	6.8 (1.2)	6.2 (2.4)
Estimated incidence using 3.8% FRR[k] (95% C.I)	0.12 (0.09-0.15)	0.13 (0.10-0.16)	0.16 (0.13-0.19)	0.18 (0.15-0.21)	0.19 (0.16-0.23)	1.18 (0.87-1.48)	1.31 (1.05-1.57)	1.43 (1.19-1.67)	1.52 (1.29-1.78)	1.48 (1.23-1.74)	0.03 (0.01-0.06)	0.02 (0.00-0.04)	0.03 (0.01-0.04)	0.02 (0.01-0.04)	0.04 (0.02-0.05)	0 (0.0)	0.04 (0.0-0.23)	0.05 (0.0-0.23)	0.06 (0.0-0.19)	0.11 (0.0-0.25)

Table 14 Sensitivity analyses: HIV incidence estimates varying the MDRI

	All					MSM					All heterosexuals					Black African heterosexuals				
Year	2009	2010	2011	2012	2013*	2009	2010	2011	2012	2013*	2009	2010	2011	2012	2013*	2009	2010	2011	2012	2013*
Estimated incidence 95% C.I) using of 181 days	0.13 (0.10-0.16)	0.14 (0.12-0.17)	0.17 (0.15-0.20)	0.19 (0.16-0.21)	0.20 (0.17-0.23)	1.24 (0.96-1.52)	1.34 (1.10-1.58)	1.44 (1.22-1.67)	1.52 (1.30-1.75)	1.46 (1.23-1.70)	0.05 (0.03-0.07)	0.03 (0.02-0.05)	0.04 (0.03-0.05)	0.03 (0.02-0.05)	0.04 (0.03-0.06)	0.18 (0.03-0.39)	0.19 (0.04-0.34)	0.19 (0.05-0.33)	0.15 (0.05-0.26)	0.17 (0.05-0.30)
Estimated incidence 95% C.I) using of 201 days	0.12 (0.09-0.14)	0.13 (0.10-0.15)	0.15 (0.13-0.18)	0.17 (0.14-0.19)	0.18 (0.15-0.20)	1.11 (0.86-1.36)	1.20 (0.98-1.41)	1.29 (1.09-1.49)	1.36 (1.16-1.56)	1.31 (1.10-1.52)	0.04 (0.03-0.06)	0.03 (0.02-0.04)	0.04 (0.02-0.05)	0.03 (0.02-0.04)	0.04 (0.03-0.05)	0.16 (0.0-0.34)	0.17 (0.05-0.30)	0.17 (0.06-0.28)	0.14 (0.05-0.22)	0.15 (0.04-0.26)
Estimated incidence 95% C.I) using of 211 days	0.11 (0.09-0.14)	0.12 (0.10-0.14)	0.15 (0.12-0.17)	0.16 (0.13-0.18)	0.17 (0.14-0.19)	1.05 (0.81-1.29)	1.14 (0.93-1.34)	1.23 (1.03-1.42)	1.30 (1.11-1.48)	1.24 (1.04-1.44)	0.04 (0.02-0.06)	0.03 (0.02-0.04)	0.03 (0.02-0.04)	0.03 (0.02-0.04)	0.04 (0.02-0.05)	0.15 (0.0-0.32)	0.16 (0.04-0.28)	0.16 (0.05-0.27)	0.13 (0.05-0.21)	0.15 (0.04-0.25)
Estimated incidence 95% C.I) using of 221 days	0.10 (0.09-0.13)	0.11 (0.09-0.13)	0.14 (0.12-0.16)	0.15 (0.13-0.17)	0.16 (0.13-0.18)	1.00 (0.77-1.23)	1.08 (0.89-1.28)	1.17 (0.98-1.35)	1.23 (1.05-1.41)	1.18 (0.99-1.37)	0.04 (0.02-0.06)	0.03 (0.02-0.04)	0.03 (0.02-0.04)	0.03 (0.02-0.04)	0.03 (0.02-0.05)	0.14 (0.0-0.30)	0.15 (0.04-0.27)	0.15 (0.05-0.26)	0.12 (0.05-0.20)	0.14 (0.04-0.24)

* FRR 1.9%

Table 15 Sensitivity analyses: HIV incidence estimates varying the FRR and MDRI

	All					MSM					All heterosexuals					Black African heterosexuals				
Year	2009	2010	2011	2012	2013*	2009	2010	2011	2012	2013*	2009	2010	2011	2012	2013*	2009	2010	2011	2012	2013*
Estimated incidence 95% C.I) using of 221 days and FRR 3.8%	0.09 (0.07-0.12)	0.10 (0.08-0.12)	0.13 (0.11-0.15)	0.14 (0.12-0.16)	0.15 (0.13-0.18)	0.93 (0.69-1.18)	1.04 (0.84-1.25)	1.14 (0.95-1.33)	1.22 (1.03-1.41)	1.18 (0.98-1.38)	0.03 (0.01-0.05)	0.02 (0.00-0.03)	0.02 (0.01-0.04)	0.02 (0.01-0.03)	0.03 (0.02-0.04)	0.0 (0.0 - 0.0)	0.03 (0.12-0.18)	0.04 (0.0-0.18)	0.05 (0.0-0.15)	0.08 (0.0-0.20)

6.1.5 Sample size considerations for observing trends over time

The utility of serological assays hinges majorly on the ability to determine trends over time which is affected by the sample size. Here I explored, using an online tool made available by CEPHIA for countries to use conducting cross-sectional surveys over varying periods of time, the sample sizes required to detect a reduction in incidence over two time points.(218) Using the characteristics of the our assay (MDRI 181 days and FRR 1.9%) and the 1.5% incidence rate in MSM in our study in 2012 (the most recent complete year), an estimated sample size of 55,000 (number of tests taken for RITA) and 5% prevalence, would have been needed to have observed a change in incidence greater than 20% to 5% significance and 80% power. Similarly, among all attendees with an estimated sample size of 540,000, incidence of 0.2% and prevalence of 1%, a change of more than 20% in incidence would also have been required to reliably infer a reduction to the same precision.

In a scenario where all new HIV diagnoses had been tested for recent infection (2,885 in MSM), and assuming the same HIV incidence (1.5%), resulting in an estimated sample size of 105,880 HIV tests and 5% prevalence, we would have needed to observe a reduction of more than 15% in incidence to infer a reduction to 5% significance and 80% power.

6.2 Discussion

6.2.1 Principal findings

This was the first attempt to estimate HIV incidence using biomarkers for recent infection and was conducted in a representative sample of sexual health clinic attendees. It was also the first study to provide national HIV incidence estimates for the heterosexual population in England in healthcare settings. It was based on unique methodology, using annual

surveillance data as a cross-sectional survey of people attending sexual health clinics, thereby enabling combining the RITA data with nation-wide HIV testing information. In this sample, the proportion of recent infection after adjusting for the FRR was 9.8% in 2009, increasing to 19.3% in 2013. Combined with the testing data, this resulted in an overall incidence estimate of 0.13% (95% C.I 0.10%-0.16%) in 2009 increasing to 0.20% (95% C.I. 0.17%-0.23%) in 2013. Among MSM, incidence was highest, varying between 1.24% (95%C.I. 0.96%-1.52%) and 1.52% (95% C.I. 1.29%-1.78%) over this period, although not significantly. Among heterosexuals, there was no change over the period, with rates lowest, fluctuating between 0.03% (95% C.I. 0.02%-0.05%) and 0.05% (95% C.I. 0.03%-0.07%). Of note was that in black African heterosexuals, considered to be the second most important risk group with respect to HIV, incidence was nearly 5 times higher each year than for heterosexuals overall, remaining stable over the period between 0.15% (95% C.I 0.05%-0.26%) and 0.19% (95% C.I. 0.05%-0.33%). These rates translate to 2.0 per 1,000 incident HIV cases in all sexual health clinic attendees annually in 2013, 1.7 per 1,000 for black African heterosexuals, 0.4 per 1,000 in heterosexuals overall and 15.2 per 1,000 in MSM.

Findings showed the number of tests per diagnosis overall was between 162 and 215 over the period and was lowest in MSM (between 26 and 41), with similar rates in black African heterosexuals (between 22 and 55) compared to the many more in heterosexuals (between 236 and 424). This increased overtime for all groups illustrating a change in testing patterns over the studied period. For 2013, the number of tests per diagnosis equated to a positivity rate of 0.47% for all attendees, 2.4% for MSM, 0.24% among heterosexuals and 1.8% for black Africans.

6.2.2 Comparison of other studies

There are previous studies using biomarkers in sentinel sites in the UK although only in MSM. Among MSM attending for HIV treatment at Brighton and Sussex Hospital between

1996 and 2005, RITA was applied to serum collected at HIV diagnosis; they found increasing proportions of incident infection with 26% recent infections of 67 new diagnoses in 1996 increasing to 47% recent infections of 122 new diagnoses in 2005. (134). Another examined HIV incidence in MSM participants of an unlinked anonymous HIV prevalence serosurvey conducted in 15 sentinel sexual health clinics in England and Wales between 1995 and 2005. Of 43,100 specimens collected, 3565 were HIV positive and 317 had recent infection; in 2001 the estimated incidence was 2.45%.(10) However these studies are considerably dated and in addition, in both, HIV incidence is likely to have been overestimated as the FRR of the assay used was not accounted for and likely longstanding specimens not excluded as part of an algorithm. Further, a different assay was used. In addition, the FRR of the assay used in the study, the BED, was later found to have been high and considerably higher than estimated here for the AxSym avidity assay.(219, 220) There have been no other UK studies which have used the biomarker data and sexual health clinic data as a cross-sectional sample. Another study has however estimated incidence in this healthcare seeking population specifically in MSM; Desai et al. identified incident HIV cases among people with a negative HIV test within the previous year using the GUMCAD data and estimated incidence to have been 2 per 100 pys (95%C.I 1.8-2.2) in 2012.(221) This is slightly higher than my estimate, with 1.5 per 100 pys (95% C.I. 1.30-1.75) in MSM. To note is that the populations of study are different as in that of Desai et al., it is an estimate for a subgroup of attendees who are repeat testers compared to all sexual health clinic attendees in my analysis. The repeat tester study will have firstly missed incident cases in people without a previous HIV test and secondly, missed people who may have tested previously in at different site to where they received their HIV diagnosis as a limitation of the GUMCAD data is that attendances can only be linked to individuals within and not between clinics. It has been shown that HIV testing is indicative of risk (222, 223) and one may therefore conclude that the Desai findings are likely to be a slight overestimate of HIV incidence in MSM attending sexual health clinics. However, overall the estimates are both very similar.

A study in the Netherlands also looked at incidence in STI clinics using a serological incidence assay (Architect HIV Ag/AB Combo immunoassay); between 2009 and 2011 and among 251 MSM tested for recent infection HIV incidence was estimated to be 3.3 (95% C.I. 2.5-4.1) per 100 pys which is slightly higher but could be considered broadly similar to findings in the UK.(224)

6.2.3 Limitations

Remis et al. have shown that particularly for the calculation of HIV incidence using the biomarker data in a cross-sectional study, findings can be overestimated due to earlier, motivated testing in MSM possibly driven by seroconversion illness or known high risk behaviour, increasing the likelihood of a recent infection diagnosis.(156) This has been termed the 'seroconversion effect'. Later in the thesis, in section 8.2 where I present primary behavioural data collected from MSM diagnosed with incident infection, I show that two thirds (66%) of participants had tested either due to feeling unwell or a recent risk event. Further, there may be differences in test-seeking behaviours not associated with symptoms but rather external factors; currently, the recommendations are for MSM to test annually or every three months if having sex with new or casual partners.(1) In the UK, MSM test more frequently than the general population; in 2011, 90% of HIV negative MSM recruited from gay social venues in London had ever had an HIV test and 55% had tested within the last year.(165) This compares to 18% (95% C.I 17%-19%) of all men and 23% (95% C.I. 22.2%-24.3%) of all women having ever had an HIV test between 2010 and 2012.(225)

Although the data from sexual health clinics enabled us to examine differences and trends in HIV testing patterns and diagnoses, and relate these to the sample of incident infections by area of diagnosis, there may have been a slight overestimation in the number of new HIV diagnoses observed as, in the GUMCAD system, patients can only be uniquely identified

within and not between clinics, and thus a patient may be coded as newly diagnosed in more than one clinic. Preliminary data from the pilot study for GUMCAD v.3 show that approximately 30% of MSM patients attended a different sexual health clinic in the previous year (personal communication Hamish Mohammed, Principle HIV/STI Prevention and Surveillance Scientist). If the number of new HIV diagnoses was overestimated, this would have resulted in an underestimate of the number of HIV tests per diagnosis and consequently an overestimate of HIV incidence.

Lastly, a limitation for the cross-sectional incidence estimates is that, although I was able to derive the estimates to a considerable precision, only very large changes over time can be reliably observed due to a combination of the sample size restriction and the HIV prevalence. A reduction in incidence to this extent is likely only to be observed in the presence of a major intervention which could be occurring more recently due to the success of combination prevention policies and the roll-out of PrEP.

6.2.4 Conclusions

Using the RITA data and the data on HIV testing in sexual health clinics, I was able to apply one of the methods proposed by WHO to determine HIV incidence in a cross-sectional study. This was the first estimate of HIV incidence in England for non-MSM populations in sexual health clinics, in particular black African heterosexuals and allowed for comparison between groups. To note is that the population attending sexual health clinics is unlikely to be representative of the general population. Among all subgroups, there was no apparent decrease in HIV incidence despite ongoing prevention and HIV testing initiatives at the time. Sensitivity analyses showed that caveats around the characteristics of the assays are unlikely to have had significant impact on the findings.

7 Population-based HIV incidence estimates

In Chapter 6 I used the RITA data to estimate incidence in attendees of sexual health clinics in England, however this population is unlikely to be representative of the general population in terms of risk. Here I used the CDC's stratified extrapolation approach which considers RITA and new HIV diagnoses data as a survey sample and applies weights to these to obtain population-based estimates. I present the estimated total number of new HIV infections over the years by transmission risk group and geography.

7.1 Results

7.1.1 Imputation of missing data and creation of incidence strata

To use the stratified extrapolation approach it was necessary to impute the missing RITA data to use the new HIV diagnoses and accompanying RITA data as a survey sample. As described in the section 3.7, I used MI to account for missing avidity data which is the process of substituting each missing value with a range of likely values, accounting for the uncertainty around the missing values.(205) This process creates and combines multiple datasets to impute the missing values. A condition for valid application of this method is that the data are MAR. If missing data are observed to be associated with a particular characteristic, that variable should be considered in the imputation model. The proportion of missing data for RITA and other variables in the regression model which I used to predict the missing data are presented in Table 16.

Table 16 Distribution of missing RITA data by year

	Overall		Missing avidity result											
	Total new HIV diagnoses*		2009		2010		2011		2012		2013		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Sex														
Male	19508	70.4	3189	67.0	2401	68.6	1923	69.2	2035	70.2	1383	70.9	10931	68.8
Female	8221	29.7	1572	33.0	1098	31.4	856	30.8	864	29.8	568	29.1	4958	31.2
Transmission category														
MSM	12686	45.7	1949	40.9	1490	42.6	1139	40.1	1264	43.6	843	43.2	6685	42.1
Heterosexuals	12519	45.2	2420	50.8	1676	47.9	1349	48.5	1249	43.1	738	37.8	7432	46.8
PWID*	542	2.0	120	2.5	83	2.4	76	2.7	55	1.9	37	1.9	371	2.3
Other	283	1.0	40	0.8	49	1.4	40	1.4	40	1.4	43	2.2	212	1.3
Missing	1699	6.1	232	4.9	201	5.7	175	6.3	291	10.0	290	14.9	1189	7.5
Age at diagnosis														
15-24	3044	11.0	502	10.5	373	10.7	278	10.0	301	10.4	214	11.0	1668	10.5
24-34	9122	32.9	1607	33.8	1140	32.6	905	32.6	848	29.3	652	33.4	5152	32.4
35-50	11596	41.8	2021	42.5	1512	43.2	1165	41.9	1251	43.1	746	38.2	6695	42.1
≥50	3967	14.3	631	13.3	474	13.6	431	15.5	499	17.2	339	17.4	2374	14.9
Ethnic group														
White	14323	51.7	2399	50.4	1737	49.6	1434	51.6	1436	49.5	986	50.5	7992	50.3
Black African	2583	9.3	290	6.1	326	9.3	261	9.4	400	13.8	329	16.9	1606	10.1
Black other	1423	5.1	214	4.5	197	5.6	126	4.5	148	5.1	106	5.4	791	5.0
Other	9400	33.9	1858	39.0	1239	35.4	958	34.5	915	31.6	530	27.2	5500	34.6

Among available variables, there was no apparent bias in which data were missing as the distribution missing was similar to that not missing. This was also the case when examining the data by year of diagnosis. As for this analysis, the data were analysed separately for people with and without testing history, I also explored the distribution of the testing data (Table 17). Here, however one would expect to observe differences between groups as certain populations are more engaged in healthcare and have higher testing frequencies.(191)

Table 17 Distribution of testing history data in repeat testers

	Repeat testers											
	2009		2010		2011		2012		2013		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
All	501	34.3	806	32.7	951	31.5	830	37.6	531	28.1	3619	30.6
Sex												
Male	398	40.1	613	36.6	770	34.7	652	29.5	453	30.6	2886	33.6
Female	103	22.0	193	24.3	181	22.6	178	22.4	78	19.2	733	22.5
Transmission category												
MSM	339	51.4	510	46.2	635	40.9	570	35.2	384	36.0	2438	40.6
Heterosexuals	158	22.4	283	23.8	302	22.4	246	20.5	128	19.8	1117	22.0
PWID*	3	15.8	11	22.9	4	10.5	9	21.4	9	37.5	36	21.1
Other	1	1.3	2	1.6	10	11.6	5	3.6	0	0.0	4	0.1
Missing	0	0	2	1.8	7	9.5	5	4.0	10	7.3	24	4.7
Age at diagnosis												
15-24	68	13.6	77	9.6	123	12.9	128	15.4	85	16.1	481	13.3
24-34	202	40.3	336	41.7	368	38.7	319	38.4	207	39.0	1432	39.6
35-50	193	38.5	336	41.7	372	39.1	315	38.0	193	36.4	1409	38.9
≥50	38	7.6	51	7.1	88	9.3	68	8.2	46	8.7	297	8.2
Ethnic group												
White	318	63.5	497	61.7	609	64.0	562	67.7	373	70.2	2358	65.2
Black African	101	20.2	187	23.2	201	24.1	159	19.2	68	12.8	716	19.8
Black other	41	8.2	38	4.7	39	0.06	33	2.7	21	4.0	172	4.8
Other	41	8.2	84	10.4	102	10.7	76	9.2	69	13.0	373	10.3

Between 2009 and September 2013, the overall proportion of people newly diagnosed with HIV that had had a previous negative HIV test fluctuated between 28.1% and 37.6%. Prior testing rates were higher in men compared to women, which over the period fluctuated between 29.5% and 40.1%, due to higher testing rates in the MSM population. Testing rates were highest in MSM fluctuating between 35.2% and 51.4% over the five years. The majority of MSM were also of white ethnicity explaining the differences by ethnic group. Lowest HIV testing rates were observed in the black other ethnic risk groups, non-MSM and non-heterosexual transmission risk groups, and in older age groups. Those youngest were also less likely to have had a previous test likely due to overall less time having been sexually active.

The number and possible sizes of the incidence strata, which should consist of groups with relatively homogenous sexual behaviour and HIV testing patterns, is constrained by the numbers of diagnoses and recent infections in each of these groups to ensure stable variance estimates. The CDC guidance (personal communication Rick Song) recommends for the minimum size of the strata to be, for each year:

- the number of new diagnoses (which are not AIDS cases) with recent infection test should be ≥ 40 and represent at least 20% of new HIV diagnoses, and
- the number of results indicating recently acquired HIV must be ≥10.

To obtain the maximum possible detail, I initially explored five mutually exclusive strata approximating a fifth of new diagnoses in each group. The strata sizes pre- and post-imputation are presented in Table 18. The imputation model included the covariates: risk group, ethnicity, age group at diagnosis, sex and diagnosis year.

Table 18 Pre- and post-multiple imputation review of analysis strata, by risk group, age and year*

		Pre-imputation		Post-imputation	
Year	Stratum	N (%) new HIV diagnoses with RITA results	N (%) recent	N (%) new HIV diagnoses with RITA results (>40 and at least 20% of ND)	N (%) recent (at least 10)
2009	MSM 15-34 yrs	323 (22.1)	78 (24.2)	1223 (19.7)	294 (24.0)
	MSM 35+ yrs	336 (23.0)	57 (17.0)	1385 (22.3)	234 (16.9)
	Heterosexual male	271 (18.6)	14 (5.2)	1252 (20.1)	80 (6.4)
	Heterosexual female	434 (29.7)	41 (9.5)	1873 (30.1)	142 (7.6)
	Other	97 (6.6)	8 (8.3)	489 (7.9)	30 (6.1)
	TOTAL	1461	198 (13.6)	6222	780
2010	MSM 15-34 yrs	544 (22.1)	152 (27.9)	1236 (20.7)	334 (27.0)
	MSM 35+ yrs	559 (22.7)	92 (16.5)	1357 (22.8)	231 (17.0)
	Heterosexual male	463 (18.8)	36 (7.8)	1168 (19.6)	88 (7.5)
	Heterosexual female	726 (29.4)	53 (7.3)	1697 (28.4)	132 (7.8)
	Other	175 (7.1)	12 (6.9)	508 (8.5)	36 (7.0)
	TOTAL	2467	345 (14.0)	5966	821

Year	Stratum	Pre-imputation		Post-imputation	
		N (%) new HIV diagnoses with RITA results	N (%) recent	N (%) new HIV diagnoses with RITA results (>40 and at least 20% of ND)	N (%) recent (at least 10)
2011	MSM 15-34 yrs	804 (26.6)	227 (28.2)	1369 (23.6)	390 (28.5)
	MSM 35+ yrs	747 (24.7)	134 (17.9)	1321 (22.8)	242 (18.3)
	Heterosexual male	578 (19.1)	45 (7.8)	1177 (20.3)	93 (7.9)
	Heterosexual female	768 (25.4)	67 (8.7)	1518 (26.2)	134 (8.8)
	Other	124 (4.1)	13 (10.5)	415 (7.2)	46 (9.8)
	TOTAL	3021	486 (16.1)	5800	905
2012	MSM 15-34 yrs	874 (29.1)	271 (31.0)	1475 (25.0)	451 (30.6)
	MSM 35+ yrs	747 (24.9)	159 (21.3)	1410 (23.4)	299 (21.2)
	Heterosexual male	457 (15.2)	43 (9.4)	986 (16.7)	91 (9.2)
	Heterosexual female	745 (24.8)	62 (8.3)	1465 (24.8)	133 (9.1)
	Other	180 (6.0)	24 (13.3)	566 (9.6)	49 (8.6)
	TOTAL	3003	559 (18.6)	5902	1023
2013	MSM 15-34 yrs	598 (31.4)	212 (35.5)	1047 (27.3)	355 (33.9)
	MSM 35+ yrs	477 (25.0)	111 (23.3)	863 (22.5)	198 (23.0)
	Heterosexual male	301 (15.8)	39 (12.8)	627 (16.3)	68 (10.9)
	Heterosexual female	353 (18.5)	45 (12.8)	756 (19.7)	85 (11.2)
	Other	178 (9.3)	21 (11.8)	546 (14.2)	67 (12.3)
	TOTAL	1907	428 (22.4)	3839	773

For all years, nearly all strata had 20% of new HIV diagnoses, ≥40 cases and ≥10 cases of recent HIV infection. The 'Other' group did not meet these requirements, but as this group was difficult to characterise, I chose to proceed with this categorisation. Importantly, and as to be expected, the proportion of recent infection for the sub-groups did not differ greatly pre- and post-imputation. In addition to the 5 strata by risk group and age, I created further strata to explore the data firstly by geography looking at rates in London versus the rest of England, Wales and Northern Ireland, and secondly by ethnicity, examining rates in black African heterosexuals versus all other heterosexuals. Tables 18-20 present these data pre-

and post-imputation. Although the stratification by ethnicity did not fulfil the rule of at least 20% of new HIV diagnoses, I decided to proceed with calculating incidence in this group as it was considered a key population.

Table 19 Pre- and post- imputation review of analysis strata by geography and year

Year	Stratum	Pre-imputation		Post-imputation	
		N (%) new HIV diagnoses with RITA results	N (%) recent	N (%) new HIV diagnoses with RITA results (>40 and at least 20% of ND)	N (%) recent (at least 10)
2009	London	914 (62.6)	131(14.3)	2780 (44.7)	372 (13.4)
	Outside London	547 (37.4)	67 (12.3)	3442 (55.3)	416 (12.1)
2010	London	1219 (49.4)	172 (14.1)	2678 (44.9)	396 (14.8)
	Outside London	1248 (50.6)	173 (13.9)	3288 (55.1)	437 (13.3)
2011	London	1543 (51.1)	272 (17.6)	2551 (44.0)	431 (16.9)
	Outside London	1478 (48.9)	214 (14.5)	3249 (56.0)	477 (14.7)
2012	London	1528 (50.9)	328 (21.5)	2764 (46.8)	547 (19.8)
	Outside London	1475 (49.1)	231 (15.7)	3138 (53.2)	505 (16.1)
2013	London	1028 (53.9)	257 (25.0)	1835 (47.8)	407 (22.2)
	Outside London	879 (46.1)	171 (19.5)	2004 (52.2)	387 (19.3)

Table 20 Pre- and post- imputation review of analysis strata in heterosexuals, by ethnicity and year

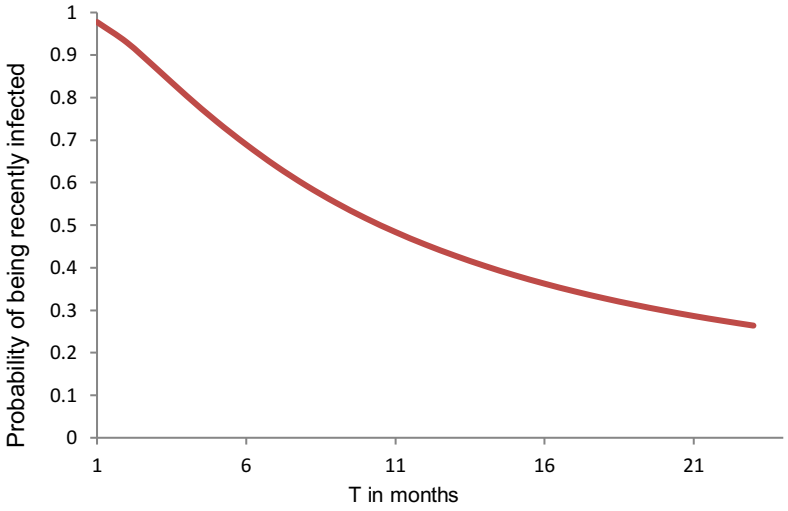
Year	Stratum	Pre-imputation		Post-imputation	
		N (%) new HIV diagnoses with RITA results	N (%) recent	N (%) new HIV diagnoses with RITA results (>40 and at least 20% of ND)	N (%) recent (at least 10)
2009	Black African heterosexuals	451 (30.9)	18 (4.0)	1966 (31.6)	92 (4.7)
	Other heterosexuals	254 (17.4)	37 (14.6)	1159 (18.6)	128 (11.0)
2010	Black African heterosexuals	719 (29.1)	36 (5.0)	1724 (28.9)	93 (5.4)
	Other heterosexuals	470 (19.1)	53 (11.3)	1141 (19.1)	127 (11.1)
2011	Black African heterosexuals	772 (25.6)	44 (5.7)	1553 (26.8)	93 (6.0)
	Other heterosexuals	574 (19.0)	68 (11.9)	1142 (19.7)	135 (11.8)
2012	Black African heterosexuals	656 (21.8)	37 (5.6)	1325 (22.5)	80 (6.0)
	Other heterosexuals	546 (18.2)	68 (12.5)	1126 (19.1)	145 (12.9)
2013	Black African heterosexuals	301 (15.8)	26 (8.6)	667 (17.4)	51 (7.7)
	Other heterosexuals	353 (18.5)	58 (16.4)	716 (18.7)	107 (15.0)

7.1.2 Estimating the probability *P* of being detected as recently infected

Calculation of P for repeat testers

Following imputation of the missing data, I estimated the weighting required for each recent infection diagnosis, which is the inverse of the probability *P* of being detected as recently infected. This was conducted separately for new and repeat testers. For repeat testers, the calculation was based on the date of the previous test, using the interval between the last negative HIV test and diagnosis date, assuming this was uniformly distributed. With the *P* a function of *T* (time), the probability of a recent infection diagnosis over time is illustrated as the following (Figure 12).

Figure 12 The probability of being diagnosed with a recent HIV infection *P* as a function of time *T* for the AxSym avidity assay for repeater testers



T	P	T	P
1	0.977602	13	0.428088
2	0.929596	14	0.403988
3	0.867705	15	0.382118
4	0.804152	16	0.362324
5	0.744305	17	0.344329
6	0.689452	18	0.327908
7	0.638857	19	0.312893
8	0.593502	20	0.299099
9	0.552885	21	0.286365
10	0.516375	22	0.274639
11	0.483797	23	0.263767
12	0.454464	>24	0.533*12/T

The calculation for *P* in repeat testers is summarised as the average probability of the estimates of all *P*'s for the group, as outlined in Section 3.7. Table 21 presents the estimated probabilities for each stratum.

Table 21 Probability *P* of being diagnosed as with a recent HIV infection for repeat testers, by stratum and year

Strata	Year				
	2009	2010	2011	2012	2013
MSM 15-34 yrs	0.4703392	0.463358	0.4894163	0.3040111	0.5206726
MSM 35+ yrs	0.3864971	0.3658756	0.3496646	0.4080193	0.4048413
Heterosexual male	0.3014373	0.2871879	0.2812326	0.2658161	0.2520797
Heterosexual female	0.265131	0.2571742	0.2440206	0.2458784	0.2658753
Other	0.3023295	0.2550733	0.3040111	0.2074827	0.2834372
London	0.4080516	0.3676784	0.3766695	0.4324274	0.453966
Outside London	0.3539945	0.3554988	0.362278	0.3755659	0.382033
Black African heterosexuals	0.313809	0.272709	0.2384677	0.2272144	0.2078609
Other heterosexuals	0.2338795	0.2308616	0.2134948	0.2403311	0.2510324

Calculation of P for new testers

For people diagnosed with HIV with no previous HIV test, the probabilities of being diagnosed during the recent period of infection were estimated using a competing risk model. As described in Section 3.7 this model accounts for multiple events possibly causing the outcome, with any one of these events preventing the others from happening. In this case the competing risks are either being diagnosed with HIV or with AIDS. This is combined with the probability of an AIDS diagnosis at the time of an HIV test. An assumption is that the testing rate is constant until AIDS diagnosis. The proportion diagnosed with AIDS in each stratum is presented in Table 22. The mathematical expression for the group probability is in section 3.7.

Table 22 Proportion diagnosed with AIDS at diagnosis within each strata and the mean weighted probability *P* of being diagnosed with a recent infection for people with no HIV testing history

Year	Strata	% with AIDS diagnosis among new testers	Scale parameter β for exponential distribution of time from infection to first test (months)	Mean weighted probability for new testers
	MSM 15-34 yrs	3.1	20.24653	0.234426
	MSM 35+ yrs	9.8	32.87087	0.1594464
	Heterosexual male	15.3	39.82623	0.1355686
	Heterosexual female	8.5	28.21937	0.1807452
2009	Other	10.2	28.42092	0.179705
	London	3.4	26.05651	0.211826
	Outside London	6.7	35.06243	0.150282
	Black African heterosexuals	7.7	37.70632	0.155694
	Other heterosexuals	7.8	37.97127	0.1542
	MSM 15-34 yrs	2.5	20.65912	0.2308786
	MSM 35+ yrs	11.0	34.91586	0.1515946
	Heterosexual male	13.1	35.11243	0.1508805
	Heterosexual female	9.6	32.90818	0.1592959
2010	Other	10.5	31.7991	0.163896
	London	4.3	28.93151	0.188129
	Outside London	6.5	34.5709	0.152912
	Black African heterosexuals	6.0	37.70632	0.147479
	Other heterosexuals	5.0	37.97127	0.171654
	MSM 15-34 yrs	2.0	17.84502	0.2574401
	MSM 35+ yrs	7.2	28.87248	0.1774173
	Heterosexual male	9.1	31.49877	0.1651878
	Heterosexual female	6.2	23.23179	0.2109682
2011	Other	6.1	24.52865	0.2021778
	London	2.3	22.55355	0.23141
	Outside London	4.1	28.41535	0.1776804
	Black African heterosexuals	4.6	33.35917	0.167881
	Other heterosexuals	2.6	30.91789	0.219749
	MSM 15-34 yrs	1.2	13.69964	0.3098376
	MSM 35+ yrs	7.8	28.36064	0.1800149
	Heterosexual male	10.8	31.8769	0.1635646
	Heterosexual female	7.0	26.28275	0.1913914
2012	Other	5.2	24.2718	0.2038602
	London	2.3	22.42114	0.238458
	Outside London	4.4	29.17628	0.1773707
	Black African heterosexuals	2.1	29.76405	0.209554
	Other heterosexuals	3.9	23.60124	0.200891
	MSM 15-34 yrs	1.1	13.6595	0.3104479
	MSM 35+ yrs	6.1	26.85259	0.1881307
2013	Heterosexual male	8.5	29.88899	0.1724748
	Heterosexual female	4.9	24.95745	0.1994303
	Other	5.8	29.88148	0.1725102

Year	Strata	% with AIDS diagnosis among new testers	Scale parameter β for exponential distribution of time from infection to first test (months)	Mean weighted probability for new testers
	London	1.2	17.88995	0.2806613
	Outside London	4.7	29.91243	0.1762028
	Black African heterosexuals	3.4	21.7708	0.209391
	Other heterosexuals	3.6	27.71399	0.205874

7.1.3 Population-based HIV incidence

The following formula depicts the relationship between HIV incidence and the probability of being diagnosed with recent HIV infection and each recent infection diagnosis (as described in Section 3.7):

$$I = I\text{new} + I\text{repeat} = (\frac{\text{Rnew}}{\text{Pnew}}) + (\frac{\text{Rrepeat}}{\text{Prepeat}})$$

where

I is the total number of new HIV infections

I_{new} is the number of new HIV infections among new testers

I_{repeat} is the number of new HIV infections among repeat testers

R_{new} is the number of recent infection diagnoses among new testers

R_{rep} is the number of recent infection diagnoses among repeat testers

P_{new} is the probability of being diagnosed as recently infected for new testers, and

P_{rep} is the probability of being diagnosed as recently infected for repeat testers

The number of new HIV infections was estimated for each strata with the total number of infections equal to the total number of infections across the strata (Table 23).

Overall, in England, Wales and Northern Ireland there were an estimated 3,533 (95% C.I. 3,113 – 3,954) new HIV infections in 2009, which increased to 3,846 (95% C.I 3,519-4,174) in 2012 (Figure 13). The number of new infections in 2013 was lower as this was for only three quarters of the year (2,937, 95%C.I. 2,669-3,205). Approximately half of all new HIV infections were in London, fluctuating between 1,646 (95%C.I. 1,431-1,860) and 2,170

(95%C.I. 1943-2396) new infections between 2009 and 2012 and 1,363 (95%C.I. 1,208-1,518) infections in the first three quarters of 2013 (Table 24). Given that London inhabits 20% of the population of England, Wales and Northern Ireland, the number of new HIV infections in London was disproportionaltely high.

Each year, approximately two thirds of new HIV infections were in MSM and just under a third in heterosexuals (Figure 14). The number and trend in numbers of new HIV infections in MSM aged < 35 years and ≥ 35 years were similar (Figure 15). In heterosexuals, examining the numbers of new infections by gender, there were slightly more in women compared to men with between 439 (95% C.I. 300-577) and 606 (95% C.I. 477-765) for each of the years between 2009 and 2012 in men compared to between 599 (95% C.I. 478-720) and 827 (95% C.I.667-988) in women (Figure16). The number and proportion of new HIV infections in black African heterosexuals decreased over the period with 552 (95% C.I 385-719) new infections in 2009 accounting for 40% of new infections in heterosexuals, decreasing to 369 (95% C.I. 270-467) new infections in 2012 accounting for 35% of new infections in this group that year (Table 25, Figure 17).

Table 23 Estimated number of new HIV infections by risk group, age and year, 2009-September 2013

Year	Transmission risk group	Number of new infections	(95% C.I.)
2009	MSM 15-34 yrs	991	(834-1145)
	MSM 35+ yrs	1057	(836-1278)
	All MSM	2048	(1762-2333)
	Heterosexual males	606	(448-765)
	Heterosexual females	761	(578-944)
	All heterosexuals	1367	(1144-1591)
	Other	118	(-2-238)
	TOTAL	3533	(3113-3954)
2010	MSM 15-34 yrs	1033	(891-1176)
	MSM 35+ yrs	1192	(1003-1381)
	All MSM	2225	(1989-2461)
	Heterosexual males	501	(373-629)
	Heterosexual females	827	(667-988)

Year	Transmission risk group	Number of new infections	(95% C.I.)
	All heterosexuals	1328	(1111-1545)
	Other	180	(37-324)
	TOTAL	3733	(3422-4045)
	MSM 15-34 yrs	1218	(1046-1389)
	MSM 35+ yrs	1069	(913-1224)
	All MSM	2287	(2070-2503)
2011	Heterosexual males	606	(466-745)
	Heterosexual females	599	(478-720)
	All heterosexuals	1204	(1020-1388)
	Other	143	(47-239)
	TOTAL	3634	(3339-3929)
	MSM 15-34 yrs	1250	(1000-1501)
	MSM 35+ yrs	1279	(1093-1466)
	All MSM	2530	(2303-2757)
2012	Heterosexual males	439	(301-577)
	Heterosexual females	630	(520-759)
	All heterosexuals	1069	(884-1254)
	Other	247	(120-375)
	TOTAL	3846	(3519-4174)
	MSM 15-34 yrs	976	(761-1191)
	MSM 35+ yrs	771	(643-900)
	All MSM	1748	(1567-1928)
2013	Heterosexual males	367	(281-453)
	Heterosexual females	431	(339-522)
	All heterosexuals	797	(650-945)
	Other	392	(238-546)
	TOTAL	2937	(2669-3205)

Figure 13 Number of new HIV infections by geography, 2009- September 2013

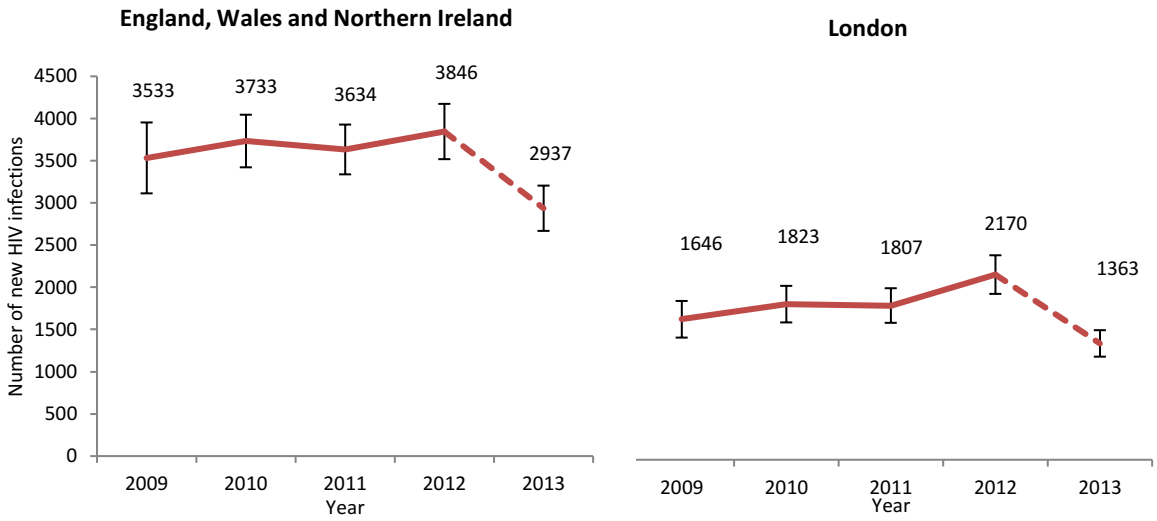


Table 24 Number of new HIV infections by geography, 2009-September 2013

Year	Geography	No of new infections	95% C.I.()
2009	London	1646	(1431-1861)
	Outside London	2211	(1862-2559)
2010	London	1823	(1609-2037)
	Outside London	2239	(1939-2540)
2011	London	1807	(1604-2010)
	Outside London	2068	(1837-2300)
2012	London	2170	(1943-2396)
	Outside London	2182	(1941-2424)
2013	London	1363	(1208-1518)
	Outside London	1733	(1565-1981)

Figure 14 Number of new HIV infections by transmission risk group, 2009- September 2013

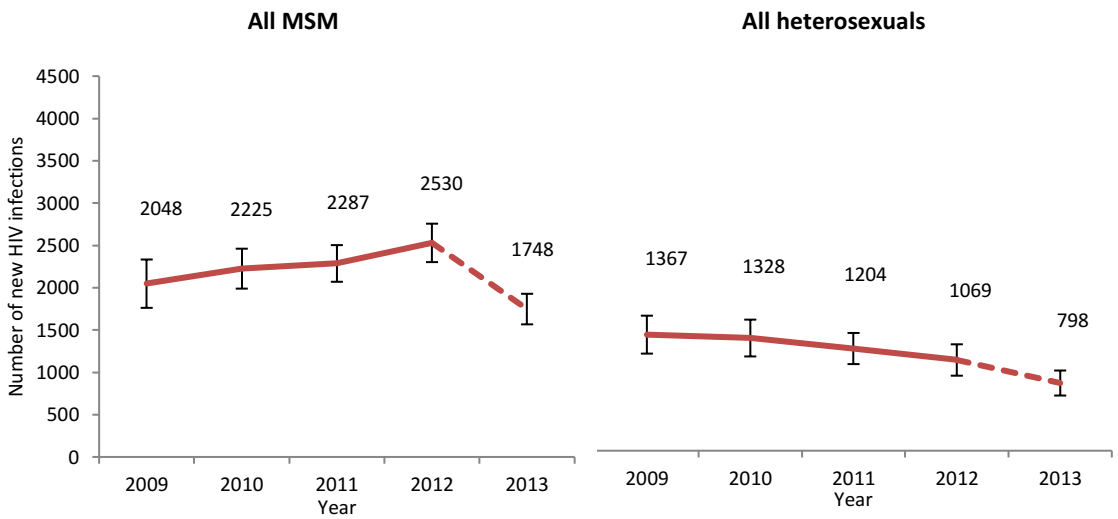


Figure 15 Number of new HIV infections in MSM by age group, 2009- September 2013

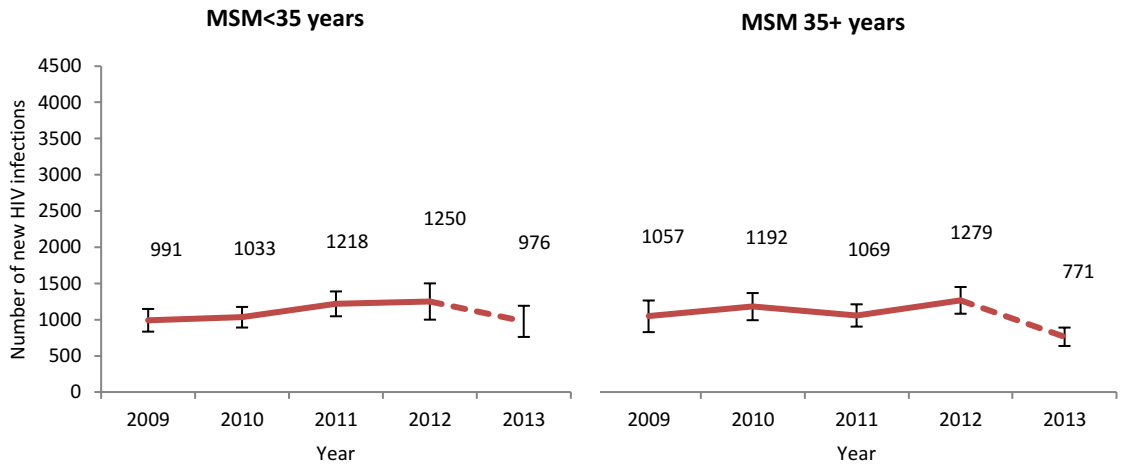


Figure 16 Number of new HIV infections in heterosexuals by gender, 2009- September 2013

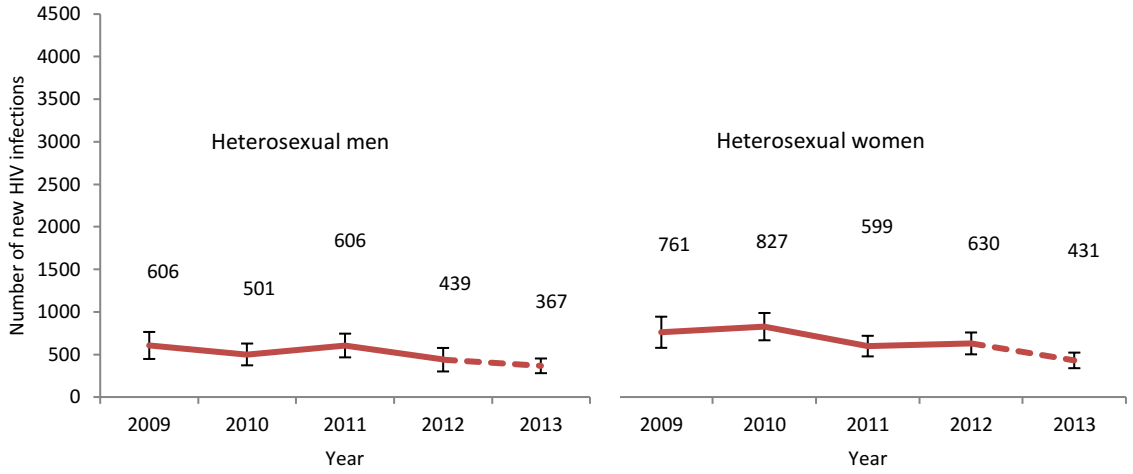
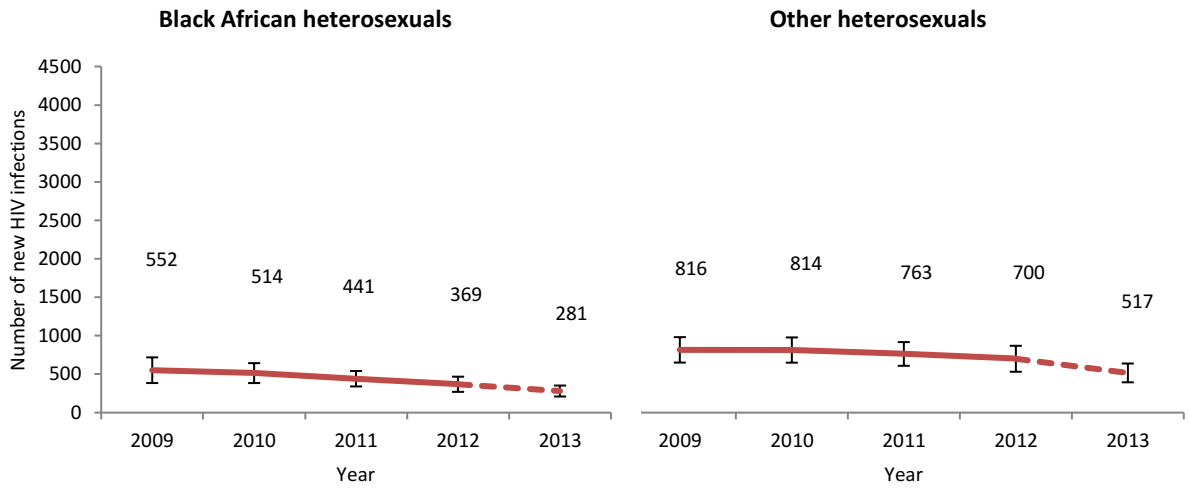


Table 25 Number of new HIV infections in heterosexuals by ethnicity, 2009-September 2013

Year	Ethnic group pf heterosexuals	Number of new infections	95% C.I.()
2009	Black African	552	(385-719)
	Other	816	(651-981)
2010	Black African	514	(385-643)
	Other	814	(649-978)
2011	Black African	441	(340-541)
	Other	763	(609-917)
2012	Black African	369	(270-467)
	Other	700	(531-869)
2013	Black African	281	(209-352)
	Other	517	(394-639)

Figure 18 Number of new HIV infections in heterosexuals by ethnicity, 2009-September 2013



In the absence of available data on the number of new infections, the number of new diagnoses has in some instances been used as a proxy to describe the state of the epidemic. Comparing the estimates with the number of new infections, it was evident that overall, the number of new diagnoses did not reflect new infections although for MSM it was close (Figure 18). The disparity was predominantly in heterosexuals with the number of new infections much lower than new diagnoses (Figure 19).

Figure 19 Comparison of new HIV diagnoses and new HIV infection (overall and in MSM), 2009-September 2013

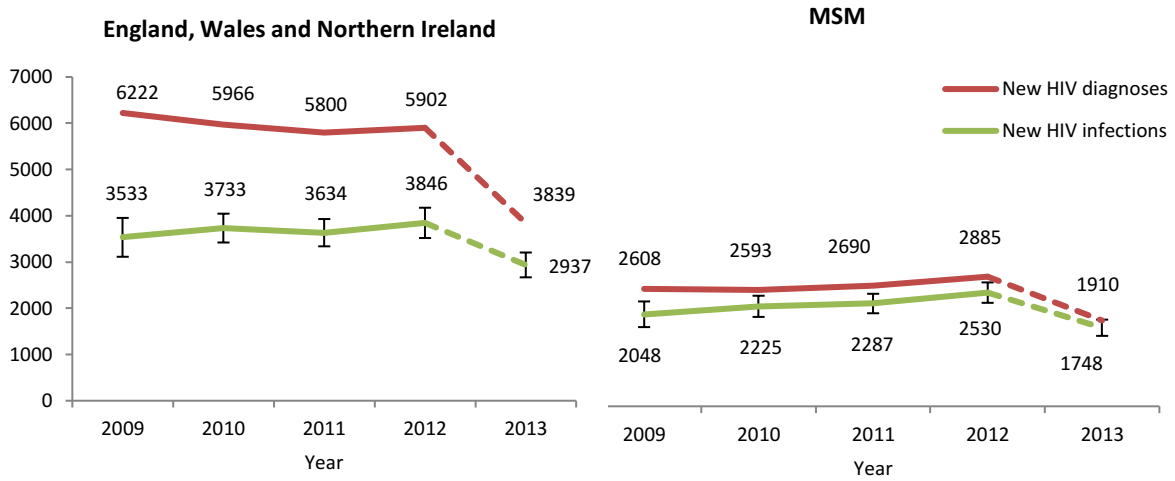
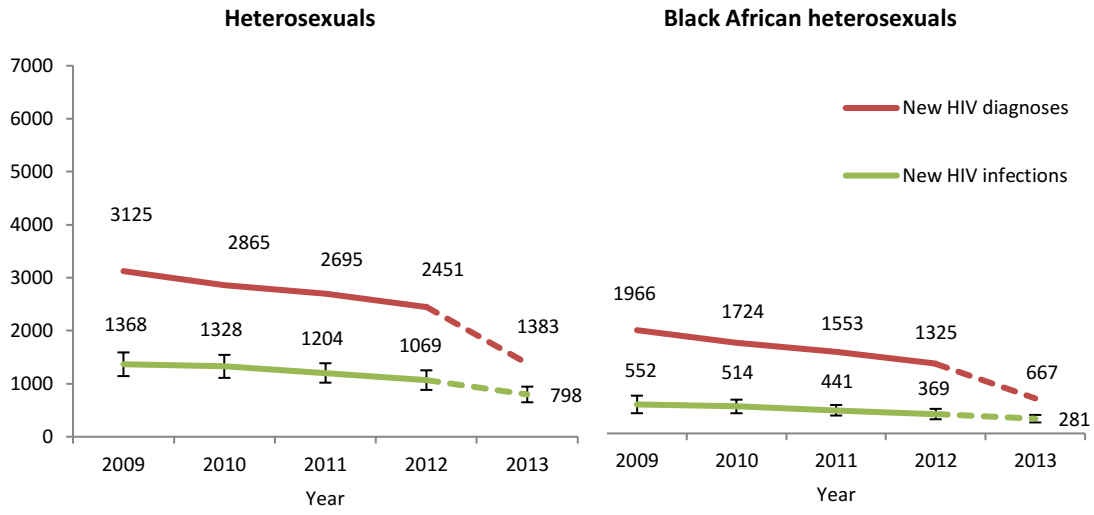


Figure 19 Comparison of new HIV diagnoses and new HIV infections (in heterosexuals and black African heterosexuals), 2009-September 2013



In Table 26, I present the annual estimates per 100,000 pys taking into account population sizes up to the year 2012. The population size of MSM was estimated using data from NATSAL which estimated 2.6% of the male population was MSM, defined as at least one male sexual partner in the previous five years.(226) The heterosexual male population size was inferred subtracting the MSM population from all men. All women were considered heterosexual for the purposes of these calculations as those not heterosexual were likely to have a lower risk of infection.

Table 26 HIV incidence by risk group, age, ethnicity and geography per 100,000 pys

Year		Population size	Incidence per 100,000	95% C.I.()
2009	All	57,985,200	6.09	(5.37-8.82)
	London	8,174,000	20.14	(17.51-22.76)
	Outside London	49,811,200	4.44	(3.74-5.14)
	MSM	741,699	276.09	(237.59-314.58)
	MSM 15-34 yrs	--	--	
	MSM +35 yrs	--	--	
	Heterosexuals	57,243,500	2.39	(2.0-2.78)
	Heterosexual men	27,785,200	2.18	(1.61-2.75)
	Heterosexual women	29,458,300	2.58	(1.96-3.21)
	Black African heterosexuals	798 000*	69.12	(48.19-90.06)
2010	All	57,497,256	6.49	(5.95-7.04)
	London	8,061,495	22.62	(19.96-25.27)
	Outside London	49,435,761	4.53	(3.92-5.14)

Year		Population size	Incidence per 100,000	95% C.I.()
	MSM	734689	302.86	(270.77-334.96)
	MSM 15-34 yrs	--	--	
	MSM +35 yrs	--	--	
	Heterosexuals	56762567	2.34	(1.96-2.72)
	Heterosexual men	27522583	1.82	(1.35-2.28)
	Heterosexual women	29239984	2.83	(2.28-3.38)
	Black African heterosexuals	--	---	--
2011	All	57,985,200	6.27	(5.76-6.78)
	London	8,174,000	22.11	(19.63-24.59)
	Outside London	49,811,200	4.15	(3.69-4.62)
	MSM	741,699.4	308.28	(279.08-337.49)
	MSM 15-34 yrs	--	--	
	MSM +35 yrs	--	--	
	Heterosexuals	57,243,501	2.10	(1.78-2.42)
	Heterosexual men	27,785,201	2.18	(1.68-2.68)
	Heterosexual women	29,458,300	2.03	(1.62-2.44)
	Black African heterosexuals	989,628	44.57	(34.42-54.71)
2012	All	58,391,430	6.59	(6.03-7.15)
	London	8,308,369	26.11	(23.39-28.84)
	Outside London	50,083,061	4.36	(3.87-4.84)
	MSM	747,185	338.55	(308.16-368.94)
	MSM 15-34 yrs	--	--	
	MSM +35 yrs	--	--	
	Heterosexuals	57,644,215	1.85	(1.53-2.18)
	Heterosexual men	27,990,715	1.57	(1.07-2.06)
	Heterosexual women	29,653,500	2.13	(1.69-2.56)
	Black African heterosexuals	--	--	

* directly from ONS(227); Data estimating the size of the black African population were only available for the years 2009 and 2011.

The overall incidence of HIV in England, Wales and Northern Ireland was estimated to be 6.1 (95%C.I.5.4-8.8) per 100,000 pys in 2009 and was similar over the four years. Rates in new HIV infections were disproportionately higher among MSM compared to all other groups increasing, although non-significantly, over the period from 276 (95% C.I. 238-315) per 100,000 pys in 2009 to 339 (95% C.I.308-368) per 100,000 pys in 2012 (Figure 20). This compared to steady rates over the period in heterosexuals fluctuating between 1.85 (95%

C.I. 1.07-2.06) per 100,000 pys and 2.39 (95% C.I. 2.0-2.8) per 100,000 pys over the period. As reflected in the overall number of new infections, rates were slightly higher in women compared to men also with no significant trends in either of these groups. Where data were available, black African heterosexuals had much higher rates of infection than heterosexuals overall, with 69.1 (95% C.I.5.2-90.1) per 100,000 pys in 2009 and 44.6 (95% C.I.3.4-54.7) per 100,000 pys in 2011 (population size estimates only available for these two years). Although the numbers of new HIV infections in London and outside London were not considerably different, the rate of infections were five to six times higher in London fluctuating between 20.1 (95% C.I. 17.1-22.8) and 26.1 (95% C.I. 23.4-28.8) per 100,000 pys over the period compared to between 4.15 (95% C.I. 3.69-4.62) and 4.53 (95% C.I. 3.92-5.14) per 100,000 pys in the population outside London (Figure 21).

Figure 20 HIV incidence in the total population of England, Wales and Northern Ireland and MSM, 2009-2012

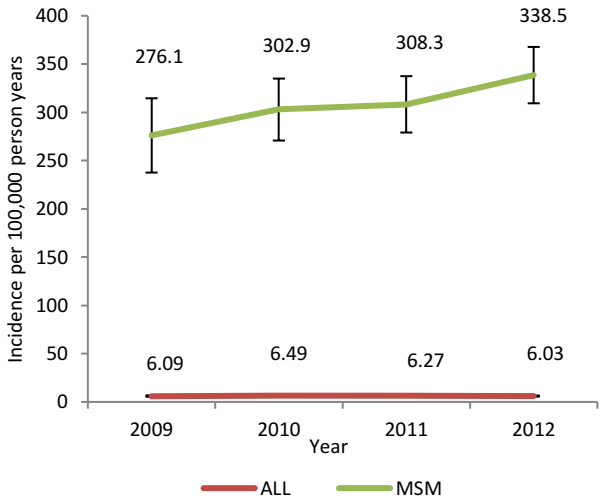
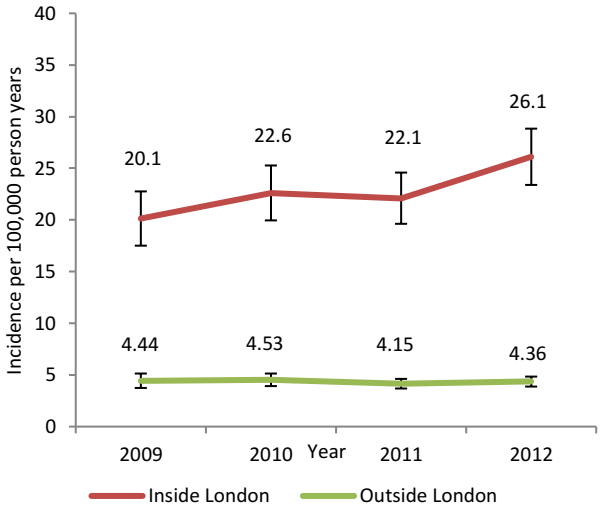


Figure 20 HIV incidence estimates in London versus outside London, 2009-2012



7.2 Discussion

7.2.1 Principal findings

At the time of writing, these were also the first population-based HIV incidence estimates for all transmission risk groups in the UK, specifically for England, Wales and Northern Ireland. Currently, these are the only estimates by gender, geography and age. Incidence seemed to have remained stable over the period, with a slight increase suggestive in the MSM group and decrease in the heterosexual group. New infections rates per 100,000 pys illustrated MSM to have had up to a 180-fold higher rate of infection than the heterosexual population at 388 (95% C.I. 308.16-368.94) per 100,000 pys compared to 1.85 (95% C.I. 1.53-2.18) per 100,000 pys in 2012. In black African heterosexuals it was 44.6 (95% C.I. 34.42-54.71) per 100,000 pys in 2011, the most recent year for which data were available. The rate of new infections was five to six times higher in London over the period with 26.1 (95% C.I. 23.39-28.84) per 100,000 pys in 2012 compared to 4.4 (95% C.I. (3.87-4.84) per 100,000 pys outside London.

The estimated total number of new HIV infections was 3,533 (95% C.I. 3,113 – 3,954) in 2009 increasing to 3,846 (95% C.I 3519-4174) in 2012. Two thirds of these were in MSM with 2,048 (95% C.I.1,762-2,333) in 2009 increasing to 2,530 (95% C.I. 2,303-2,757) in 2012. For MSM, the number and trends of new infections were comparable to the number and trends in new HIV diagnoses over the period, which has often been used as a proxy. This was however not the case in heterosexuals, in which the number of new HIV infections decreased over the period from 1,367 (95% C.I.1,144-1,591) in 2009 to 1,069 (95% C.I. (884-1,254) in 2012 and was slightly higher in women (annually between 600-830 over the years) compared to men (annually between 440-600). In black African heterosexuals the number and proportion of new HIV infections also decreased over the period, although not significantly, with 552 (95% C.I. (385-719) in 2009 accounting for 40% of new HIV infections

among heterosexuals (16% overall), decreasing to 369 (95% C.I. (270-467) in 2012 accounting for 35% of all infections in heteosexuals. Between 45-55% of all new HIV infections were in London. Due to overlapping variance estimates, no significant trends on the overall number of new HIV infections was observed, and also none for any of the subgroups.

7.2.2 Comparison with other studies

Other UK population-based HIV incidence estimates available at the outset of the thesis were for the MSM population, first published by Presanis et al. using a Bayesian evidence synthesis model.(228) This methodological paper showed HIV incidence in MSM between 2002 and 2007 to have been between 0.005 and 0.01 which equates to between 500 and 1000 per 100,000 pys (data only presented in a figure with no accurate numbers provided for the variance). A subsequent publication, and currently the most cited study, by Birrell et al. are estimates using the CD4 stage back calculation model based on PHE surveillance data using information on the number of new HIV diagnoses and the CD4 count at diagnosis.(95) These are updated annually and published as a routine output by PHE.(5, 11-13, 73) They found that between 2001 and 2010, the annual number of new HIV infections remained unchanged throughout the decade with between 2,300 and 2,500 each year. This is slightly higher, although not significantly, than my estimates for the overlapping years 2009 and 2010, with 2,048 (95% C.I.1,762-2,333) and 2,225 (95% C.I. 1,989-2,461) new infections, respectively. Birrell et al.'s data show estimates to have been increasing from 2,760 (95% C.I. 2,170-3,441) in 2011 to 2,960 (95% C.I. 2,260-3,910) in 2013, which, overlap with the estimates found here 2,287 (95% C.I.2,070-2,503) in 2011 and 2,530 (95% C.I.2,303-2,757) in 2013.

Phillips et al. used a dynamic, individual based simulation model to examine rates of HIV incidence in MSM pre and post the availability of ART.(96) Here, a mean HIV incidence for

the five year period of 2006-2010 was estimated to have been 530 per 100,000 pys, similar to the Presanis estimate. A further study of Phillips et al. reviewed the potential impact of higher HIV testing rates and earlier ART initiation on HIV incidence.(110) He modelled incidence for future years with the earliest having been at 2015 at a rate of 600 per 100,000 pys (no variance data available) for MSM, which is only slightly higher than my findings for earlier years, for example of 390 per 100,000 person-years in 2012.

In a study published very recently (2017) by Nakagawa et al., HIV incidence was estimated for black African heterosexuals. This was based on an individual-based stochastic simulation model. The authors estimated that between 2010 and 2014 there were 1,200 (90% plausibility range between 800-2,300) new infections annually which would equate to 1.2 new infections per 1,000 pys. This is also only slightly higher than my findings for 2011 which equates to 0.4 (95% C.I 0.3-0.5) per 1,000 pys for 2011.

The population-based estimates using serological incidence assays in France and the US may not be directly comparable, due to different populations with different epidemics and different assays used, however the findings may be considered of interest. Firstly, in the US, the most recent estimates using incidence assays were published in 2017 for the years 2008 to 2013.(124) These estimates were based on serological incidence assays as well as CD4 and Bayesian hierarchical models. A comparison of the outputs of these models showed that over the period slightly different results were produced with a drop in incidence noted by the CD4 model (by 4.6%, $p<0.001$) and a smaller drop noted by the Bayesian model (2.6%, $p<0.001$) and a stable incidence for the period estimated using RITA. Between 2008 and 2013, they estimated a total of approximately 35,000 to 45,000 new infections, implying that the epidemic was approximately 10-fold larger than that in the UK. As mentioned previously, the assay used was the BED EIA HIV-1 and data were only available for selected regions (here 18 of 50 states and 3 cities) with the remaining data imputed. More recently, only

estimates from the CD4 back calculation method have been published on the CDC website.(229, 230)

In France, HIV incidence was estimated for the years 2003-2008.(211) As described earlier, the assay used there was a EIA-RI test, calibrated with data from French HIV seroconverters. They estimated that in 2008, the number of new HIV diagnoses and new HIV infections were similar, with 6,480 (6,190-6,780) and 6,940 (6,200-7,690), respectively, with an incidence rate of 17 per 100,000 pys. If we compare this figure with our estimate for 2009, the epidemic in France was approximately twice the size of that of the UK, with the rates per 100,000 population 3-fold higher. In both countries, as in the UK, over half of all new HIV infections occurred in the MSM population.

7.2.3 Limitations

The population-based incidence estimates make an important contribution to the knowledge base of the HIV epidemic. However the estimation approach relies on a number of assumptions. Firstly, to conduct the MI, it was assumed that the data were MAR. I explored this for the demographic characteristics for which data were available and found no apparent bias, however missing data could have been associated with factors for which information was not available. For example, as stated earlier, clinicians may have been more likely to submit specimens to PHE for avidity testing from people who reported a recent risk event in attempt to confirm a recent infection and hence missing data could more likely have been longstanding cases. If this were the case, my estimates may be inflated. However, I believe that this type of bias is likely to have been confined to a small number of clinicians and is unlikely to have had a significant effect on the estimates overall. In addition, the coverage of the serological incidence programme was seemingly representative of all persons newly

diagnosed. Due to budget constraints, no further efforts were put into increasing the coverage of incidence testing which plateaued at 50% of new HIV diagnoses.

Secondly, the model assumes independence between HIV infection and HIV testing. Data on trends of CD4 count at diagnosis show the median time from infection to diagnosis over the years has decreased.(5) This is reflective of a change in terms of more frequent testing in key populations, in particular MSM. With the recommendations for MSM to test at least annually or every three months if having sex with new or casual partners(5) in the primary behavioural data collected (Chapter 8), it is unlikely in many instances that testing and diagnoses were independent of infection. With evidence of motivated testing apparent, the estimation of the probability *P* for the likelihood of being diagnosed with a recent infection is in such cases probably too great. However, to note is that this is likely to only apply to the MSM population as testing rates are much lower in other groups. In fact, late HIV diagnoses, defined as being diagnosed with a CD4 count<350cell/mm^3 was highest in heterosexuals at 63% among heterosexual men and 52% among heterosexual women in 2013 compared to 31% in MSM.(3)

Thirdly the model assumes accurate inter-test intervals. The testing history data here were sourced from two separate surveillance systems, the new HIV diagnoses database and GUMCAD. Testing history data are likely to be missing in both datasets. For the new HIV diagnoses database, clinicians may not have routinely asked patients if they had tested previously once diagnosed, and if these data were collected at clinic level, they may not necessarily have been reported to PHE as until recently, these data were not specifically requested. In the GUMCAD system every HIV test in a sexual health clinic setting is recorded, however, testing history data are likely to be underestimated as patients may test at numerous clinics and data cannot be linked between clinics only within. The linkage between GUMCAD and the new HIV diagnosis database is likely to have identified some additional cases however linkage was only 70%. It is difficult to predict what the impact of

missing testing data is likely to be. MSM are more likely to have had a previous test and hence are more likely to be diagnosed in the recent period of their infection. As such, if the testing history data are missing, these incident cases may be more heavily weighted than ought to be in the calculations. This would also be the case if the most recent HIV test date is missing or was wrongly recorded and the inter-test interval is longer than it should be. For persons diagnosed at their first test, a distribution of the inter-test interval is assumed. With stark changes in HIV testing behaviours observed in GUMCAD over the period of study, this assumption is also unlikely to hold true.

Fourthly, and importantly is the estimation of the MDRI; whilst there have been studies examining this, the population sample was firstly small (among only 103 persons) and is unlikely to be representative of the UK population (the study was undertaken in Italy among people who seroconverted between 1990 and 2000).(153) As mentioned previously, such studies require accurate seroconversion dates and a number of subsequent serum samples from a diverse group of patients to plot the window period and obtain a mean value specific to the population.

Lastly, this approach assumes HIV incidence is relatively constant. This seems to be true for the studied period in particular for MSM populations as other estimates are available for comparison.(5, 96, 110) However moving forward, reviewing trends in more recent years, this is unlikely to continue to be the case.(5)

Other limitations of this analysis were that I assumed HIV diagnosis reporting was complete and, for the calculation of rates, that the population size estimates were correct. As multiple reports are received for patients newly diagnosed and those attending care, the data were considered to have high completeness. Each year, adjustments to any figures of the previous years are minor indicating that reporting delay is also not likely to have a considerable impact. In addition, the various surveillances systems are regularly linked for

comparison, data validation and to top-up any missing cases. With the national population size estimates being large numbers, any inaccuracies here are likely to have little effect.

Due to limitations in sample size, I was not able to obtain estimates for population sub groups other than the ones presented here. Of interest may be further age-specific incidence rates and to generate more localised estimates which local authorities could also consider for directing and prioritising prevention efforts.

7.2.4 Conclusions

These are the first population-based HIV incidence estimates produced for the UK which are able to show trends in the number of new HIV infections by sub population groups including transmission risk, age and geography. Despite the potential caveats around the estimates relating to limitations of the model, one can seek confidence in the findings through triangulation of the results with estimates for other models where data are available, in particular the MSM population, which show similar estimated figures. In view of the ongoing roll out of combination prevention initiatives, and more recently, the decline in new HIV diagnoses and the roll out of a PrEP programme, timely estimates for new infections which can be presented by sub population groups are vital to understand both the need and/or demand for services and the impact of programmes on the epidemiology of HIV in the UK.

8 Pilot of behavioural surveillance in MSM with recent HIV infection: potential for RITA as an outbreak investigation tool

Having used the RITA data to establish predictors for being diagnosed with recent HIV infection and estimated HIV incidence both in clinic settings and the whole population, I subsequently took a closer look at what additional information could be obtained from patients with new infections that could aid active case finding and contribute to improved control of infection. This chapter describes the results of a pilot survey for enhanced HIV surveillance conducted in MSM. These data were presented at the British HIV Association Conference in Edinburgh, 2018

As outlined in section 3.7 MSM diagnosed with incident HIV recent (identified either with RITA, a recent negative HIV test or a p24 antigen positive HIV antibody negative test result) in seven clinics in England took part in a feasibility study for enhanced behavioural surveillance. This entailed MSM completing a questionnaire on behaviours in the 6 months prior to diagnosis (reflecting the MDRI) shortly after their diagnosis, with the aim of collecting these data close to real-time. The questionnaire included information on demographic variables (e.g. age, ethnicity, sexuality and the first half of their postcode), behaviours (e.g. reason for test, testing history, previous use of PEP and/or PrEP, history of a STI diagnosis, number of sexual partners in the 6 months before diagnosis) partner meeting venues, history of recreational drug use and any PN activities. Men were additionally asked how they thought they had acquired their infection to obtain insight into the circumstances that led to HIV transmission.

8.1 Results

8.1.1 Data collection and participant characteristics

Between February 2014 and February 2015, 61 MSM were recruited from seven clinics, four of which were in London. One person refused to complete the questionnaire. Clinics reported difficulty in recruiting patients due to staff and time constraints and, in some instances, a perceived inappropriateness in burdening the patient with such a task at the time of their diagnosis. In Table 27 I present the survey coverage to all incident infections identified through RITA.

Table 27 Number of MSM diagnosed with recently acquired HIV and coverage of enhanced surveillance survey between February 2014 and February 2015 in the seven selected pilot sites

Clinic	N MSM diagnosed with HIV	N (%) with avidity tests (linked)	N (%) classified with recently acquired HIV	N questionnaires returned (% coverage)
Dean Street	584	429 (73)	199 (46)	29 (15)
Homerton	39	27 (69)	10 (37)	4 (40)
St Thomas	169	154 (96)	47 (31)	4 (9)
Barts and the London	80	40 (50)	11 (28)	2 (18)
Manchester	98	60 (61)	11 (18)	17 (155)*
Liverpool	55	27 (49)	8 (20)	4 (50)
Sheffield	18	13 (72)	2 (15)	1 (50)
Total	1043	750 (72)	288 (38)	61 (21)

*PHE may have less recent infection diagnoses recorded than individual sites have due to the deduplication and linkage process (see section 3.7).

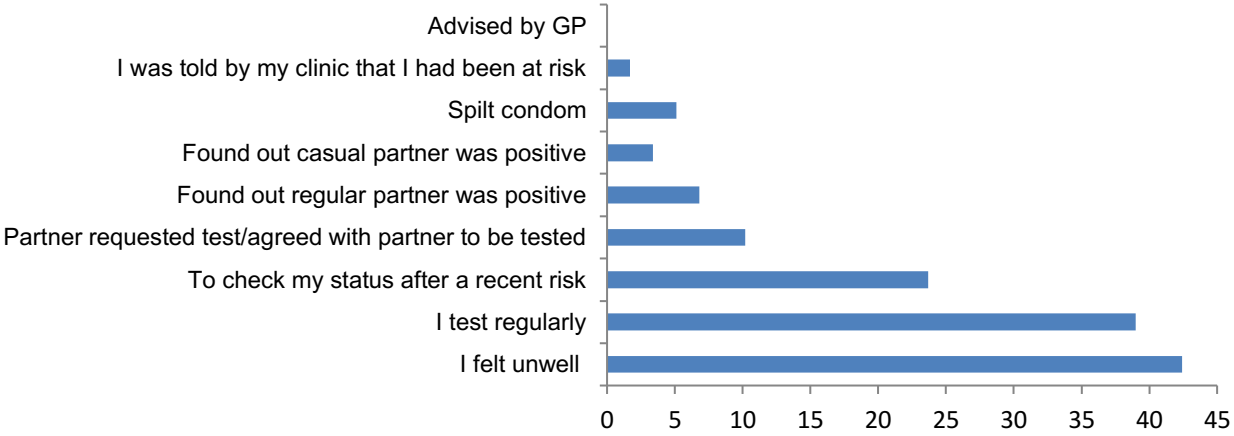
Overall, just over 1 in 5 MSM with incident infection identified through RITA in the participating clinics completed a behavioural questionnaire. Half (n=29) were from one clinic in London (Dean Street), which was where 20% of all new HIV diagnoses and 46% of all diagnosed incident cases in UK MSM were made during that year. I compared the demographic characteristics of all people with recent infection and survey respondents and found that the respondents were broadly similar with the median age 32 years (IQR 26,36; range 20-57 years) compared to 31 (IQR 26, 38; range 17-72) in all MSM and 88% of participants were of white ethnicity compared to 72% overall. Just over half (62%) were born

in the UK which was slightly higher than in all MSM (47%). Among the 38% of respondents born abroad, half (21% overall) were from European countries. The remaining were from Australia, South America, Taiwan and the US. A higher proportion of men were from outside London (mostly from the north of England) compared to all MSM with recent infection, due to the selection of participating clinics.

8.1.2 HIV testing and STI diagnoses in the 6 months before HIV diagnosis

Reviewing the reason for the HIV test at the time of diagnosis, the two most commonly cited were either because they had felt unwell (40%, n=25) or because this was part of a routine check (39%, n=23) (Figure 22,Table 28). A quarter were prompted by a recent risk event. Nearly all (for whom information was available, (95%, n=56) had tested previously and most had tested in the last year (79%, n=42/53). Half (47%, n=25/53) had tested as recently as six months prior to diagnosis with a median of 2 HIV tests ever (IQR 1,3). Only five men reported the test at diagnosis to have been their first test. The high rates of previous testing likely reflect the design of the pilot as a recent negative test was one of the selection criteria. Half (49%) of all participants reported having had a STI diagnosed in the previous six months with the most commonly diagnosed infections gonorrhoea (36%), chlamydia (20%) and syphilis (7%) (three men had multiple STIs).

Figure 22 Reason for an HIV test at the time of HIV diagnosis (n=59, participants were asked to tick all that applied)*



* 4 participants reported 'other reasons' which were:
came in for PEP (1), check status (1), wanted PROUD study (1), diagnosed in hospital

Table 28 History of HIV testing and STI diagnoses

HIV testing and STI history	% (n)
Ever tested previously (n=59)	
Yes	91.5 (54)
No	8.5 (5)
Tested in the last year (n=53)	
Yes	79.3 (42)
No	20.8 (11)
Tested in the last 6 months (n=53)	
Yes	47.2 (25)
No	52.8 (28)
Tested in the last 2 years (n=53)	
Yes	94.3 (50)
No	5.7 (3)
Number of HIV tests	
Mean (SD, range)	2.8 (4.2, 0-30)
Median (IQR)	2 (1,3)
STI in the last year (n=59)*,**	
No	50.9 (30)
Yes	49.2 (29)
Gonorrhoea	35.6 (21)
Chlamydia	20.3 (12)
Syphilis	6.8 (4)
LGV	0.0 (0)
Hep C (ever)	0.0 (0)
Other (HPV/warts or herpes)	5.0 (3)

* Respondents were asked to tick all that applied
** three patients were diagnosed with multiple STIs

8.1.3 Risk and protective behaviours (PEP and PrEP use) in the 6 months before HIV diagnosis

The distribution of risk and protective behaviours is shown in Table 29. The range in the number of partners the men reported having had in the preceding 6 months varied widely. Seven MSM reported no UAI in the 6 months prior suggesting either a longer period of infection, incorrect recall or infection via a different route. More participants reported receptive than insertive UAI (88% vs. 63%) although the sample of men was very small. Of all receptive UAI partners (n=297), 16% (n=48) were HIV positive with no treatment information indicated and 26% (n=77) were HIV positive and on treatment (Figure 23). A further third (32%, n=94) were negative and for a quarter of UAI partners (26%, n=78) the status was not known. A higher proportion of insertive partners were positive (33%, 46/140) and a smaller fraction HIV positive and on treatment (23%, n=32); for 30.0% the status was unknown and only 14.0% were negative.

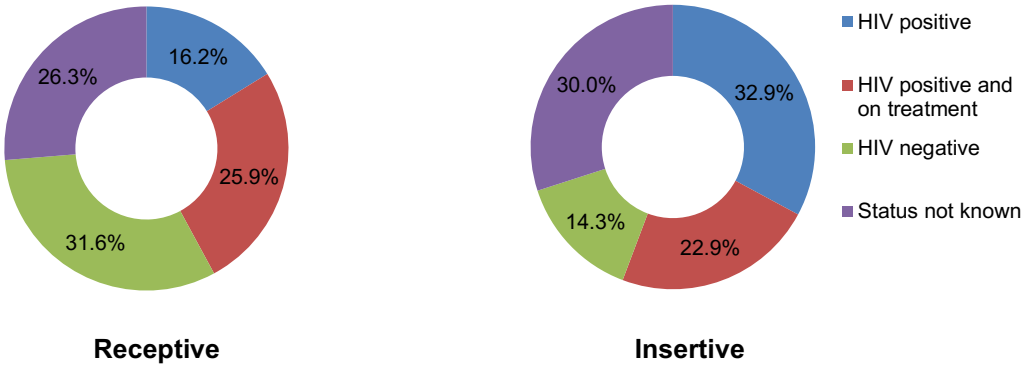
The most common other types of sexual activities were rimming (62%, n=34) and group sex (42%, n=23), followed by fisting (13%, n=7) and water sports (11%, n=6).

Half of men (47%) reported using drugs before or during sex in the previous six months including chemsex defined as having used crystal meth, G (included GHB and GBL), or mephedrone. Five (of 49, 10%) people had injected drugs. Cocaine, Viagra and poppers were also commonly used (35%, 36% and 42%, respectively).

Table 29 Number and types of sexual partners and drug use in the 6 months prior to HIV diagnosis

Sexual behaviour and drug use	% (n)
Number of sexual partners (anal and/or oral) (n=59)	
Mean (SD, range)	14.8 (19.3, 1-100)
Median (IQR)	8 (4,20)
UAI partners in the last 6 months (n=59)	
Yes	88.2 (52)
No	11.8 (7)
Number of UAI partners	
Mean (SD, range)	5.3 (8.5, 0-60)
Median (IQR)	3 (2,5)
Receptive UAI partners in the last 6 months (n=58)	
Yes	87.9 (51)
No	12.1 (7)
Number of receptive UAI partners	
Mean (SD, range)	5.2 (14.5, 0-100)
Median (IQR)	2 (1,3)
Insertive UAI partners in the last 6 months (n=59)	
Yes	62.7 (37)
No	37.3 (22)
Number of insertive UAI partners	
Mean (SD, range)	2.2 (4.2, 0-20)
Median (IQR)	1 (0,2)
Type of sexual activity (n=55)	
Fisting	12.7 (7)
Rimming	61.8 (34)
Group sex	41.8 (23)
Sharing of sex toys	3.6 (2)
Water sports	10.9 (6)
Scat play	1.8 (1)
Other	0.0 (0)
None of these	30.9 (17)
Use of drugs in the last 6 months (n=58)	
Yes	53.4 (31)
No	46.6 (27)
Type of drug used (n=31)	
Amphetamine	16 (5)
Ecstasy	32.3 (10)
G, GHB, GBL	61.3 (19)
Mephedrone	54.8 (17)
Cannabis	25.8 (8)
Cocaine	35.4 (11)
Amyl Nitrates (poppers)	41.9 (13)
Ketamine	19.4 (6)
Crystal meth	25.8 (8)
Crack	6.5 (2)
Viagra	35.5 (11)
Other	--
Drugs injected (n=49)	
Yes	10.2 (5)
No	89.8 (40)

Figure 21 Types of receptive and insertive UAI partners



The reported use of PEP was relatively common with a third of participants stating to have used it ever (Table 30). Among those that had used it, the median number of times of PEP use was 1 (IQR 1, 2). Only three (7%) participants reported to have used PrEP (not widely available at the time of data collection). The PrEP medication was sourced from a clinic by two men and from a friend by another.

Table 30 Previous PEP and PrEP use in the 6 months prior to HIV diagnosis

PEP and PrEP use history	% (n)
Use of PEP (ever) (n=53)	
Yes	36.8 (19)
No	64.2 (34)
Median (IQR) no of times PEP used	0 (0,1)
Median (IQR) no of times PEP used among men that have used it	1 (1,2)
Use of PrEP (ever) (n=45)	
Yes	6.7 (3)
No	93.3 (42)
Median (IQR) no of times PrEP used	0 (0,0)
Median (IQR) no of times PrEP used among men that have used it	1 (1,5)

8.1.4 Partner meeting venues

As may have been expected with the popularity of internet sites and mobile apps to meet partners, men reported mostly (88%) having used these to meet sexual partners in the 6 months prior diagnosis, followed by the more traditional venues of bars clubs and saunas (58%, Table 31). Five participants had met partners at a sex party either in the UK or abroad. The most commonly reported internet site/app was Grindr (80%).

Table 31 Partner meeting venues and internet sites used in the 6 months prior to HIV diagnosis

Partner meeting venue/internet app used to meet partners	% (n)
Bars/clubs/saunas (n=56)	58.2 (32)
Internet/mobile phone apps	87.5 (49)
Backroom	1.8 (1)
Sex party in the UK	5.5 (3)
Sex party abroad	3.6 (2)
Cruising ground	5.5 (3)
Escort service	1.8 (1)
Sex abroad	1.8 (1)
Other	3.6 (2)*
Internet sites (n=40)**	
GRINDR	80.0 (32)
BBRT	10.0 (4)
Manhunt	7.5 (3)
Scruff	10.0 (4)
Gaydar	7.5 (3)
Squirt	5.0 (2)
Recon	5.0 (2)
Slaveb	2.5 (1)
XXL	5.0 (2)
Fitlads	2.5 (1)
Hornet	5.0 (2)
Bender	2.5 (1)
Jackd	5.0 (2)

* those that marked other listed apps
**some participants listed more than one app

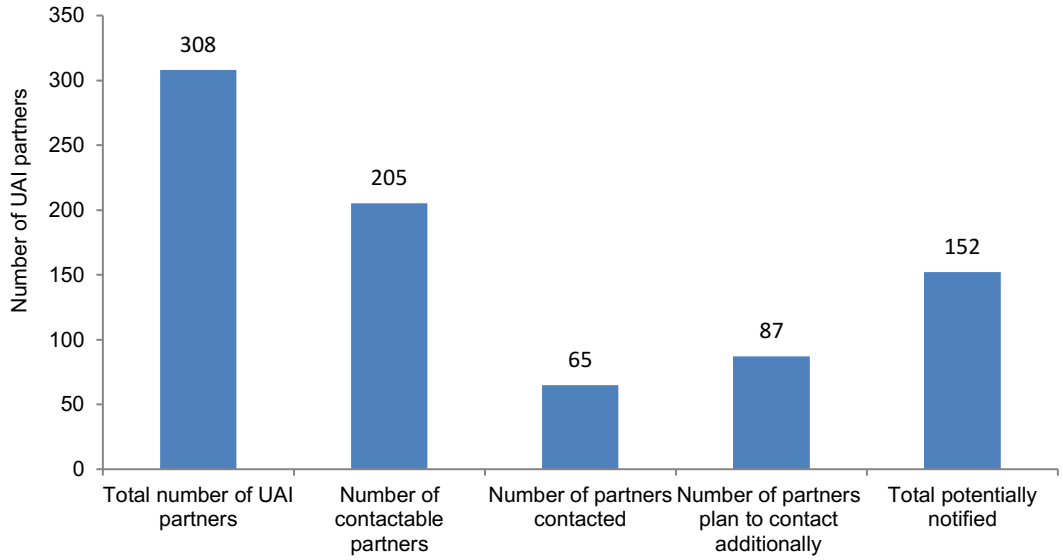
8.1.5 Numbers of sexual partners contacted and contactable

In comparison to a mean of 5.3 UAI partners overall, men reported a mean number of 2.7 UAI (SD 3.4, range 0-20) contactable partners (Table 32). Overall, of a total of 308 UAI partners, 205 (67%) were contactable (Figure 24). Only a small fraction (32% of contactable partners and 21% of all partners) had been contacted at the time of questionnaire completion which was within 3 months of diagnosis). Participants stated they additionally intended to contact a total of 87 partners and hence the overall number of partners potentially notified in this sample was 152, 49% of all partners and 74% of contactable partners. The partners were largely contactable by phone (69%) or text (63%) or through an app or website (31%). Nearly all men (84%) preferred contacting partners themselves followed by through a health visitor or chosen clinic (24%); 12% preferred to contact them anonymously through an app. One person indicated that they would not contact them.

Table 32 Partner notification preferences, potential and past activities

Contactable sexual partner and partner notification method	% (n)
Number of partners contactable (n=51)	
Mean (SD, range)	2.7 (3.4, 0-20)
Median (IQR)	2 (1,3)
Methods partners contactable by (n=48)	
Text	62.5 (30)
Phone	68.8 (33)
Through and app or website	31.3 (15)
Email	12.5 (6)
Social networking site (e.g. facebook)	14.6 (7)
Back at the place I met them (e.g. bar, club, sauna)	0.0 (0)
Other*	4.2 (2)
Best method considered to contact partners (n=50)	
I would contact them myself	84 (42)
Through a health advisor/clinic staff	24 (12)
Anonymously online/through an app	12 (6)
I wouldn't contact them	2(1)
Other	--

Figure 22 Number of partners notifiable in 51 MSM diagnosed with recent infection



8.1.6 How respondents believed they acquired their HIV infection

When asked '*How do you think you acquired HIV',* nearly all men (92%) described a recent risk event to which they attributed their infection. Responses described situations of higher and lower risk UAI, drug use, group sex situations, failed preventative measures including PEP, spilt condoms, serosorting and dipping. Issues concerning disclosure and perception of

status versus actual status, and trust in both regular and casual partners were raised. Very few men indicated that they had no idea how they acquired their infection.

The responses could broadly be categorised into the following four themes:

i) men who had been aware of high risk as they engaged in UAI, (n=17; UAI with casual partners and or multiple partners);

> *"I think end of November, early December I was at a sauna in [small UK town], I had receptive anal sex with a man unprotected and he came inside me. I think he was positive, but I can't be sure and I don't know him."*
>
> 25-30 year old British male

> *"Someone I met online told me he was negative. I knew I was. I don't think he was. We both had vers sex."*
>
> 35-40 year old British male

ii) men reporting that their ability to negotiate safe sex had been compromised, (n=6; UAI due to drug-induced disinhibition (4), lack of opportunity to negotiate safe sex in a group sex situation (1), and rape (1);

> *"I am using a lot of drugs right now. I live in a flat where there are loads of parties, I have had lots of sex with men coming over so think I got HIV from that. Most of them already have HIV, now I do too."*
>
> 25-30 year old non British European male

> *"A group situation and someone inserted their penis without a condom, but didn't cum. I didn't know his status and didn't realise I'd been put at risk."*
>
> 20-25 year old Australian male

> *"I was raped and forced to have oral sex with them."*
>
> 35-40 year old British male

iii) men who reported attempting to protect themselves but that this was unsuccessful (n=21; split condom (7), believing partner had an undetectable viral load (2), dipping (5), serosorting (6), oral sex only (1).

"*I received anal sex, condom came off inside. There was blood so I came to get tested*."

30-35 year old British male

"*All the people were undetecable that I slept with*"

30-35 year old British male

"*From a person who thought they were negative through anal sex*"

40-45 year old non British European male

"*I had oral sex with someone I met with a cut in my mouth. That's how I believe I got it.*"

25-35 year old American male

iv) men who believed transmission to have been from a regular partner (n=3)

"*With a regular partner. Had unprotected sex in a relationship - justification for unprotected sex is rather stupid."*

20-25 year old British male

Interestingly, 72% (33/46) of those that described a specific incident also reported UAI with >1 partner in the previous 6 months, indicating that there may have been multiple opportunities for infection. However participants may have had other reasons (not disclosed) to believe that transmission occurred at the event described. Even among those that suspected transmission from a regular partner, two of three had had UAI with more than 1 partner in the previous 6 months. Nearly half of the men (46%, n=21) were also diagnosed

with an STI, however this may have been how they knew that they were recently HIV negative as nearly all STI screens include a test for HIV.

8.2 Discussion

8.2.1 Principal findings

The pilot of enhanced behavioural surveillance of MSM with incident HIV infection examined HIV testing, sexual risk behaviours, partner meeting venues, PN and HIV transmission events close to the time of seroconversion. It was a feasibility study for patient-led surveillance in MSM with data collected from seven sites across the country. One in 5 men diagnosed with recent infection (identified by RITA) in the selected venues took part. Verbal feedback from clinicians and health advisors was that the questionnaire was well received, although there were pressures on time and staff to explain the initiative to patients. In addition, in some sites other ongoing research studies were competing for the same patients. This is likely to be an ongoing issue for surveillance which collects data directly from patients.

Although numbers were small, our data show that most were high risk and regular testers in the 6 months before their diagnosis. Common reasons for testing were feeling unwell (4 of 10 men) and a routine check (also 4 of 10 men). Half of the men had been diagnosed with an STI in the previous 6 months and an equal fraction had used drugs before or during sex with the most common drugs reported having been G, GHB, GBL and Mephedrone. Nearly all men met sexual partners through internet sites or mobile phone apps and two thirds indicated they visited bars, clubs or saunas. Grindr was by far the most used mobile phone app. There was limited potential for PN with only half of all sexual partners contactable and men intending to contact only three quarters of these. Most men preferred to contact the

partners themselves followed by through a health visitor or clinic. Conducting PN anonymously through an app was not considered favourable.

When men were asked how they believed they acquired their HIV infection, almost all recalled and reported a specific risk event, although these may have been subject to potential inaccuracies due to numerous exposures and recall bias. Risk events could be categorised into four types: i.) instances where men knew they had engaged in high risk sex with multiple partners, ii.) instances where men had tried to negotiate safe sex but their ability to do so was compromised either by drugs and or by others in a group sex situation; iii.) instances where men reported to have attempted to protect themselves but were unsuccessful, (e.g. split condom, being told the partner had an undetectable viral load and or serosorting), and lastly, although reported by very few, iv.) transmission from a regular partner. The data showed that while there were high levels of risk behaviour shortly before diagnosis, nearly half reported having taken measures to prevent infection indicating men could be likely to self-select for interventions such as PrEP.

8.2.2 Comparison with other studies

Although the pilot study was not designed to assess the behavioural characteristics of the MSM quantitatively, there are numerous studies which have collected behavioural data from this group which are able to provide context to the sample of men studied here. With a wealth of data available on trends in partner numbers and types, STI history and PN, here I summarise a few to allow comparison of methods and data. Although, only very few UK studies have behavioural data from recent seroconverters.

One such study that collected very similar behavioural data was another PhD research study ongoing at the time of my data collection.(231) The thesis examined attitudes towards earlier initiation of ART in MSM and also in MSM with recently acquired HIV. The behavioural data

was collected from men recruited to the UK Register of Seroconverters which was a study that commenced in 1994 with the initial aim of estimating an accurate incubation period for HIV.(232-234) At the time, the UK Register of Seroconverters collected information on a cohort of people with the following eligibility criteria:

- An inter-test interval of 12 months between a negative and positive HIV test (prior to 2004 this interval was three years)
- A RITA positive result (data provided by PHE)
- An equivocal antibody test followed by repeat testing after two weeks showing increased OD
- An antibody negative with positive reverse transcriptase chain reaction (RT-PCR)
- Symptoms of seroconversion alongside antigen positivity and less than four bands on Western Blot.

Consent was obtained from individuals for the research team to collate all previous and future medical information related to their HIV infection and to follow up patients annually. The register collaborated with PHE to cross-check the database against that of PHE to assist with the identification of all seroconverters diagnosed. Therefore, there was considerable overlap between the seroconverter and RITA databases.

At the outset of the pilot for enhanced surveillance, I met with the research student to discuss the possibility of combining the results of the two studies for a greater sample size as many of the behavioural data collected were similar. However, after consideration that the main aim of the pilot for enhanced surveillance was to evaluate feasibility of data collection for surveillance purposes, and the differences in the ethical requirements for the data collection, I decided against pooling these data.

For the PhD study by Parsons et al., eligible MSM were aged ≥16 years, and were invited to complete a survey within 12 months of their diagnosis between July 2013 and December

2014. The 117 men included in her analyses were recruited mainly from three London clinics; St Mary's Hospital (29%), Guy's and St Thomas' (13%) and Mortimer Market (10%). The demographic characteristics of the survey respondents were similar to those in the enhanced surveillance initiative, with 84% of white ethnicity, and the median age at seroconversion having been 33 years. This survey also collected data on the reasons for HIV testing at the time of diagnosis and her findings were broadly similar to mine in that 41% reported it to have been a routine test and 35% tested because they felt unwell. A lower proportion reported previous PEP use (23% versus 37% in the enhanced surveillance), however overall numbers were small. In terms of behaviours in the 6 months prior to diagnosis, the median number of UAI partners in this sample is similar to that of the enhanced surveillance with 2 (IQR 1, 5) versus 3(IQR 2,5). A similar proportion reported illegal drug use before or during sex (52% vs 53% in enhanced surveillance) and a slightly higher proportion engaged in chemsex activities (47% vs. 30%). Data were also collected for sex partner meeting venues; 67% used smart phone apps and 61% internet sites, versus 80% in the enhanced surveillance. A similar fraction (49%) met partners at bars and clubs. Other behavioural studies on seroconverters have been comparatively small due to the fact that they identified the incident infections prospectively in a cohort of HIV negative men. A recent pilot study in HIV negative men attending sexual health clinics explored behavioural predictors for HIV infection to develop a tool for selecting high risk patients to intervention programmes (personal communication Dr Sarika Desai, Senior HIV/STI Surveillance Scientist, PHE). Of 1601 attending men, there were 11 that went on to seroconvert a year after recruitment; 6 had had an STI the previous year, 2 had used PEP and none had used PrEP. The average number of receptive UAI partners in the last 3 months was 0.875 and insertive UAI partners was 0.75 which compares to 5.2 (14.5, 0-100) and 2.2 (4.2, 0-20) over a 6 month period in my sample of men with incident infection. Following on from this study was another pilot for the expansion of the routine GUM clinic activity surveillance to incorporate behavioural data collected by clinic staff during consultations into GUMCAD (GUMCAD v3).(235) Similarly, this entailed collecting data on the number of receptive and

insertive UAI partners (over the past three months), whether the HIV status of sexual partners was known, the reason for not using a condom at the last sexual encounter, any STI diagnoses in the previous year, the date of the last negative HIV test (if tested previously) and history of PEP and PrEP use. To date there have been no publications on the sexual partner numbers in these data with full roll out of GUMCADv3 expected in 2019 (personal communication Hamish Mohammed, Principle HIV/STI Scientist, Public Health England).

Other behavioural studies in the UK include the Antiretrovirals, Sexual Transmission Risk and Attitudes (ASTRA) study which was among diagnosed positive men attending clinics for HIV-related care.(236) Here, eligible men were diagnosed for a minimum of three months (median time since diagnosis in the study was 10 years) and the data collected related to the three months prior attendance. Consequently these data, and other similar studies in men which had been diagnosed for some time, are not comparable as it has been shown that men often change their behaviours after diagnosis.(237, 238) In the ASTRA study they did not report the overall median number of UAI partners, however in men that reported condomless discordant UAI in the previous three months (n=320 of 1,352), 31% had 2-4 condomless discordant UAI partners and 16% had had five or more. An STI diagnosis in the previous three months was reported for 11% of men which, although is considerably high, is far lower than my findings in the small sample of incident cases and also that of Desai.
A community-based study of MSM attending bars, clubs and saunas in London I had worked on outside of this thesis reviewed trends in sexual behaviours over more than a decade (2000-2013) and was able to examine these by HIV status.(165) In this study, men were invited to complete a questionnaire on sexual behaviours and provide a saliva specimen for HIV-antibody testing. This study included data from just under 12,000 MSM, of which 1,512 (13%) were HIV positive and 531 had undiagnosed infection. Findings demonstrated that the proportion of men that had had UAI with partners of unknown status was consistently higher in diagnosed positive men than undiagnosed positive and negative men. In addition, the

mean number of sexual partners in the previous year was consistently higher in diagnosed HIV-positive men with 9.7 (SD 22.5) in 2013.

To note, a comparison of different types of survey methods and estimates found that national probability sample surveys such as NATSAL best reflect the MSM population but have the limitation of small sample sizes.(239) It was found that partner numbers are higher in convenience sample surveys which may intentionally seek to sample higher risk men in known sex partner meeting venues(165, 240), gyms (240) and internet sites(207, 241). In the most recent NATSAL survey (2010), the mean number of reported partners in the past year was 4.5 (SD 8.5) and median 2 (IQR 1-5) among a total of 190 MSM.(242). Interestingly, only 4.9% of MSM reported an STI diagnosis in the past year and 33% had attended a sexual health clinic.

Outside of the UK, there have been other behavioural studies in recent seroconverters; published in 2017, in Australia, the HIV Seroconversion Study was an online cross-sectional survey in gay and bisexual men recently diagnosed with HIV. (243) The aim of this study was to compare occasions of condomless anal intercourse with casual partners that resulted in HIV transmission with similar incidents where transmission did not occur. This was done by comparing HIV negative men enrolled to another online study, the Pleasure and Sexual Health Study (PASH) involving 2,306 Australian gay and bisexual participants in 2009. Men were asked to describe their most recent incident of condomless anal intercourse with a casual partner. The comparison included 169 men in the Seroconverter Study and 194 men in PASH, with similar demographic characteristics in both groups. Slightly fewer were in a regular relationship at the time in the Seroconverter group (33% versus 41%) and findings showed that men who seroconverted were more likely to have met their casual partner with whom they had condomless sex with for the first time at last incident (68% vs 40%). The seroconverters were also less likely to have reported believing their partners status at the time was HIV negative (29% vs 70%), although the authors acknowledge that this may be

influenced by recall bias and on reflection of their own status. They also found a difference in the location the event occurred with less events occurring in the home (20% vs 38%) and many more having been a group sex event (37% vs 9%). In addition, the seroconverters were more likely to have been the receptive partner with 15% reporting only insertive condomless anal intercourse with the casual partner compared to 35% in PASH. In contrary to my findings however, this study concluded that among seroconverters there was little evidence of risk reduction strategies adopted at the event the transmission was attributed to, in particular referring to receptive anal intercourse. However, the authors do highlight that they were unable to determine whether positioning was considered a risk reduction strategy. Of interest is, however, that a large proportion (a third) of seroconverters had engaged in group sex, which is similar to my findings of a 40%, likely a more difficult environment to negotiate safer sex practices in.

In another publication by the same authors, more detail is provided on the reported high risk events that led to infection in the HIV Seroconversion Study with 84% reporting condomless anal intercourse and 72% in the receptive position.(244)

A further relevant study from Australia in 2007 reports on how homosexual men believed they became infected with HIV and the role of risk reduction strategies; among 158 men recently diagnosed with primary HIV infection between 2003 and 2006 recruited in sexual health clinics, 91% were able to identify at least one high risk event they believed was associated with their HIV acquisition (multiple events were reported by 52%).(245) More comparable to my findings, this study reported 38% of high risk events to have included a risk reduction strategy, such as serosorting, strategic positioning or believing partners had an undetectable viral load. A large number reported transmission from a regular partner (n=30).

Of interest are the predictors of HIV acquisition itself (not possible to determine in the enhanced surveillance data); in the PROUD trial, among 253 participants who were not on PrEP, 20 HIV infections occurred over a total of 220 person years which equated to an incidence rate of 9.1 per 100 person years.(246) The strongest risk factors for HIV infection were found to have been ≥2 anal sex partners without a condom in the last 90 days and having had a bacterial rectal STI in the previous year.

Expanding on this, a qualitative study exploring the social and environmental context of 21 MSM with recently acquired HIV recruited to the UK Register of Seroconverters found that individual psycho-social factors such as such recent life stressors, mental health and personal history increased a person's susceptibility towards high risk situations and that this was further enhanced with the normalisation of social environmental factors such as chemsex, social media and community beliefs regarding treatment.(247)

In addition to trends in sexual behaviour there are published data on PN in the UK. A nationwide audit undertaken by the British HIV Association (BHIVA) in 2013 presents data on PN among adults diagnosed with HIV in England. The audit covers 169 HIV services (156 GUM and 13 non GUM), 2,964 index cases and over 6,400 contacts.(195) Of these, a total of 3,211 contacts were audited, 84% (2,692) were deemed potentially at risk, 44% (1399) attended for testing and 21% were newly diagnosed HIV positive, representing one new diagnosis through PN for every 10 cases. In this study, importantly there was little difference in the proportion of contacts diagnosed among those recently infected compared to those not recently infected (18.6% versus 21.9%). Highest positivity rates were among regular partners (26.5%) compared to ex-regular (13.6%) and casual (11.7%). It was estimated that, using the average HIV prevalence of 21% in partners, that overall 422 potentially contactable sexual partners would have been infected with HIV, of which 67% diagnosed. This implies that among the 3,211 audited, 63% (2009 (422/0.21)) were contactable which is similar to my findings with 67% of partners contactable, although only half of all contacts

were potentially notified. In the audit, 0.48 contacts per index case attended HIV services; I would expect this to have been lower in my sample as this is equal to my findings of the proportion of contacts potentially notified.

Since the publication of the audit, PN data are now routinely collected and reported in GUMCAD.(192) Latest data show in 2016, among 3,065 new HIV diagnoses in GUMCAD, 2,261 contacts were recorded of which 1,906 (84%) were tested. Overall, the proportion of tested contacts diagnosed was lower than that found by the BHIVA audit, at 4% with the overall proportion of contacts diagnosed (including those not tested) 3%. However, these data changed over the years with 10% of tested contacts diagnosed in 2012 (8% overall) and 6% (5% overall) in 2013. To note is that the number of contacts reported to have been tested (numerator) increased over the five year period from 1,346 to 1,906 (a 68% increase) whilst the overall number of contacts (denominator) increased by only 32% in comparison from 1,715 to 2,261. In London the figures were slightly higher and the overall decline steeper with 24% of tested contacts and 14% of contacts overall diagnosed in 2012 dropping to 6% of tested contacts and 4% of contacts overall in 2016. Compared to my data and the BHIVA audit, the number of contacts per index case reported is much lower in GUMCAD, with overall fewer contacts than diagnosed index cases.

Since 2015, the new HIV and AIDS reporting system also has data on PN. Outside of the thesis, I analysed preliminary data from 2016 and found among 2,033 persons newly diagnosed in 2016 for whom data were available, there were a total of 6,077 contacts recorded of which 1,930 (32%) were contactable and 1,265 (21%) were tested. There was no information available on how many of these were diagnosed with HIV.

Lastly, with regards to partner meeting venues, there were few published data. Most on sex partner meeting venues are from the US. Jennings et al. in Baltimore reviewed sex partner

meeting places among 764 newly diagnosed MSM from 2009-2014 and showed that there were 5 bars and or clubs that represented more than half of all bars and or clubs reported, of a total of 306 unique places.(248) They found that the number of bars and or clubs frequented reduced over time as reports of internet sites increased. A study by Oster et al. in Mississippi interviewed 22 black MSM aged 17-25 years who had been diagnosed with HIV between 2006 and 2008 and also reported these to be linked by a small number of venues with three venues reported by 60% of participants.(249) In Los Angeles in 2005, among 526 MSM aged between 18 and 24 years, nearly all men were connected by a single venue and over 87% were connected by the 6 most central venues.(250) A study in Germany found that (among HIV negative men), compared with meeting partners online, meeting partners at sex or social venues was associated with an increased risk in bacterial STIs (OR 1.6 (95% CII 1.0-2.5) and 1.9 (95% C.I 1.4-2.6), respectively).

In the UK a study by Weatherburn et al. reports on the type of setting visited rather than actual venues in 2002; 62% of 11100 MSM recruited to the Gay Men's Sex Survey met a sexual partner at a bar/pub/club in the last year and 51% via the internet.(251) This study is now however considerably dated. For comparison, in our study a similar proportion used bars and clubs to meet partners in the last 6 months but just under 90% had used internet sites/apps.

8.2.3 Limitations

For the pilot of enhanced behavioural surveillance in MSM, the survey in the selected patients was able to characterise and examine the behaviours of 60 MSM seroconverters shortly before diagnosis which may add to the few published data on seroconverters in the UK. Only one person refused to complete the questionnaire although this is likely to have been due to how participants were selected by healthcare staff. It covered a wide range of topics including current sexual partner venues and PN rates and preferences, and uniquely

collected information on participants' presumed transmission event providing insight into the likely circumstances under which infection occurred. Consequently, I was able to present types of transmission events and the fraction of men that attempted to protect themselves from infection. The pilot study complements other behavioural surveillance activities at PHE and has fed into the design of a further survey, the Surveillance of Recently Acquired HIV: Enhanced (SHARE) which I am currently rolling out (see section 9.2).

Limitations were that as this was a feasibility study, it was a small sample. The data were difficult to collect with clinic staff not approaching all eligible patients, either due to time/resource constraints or because they deemed it inappropriate for the patient at the time. Verbal feedback from healthcare staff emphasised the need for additional resources to conduct any activities beyond routine, standard care. I also only provided paper questionnaires so healthcare staff needed to collect these (batch wise) to post back to PHE. Whilst this is likely to have prompted higher completion rates (participants needed to complete the questionnaires in the clinic), it required more healthcare staff time to manage data collection materials. Options for patients completing the survey online were explored however, typically this method of recruitment experiences low completion rates. Another pilot survey, Positive Voices, also conducted at PHE, gathering behavioural data directly from HIV positive people during the period of study(252) collected survey data online and previously reported a 29% response rate (personal communication Meaghan Kall, Positive Voices Project Coordinator).

Although only one refusal was noted not all eligible patients were invited to take part (based on verbal feedback from healthcare staff) suggesting the sample of men may have been highly selective. Without identifiers such as the patient's clinic ID number, the date of birth or soundex, the data could not be linked to PHE's epidemiological data to determine any selection bias. No identifiers were collected on the advice of healthcare staff to encourage

patients to answer honestly and completely. In addition, as with any questionnaire of this type, the data may be subject to recall bias despite the relatively short recall period.
Other limitations of the survey design included firstly the phrasing of some of the questions; for people that reported previous PrEP and PEP use, we did not collect the date of use and were unable to establish whether use was associated with the current diagnosis or a previous risk event. Secondly, the question on naming venues attended in the past six months to meet partners was poorly completed with only two stating the sauna Chariots Vauxhall. This is puzzling given that the following question about which internet sites and apps were used was similarly phrased and completed by nearly all participants. Additional qualitative research would be required to explore reasons for this. One hypothesis may be that although over half of men used bars/clubs/saunas to meet men, internet sites and apps were the primary method and participants therefore focussed more on that question.

8.2.4 Conclusions

This study assessed the feasibility and value of collecting behavioural data from men with incident infection in real-time in anticipation that these data could be valuable for HIV control efforts. Whilst it was feasible to collect the data with huge support from clinic staff, the potential for high coverage of the data is questionable as the coverage rate was considerably low with returns from 1 in 5 men with incident infection (based on RITA data) in the selected survey sites. In addition, with resource and staff constraints in the NHS more widely and ongoing cuts to sexual health services, conducting enhanced surveillance among patients over a longer period of time may be unfeasible. The use of open ended questions does have the potential to flag new trends in behaviours and possible new risk behaviours for HIV however a qualitative research approach with the use of focus groups or one-to one interviews is likely to provide richer data and may be a more sensitive approach to improving insights into the circumstances leading to a HIV infection. Of importance however is that the main way for this sample of men to have met partners was through internet or mobile phone

dating apps and there was limited PN potential with only half of all sexual partners contactable which may call for innovative approaches for PN, perhaps using the dating apps. Just recently (May 2018), a news report was published that Grindr and other major dating apps are looking into incorporating an STI notification function. If designed in a user friendly, acceptable way, this could overcome a major PN barrier of high numbers of uncontactable partners. A suggestion was for the app companies to own the notification process, notifying the affected person on behalf of the sexual partner, thereby facilitating anonymity in the process.(253)

Insights that were gained from this study were that reported HIV transmission risk events could be grouped into four categories and showed that most men attempted to protect themselves from infection. These categories were i.) instances where men had high risk UAI with multiple casual partners, ii.) instances where men had tried to negotiate safe sex but their ability to do so was compromised either by drugs and or by others in a group sex situation; iii.) instances where men reported to have attempted to protect themselves but were unsuccessful, and iv.) transmission from a regular partner. These groupings could be used for the wider monitoring of seroconverters and inform the demand for different types of prevention services, e.g. drugs and alcohol counselling, the availability of PEP and PrEP. Particularly in the context of changing sexual health messages over the years for the MSM community with the availability of different preventive tools, it may be of value to monitor the nature of HIV transmission events. Prior to the roll out of TasP and PrEP, serosorting (choosing partners with the same assumed HIV status) was a commonly used risk reduction tool.(165) However the latest campaign is U=U, where an undetectable viral load=untransmittable (or not infectious) HIV, (254) likely impacting on how men choose partners and the further relevance of HIV status disclosure.

9 Summary and discussion of thesis

In Chapters 4-8 I explored characteristics of the AxSym avidity assay in determining recent HIV infection and the application of these to UK surveillance data to estimate the rate of new HIV infections over a five-year period and conduct behavioural surveillance. In this chapter I review the results and discuss the findings in the context of the aims of the thesis which are to

i.) utilise PHE's recent HIV infection testing data to estimate HIV incidence

ii.) to assess the validity of HIV incidence measurements and compare these against existing methods and findings for determining incidence in the UK, and

iii.) explore if recent HIV infection data can enable the collection of additional behavioural information facilitating the application of more conventional infectious disease control measures

To address the question, what is the public health utility of tests for recent infection with HIV in the UK, I review the contribution of these data to the current knowledge of the UK HIV epidemic. I compare the findings to other studies, highlight strengths and limitations of each of the analyses and review gaps and opportunities for further research. In addition, I explore other data sources which have arisen since the beginning of the study and review how these may impact the value of RITA data in the future. Lastly, I comment on the public health implications of my findings and conclude with a discussion of how this research may influence public health and surveillance activities going forward. The key findings are summarised at the end of each section.

9.1 Critical appraisal of findings

9.1.1 Analyses of PHE's recent infection surveillance data

In this thesis, in order to address the aims:

i.) to utilise PHE's recent HIV infection testing data to estimate HIV incidence, and

ii.) to assess the validity of HIV incidence measurements and compare these against existing methods and findings for determining incidence in the UK

I undertook analyses attempting to explore the characteristics of the recent infection assay (Chapter 4) and three distinct analyses of the testing data covering England, Wales and Northern Ireland to examine the predictors of a recent infection diagnosis (Chapter 5) and estimate HIV incidence (Chapters 6 & 7). In general, this body of work showed the incorporation of serological HIV incidence testing into case-based surveillance was feasible and that despite numerous caveats, generating estimates for the number of new HIV infections over time was possible.

In Chapter 4 I examined characteristics of the assay to the extent that was feasible using available data and found that incorporating additional clinical data as part of the recent infection testing algorithm did reduce the misclassification rate of the assay. However, which of these additional components was included in the algorithm had little impact on the overall resulting proportion of recent infection. Moving forward, the development of improved assays may reduce the uncertainty around false recency and MDRI which would improve confidence in the incidence estimates. However, challenges will remain in establishing a locally derived FRR which would require sufficient numbers of people with longstanding infection who are treatment naïve. Reassuringly, sensitivity analyses around the key

parameters in the incidence estimation models indicated that any likely divergence was unlikely to have had a significant effect on the final estimates.

In Chapter 5 I showed that despite incomplete coverage of avidity testing for new HIV diagnoses, the data were representative of the population of people diagnosed with HIV (p94). I showed that there was wide disparity between risk groups in the proportion diagnosed with recent infection and that these proportions increased over time. Although these analyses were useful to characterise people diagnosed with recent infection, a proxy for the characteristics of people with incident infection, my findings largely confirmed patterns already well established such as lower rates of recent infection in heterosexuals born abroad and those with lower CD4 counts, higher rates in those with younger age and in MSM. As recent infection diagnoses are affected by testing patterns, interpretation of these data in relation to incidence is difficult. For instance, an increase in recent infection diagnoses could be due to an increase in testing rather than an increase in transmission. A study by Rice et al. using a back-calculation model combining CD4 decline data and information on year of arrival of patients into the UK found that half of heterosexuals with HIV born abroad likely acquired their infection in the UK.(210) This suggests that the lower odds of being diagnosed with a recent infection in this group was attributable to a large extent to HIV testing patterns (with less frequent testing in the group) as opposed to risk of HIV acquisition. Of note is that, the increase in recent infection diagnoses over the years which is largely due to increased HIV testing, is also likely to be a reflection of a reduction in undiagnosed cases as more people are being diagnosed during the earlier stages of infection. Reviewing the data, in 2009, there were an estimated 9000 MSM with undiagnosed HIV (75), compared to 7200 in 2013.(80) However, as the recent infection data are difficult to interpret without information on HIV testing patterns, I recommend to not publish these data in the absence of the incidence estimates generated through models which take testing behaviours into account.

In Chapters 6 & 7 I used two approaches to estimate incidence, firstly employing a cross-sectional sampling method in a population where both HIV negative and positive tests are known, secondly using the stratified extrapolation approach to obtain estimates for the whole population. The cross-sectional analyses (Chapter 6) showed a marginal increase in HIV incidence in the population attending sexual health clinics in England. My findings reiterated the disparity in the populations most affected by HIV with the highest rates of new HIV infections in MSM, followed by black African heterosexuals. I found 2.0 per 1,000 incident HIV cases in all sexual health clinic attendees in 2013, 1.7 per 1000 for black African heterosexuals, 0.4 per 1000 in heterosexuals overall and 15.2 per 1000 in MSM. Despite the caveats around this analysis, including limitations concerning the large sample sizes required in order to detect significant changes over time, these estimates were the first to show the magnitude of the difference in HIV incidence between the key population groups in England.

A major difference in this particular cross-sectional study design compared to other cross-sectional studies using RITAs was that in the sample I used people had self-selected to attend a sexual health clinic and consequently, to get tested for HIV. As mentioned in Chapter 6, Remis et al. found that if people are prompted to test at an earlier stage of infection e.g. due to symptoms of seroconversion or a recent risk event, the number of recent infection diagnoses could be inflated and thus consequently inflate incidence estimates.(156) Therefore the results from this analysis must also be interpreted with caution. However, nevertheless, these data could be utilised for assessing the level of need and or demand for prevention services including PrEP in this setting. Furthermore these estimates may be considered to be particularly timely given the reconfiguration of sexual health services in England. In 2013, the reconfiguration entailed a split of the commissioning for sexual health services from HIV care with local authorities responsible for sexual health and STI prevention services and HIV treatment and care funded centrally by NHS England.(255) Other changes included the move towards web-based service provision such

as sh24[2] which will have the effect of the need for fewer clinic visits and consequently fewer sexual health clinics, as well as the expansion of home sampling and home testing. Given these service provision changes, it is crucial to have baseline HIV incidence estimates to monitor the impact over the years, in particular on HIV testing and diagnosis rates and most importantly HIV incidence in subpopulations. Additional granularity in the estimates would be beneficial to explore if within the transmission risk groups, certain subgroups may be less likely to access care, for example older people less likely to use online services. Lastly, particularly in context of the general population-based estimates, for the first time, a comparison could be made to determine how the risk of people attending sexual health clinics compared to the general population which is crucial not only for the interpretation of crude surveillance data but also for the design of prevention initiatives which use a targeted approach in sexual health clinics. The comparison of my incidence estimates in the different settings is discussed in later in this Chapter.

In Chapter 7, findings from my thesis on population-based estimates have contributed to the sparse pool of evidence for the rate of new HIV infections in various population groups. Table 33 summarises those from this thesis and those available in the literature. Although the model using the serological incidence data is based on a number of assumptions, my estimates are remarkably similar to the other published studies based on different approaches which provides confidence in the findings.

[2] https://www.sh24.org.uk/

Table 33 A comparison of UK HIV incidence estimates from this thesis with those from published literature using other methods: 2009-2013

Outcome	Publication	Method	Estimate from publication	Method in thesis	Estimate from thesis
HIV incidence in sexual health clinics in England in MSM	HIV incidence in an open national cohort of men who have sex with men attending sexually transmitted infection clinics in England.(221)	Analyses of MSM repeat attenders in sexual health clinics.	**20 (95%CI 18-22) per 1000 person years, 2012**	Cross-sectional analysis of sexual health clinic attendees using RITA(217)	**15 (95% CI 13-18) per 1000 person years, 2012**
HIV incidence in sexual health clinics in England in non MSM risk groups	N/A	N/A	N/A	Cross-sectional analysis of sexual health clinic attendees using RITA(217)	**2 (95% C.I. 0.5-3.0) per 1000 person years in black Africans, 2013;** **0.5 (95% C.I. 0.3-0.7) per 1000 person years in all heterosexuals, 2013;** **2 (95% C.I. 1.7-2.3) per 1000 person years in all sexual health clinic attendees, 2013**
HIV incidence in the general population	An epidemiological modelling study to estimate the composition of HIV-positive populations including migrants from endemic settings(256)	Mathematical model; individual-based stochastic simulation used to calibrate routinely collected surveillance data	**0.08 per 1000 person years, 2011*, ****	Population-based analysis using RITA and the stratified extrapolation approach	**0.06 (95% C.I.5.8-6.8) per 1000 person years, 2011**
HIV incidence in population-based MSM	HIV incidence in men who have sex with men in England and Wales 2001-10: a nationwide population study.(95) HIV in the UK, 2016 report(5)	Back-calculation method based on CD4 count at diagnosis.	**3.9 (95% C.I. 3.0-4.9) per 1000 person years in MSM, 2012**	Population-based analysis using RITA and the stratified extrapolation approach	**3.8 (95% C.I 3.1-3.7) per 1000 person years in 2012 in MSM**
	Increased HIV Incidence in Men Who Have Sex with Men Despite High Levels of ART-Induced Viral Suppression: Analysis of an Extensively Documented Epidemic(96)	Individual-based simulation model	**Mean annual incidence for 2006-2010, 5.3 per 1000 person years**(95%C.I.s only graphically presented in manuscript)	Population-based analysis using RITA and the stratified extrapolation approach	**2.8 (95% C.I. 2.4-3.1) per 1000 person years, 2009**
	An epidemiological modelling study to estimate the composition of HIV-positive populations including migrants	Mathematical model; individual-based stochastic simulation used to calibrate routinely collected	**3.3 per 1000 person years in MSM, 2012 *, ****	Population-based analysis using RITA and the stratified extrapolation approach	**3.8 (95% C.I 3.1-3.7) per 1000 person years in MSM, 2012**

Outcome	Publication	Method	Estimate from publication	Method in thesis	Estimate from thesis
	from endemic settings(256)	surveillance data			
HIV incidence in population-based black African heterosexuals	An epidemiological modelling study to estimate the composition of HIV-positive populations including migrants from endemic settings(256)	Mathematical model; individual-based stochastic simulation used to calibrate routinely collected surveillance data	**1.2 (90% plausibility range 0.8-2.3) per 1000 person years in heterosexuals, 2011*, ****	Population-based analysis using RITA and the stratified extrapolation approach	**0.4 (95% C.I.0.3-0.5) per 1000 person years, 2011**

*based on corresponding population figures from ONS for that year; see section 7.3
** Derived from figures presented in the publication

At the outset of my studies, population-based HIV incidence estimates were not available for non-MSM risk groups in the UK. With new estimates published in the meanwhile, one may conclude that no new insights have been gained from the serological incidence data as estimates are similar using the various other methods. However, with such few estimates available, there is utility in the ability to corroborate the results through triangulation with other studies. In addition, my estimates can be presented by more demographic and geographic detail than the other methods providing additional granularity.

Since the start of the research the HIV epidemic in the UK has changed.(1) A decline in new HIV diagnoses among MSM was observed for the first time since the beginning of the epidemic in early 2015. This reduction was 21% from 3,570 new diagnoses in 2015 to 2,810 diagnoses in 2016, and was initially concentrated in 5 London clinics.(4) This decline has continued into 2017 with a 17% further reduction to 2,330.(3) The decline has been attributed to the successful implementation of combination prevention initiatives which include high levels of HIV testing and higher condom use, alongside earlier initiation of ART. In addition, the roll out of the PrEP Impact trial, which has been the centre of much debate regarding the implementation of this intervention, is expected to further accelerate this decline. Due to government budgetary constraints, the trial, which is an implementation trial rather than an effectiveness or efficacy trial, sought to identify 10,000 high risk persons in

the first instance to prevent HIV infection in this population (https://www.prepimpacttrial.org.uk/). The expected effect is believed to be similar to a vaccine in that herd immunity would result in fewer people becoming infected overall. With a reduction in new HIV infections among those at highest risk, fewer infections are expected to spread and occur among lower risk populations. However, due to a high level of demand and indications of the trial having success in reducing new infections, since the beginning of the trial, more places have become available (an additional 3,000 in 2018 and an additional 13,000 in 2019) which is likely to accelerate the decline even further ahead of a full PrEP programme. Estimates from the CD4 back calculation model mirror a continued drop in the annual number of new HIV infections in MSM from 2012 to 2016, the most recent year an estimate is available for.(1)

With this decline in new HIV diagnoses and apparently also in new infections, and with the increasing uptake of PrEP, there is a move towards developing more sensitive surveillance systems which can track and report on the number of new HIV infections closer to real time. In the context of a declining epidemic, the serological incidence data have high utility given the geographical and age specific estimates it can provide. Reducing the number of people with undiagnosed infection will be key in the strive to reach zero infections by 2030. It is believed that a large number of undiagnosed infection is likely to be recently acquired infection given the increasing median CD4 cell counts of people newly diagnosed and the decreasing number of people diagnosed at late stage of infection.(74, 76, 257) The identification of incident infections in real-time will enable insights into which population groups infections are occurring and will enable effective allocation of resources for prevention initiatives.

Given the additional granularity and the and the estimates for the non-MSM risk groups the RITA data provide, I recommend for these incidence estimates to be added as one of PHE's routine outputs next to the back-calculation method used for estimates of the number of new HIV infections in MSM. In the US, incidence estimates are presented as such, showing

trends in estimates over time and the differences and/or homogeneity between them.(124) This would be a good way for PHE to showcase the different estimates.

In October 2017, UNAIDS convened a panel of experts to work towards building consensus on the definition for epidemic control and the elimination of HIV.(258) The definitions of the basic epidemiological measures of disease occurrence were outlined in their report with the first three being (taken from the report):

i.) Control: reduction of incidence, prevalence, or mortality in a geographically defined area to a locally acceptable level via evidence-based interventions.

ii.) Elimination of transmission: complete cessation of incidence in a geographically defined area. Because the disease causing agent persists, elimination requires ongoing intervention to maintain.

iii.) Elimination as a public health problem: reduction of incidence and morbidity below a specific (globally defined) level.

The group agreed that potential metrics or milestones are needed to achieve these such as percentage reductions or an absolute rate with an annual incidence for example of less than one per 1,000 suggested which, again, would require extremely sensitive monitoring systems to estimate particularly in harder to reach groups.

With healthcare data the main source of information for surveillance, one of the strengths of this thesis is that it can shed light on the magnitude in the difference in risk among people attending sexual health clinics and the general population, as the healthcare data are often used to infer trends in the epidemic. My findings show, for the studied period, the incidence in sexual health clinics was 1.3 per 1000 pys in 2009 increasing to 1.9 per 1000 pys in 2012; this compares to 0.06 per 1000 pys in the general population in 2009 which remained virtually unchanged 4 years later at 0.07 per 1000 pys in 2012, which is a difference of a factor of 27. For MSM the disparity was smaller but still considerable with a difference of a factor of between four and five over the period. Likewise, for heterosexuals, in sexual health

clinics there was a difference of a factor between 15 and 25 over the period. Interestingly, among black Africans, as with MSM, the factor was comparatively smaller with 3 and 4 for the years of available data. One may expect to find that the MSM population attending STI clinics is more similar in risk to the general MSM population as it is known that HIV testing in this population is comparatively high, and therefore a larger fraction of lower risk people is likely to attend clinics. However, this may be considered to be a new finding for black African heterosexuals as HIV testing rates are lower and late stage diagnosis predominantly an issue for this population group.(1) In general, for all groups combined, there is a substantial difference in the rates of infections in clinics compared with the general population the extent to which may vary over time.

Further to comparing the incidence estimates in the sexual health clinic and general population, of huge interest is what fraction of new HIV infections are diagnosed each year as this provides insight into the effectiveness of current HIV testing efforts. Using the 0.15% annual HIV incidence estimate in black Africans attending sexual health clinics in 2012 and applying this to the 71,370 that attended the same year equates to 107 people with incident infections having been diagnosed within the year. From my population-based estimates, there were an estimated 369 new infections in 2012; this implies a third (29%) of all new infections were diagnosed in sexual health clinics the same year.

Similarly, for MSM, considering the 1.5% HIV incidence in this group attending sexual health clinics in 2012 and the 88,431 MSM that attended a clinic in 2012, this equates to 1,326 MSM with incident infection having attended and been diagnosed that year. This implies that half (52%) of a total of 2,530 estimated new infections in that population that year were diagnosed in sexual health clinics. As such, behaviour change interventions and PrEP are extremely well placed to be conducted in STI clinics among this health care seeking population, in particular for MSM. More efforts are needed to identify those that do not attend

within a year of infection and do not follow (or perhaps are aware of) the guidelines to test annually or after every new partner.

Whilst, in addition to MSM, there has been a lot of focus on black Africans as a key population, which is justified comparing rates of new infection in this group to the general population, one must consider that in comparison to MSM the absolute number of new HIV infections is comparatively low and seems to have been declining. Undiagnosed and late diagnoses are of primary concern in this group which must be tackled with higher testing rates in this community. As is evident with the new HIV diagnosis data, the burden of infection was vastly in the MSM population.

Other aspects to consider for the utility of serological incidence data are if other data sources may be able to provide the same information. Desai et al. identified MSM with incident HIV infection in the data from sexual health clinics examining people newly diagnosed with HIV that had had a previous negative HIV test. With HIV testing increasing over time (in particular for MSM),(259) it may be of interest to explore how many seroconverters detected with the serological incidence assays would have been identifiable solely through testing history information. I reviewed these data and found that between 26% and 43% of RITA positive cases were identifiable as seroconverters through the GUMCAD surveillance data (Table 34). This was slightly higher for MSM (between 30% and 54%) and lower for heterosexuals (between 10% and 24%). Conversely only between 15% and 25% of all seroconverters identified in GUMCAD would have been identifiable using the RITA data.

Table 34 Comparison of seroconverters identified by the serological incidence assay and GUMCAD testing history data, 2009-2013

	2009	2010	2011	2012	2013	Total
All						
Number of RITA recents*	198	345	489	559	428	2019
Number (%) of RITA recents with a negative HIV test in the last year	87 (43)	118 (34)	133 (27)	147 (26)	121 (28)	606(30)
Total number with a negative HIV test in the last year	605	558	571	595	413	2742
MSM						
Number of RITA recents*	135	244	361	430	323	1493
Number (%) of RITA recents with a negative HIV test in the last year	73 (54)	97 (40)	118 (33)	128 (30)	100 (31)	516 (35)
Total number with a negative HIV test in the last year	476	431	463	506	357	2233
Heterosexuals						
Number of RITA recents*	55	89	112	105	84	445
Number (%) of RITA recents with a negative HIV test in the last year	13 (24)	19 (21)	11(10)	18 (17)	18 (21)	79(18)
Total number with a negative HIV test in the last year	117	118	99	84	48	466

*based on the AxSym avidity assay

The low level of overlap can be explained in part by the fact that the mean recency duration for the avidity assay is only approximately six months; a negative test in the last year will include a significant fraction that seroconverted more than six months ago. Secondly, is the issue of the incomplete coverage of the serological incidence testing. Although the absolute number of incident cases missed in the absence of serological incidence testing in heterosexuals would be small, these have been key, and heavily weighted in the various incidence estimates. Moving forward, efforts should be made for HIV incidence estimation models to combine all available information which is able to identify a case of recent seroconversion.

In summary, the key findings and outputs from the four analysis Chapters are:

i.) In 2012, HIV incidence in the general population was 0.06 per 1000 pys and 3.8 per 1,000 pys in MSM. In 2011 (the most recent year for which information on the size of the black African population was available) it was 0.4 per 1000pys in black African heterosexuals.

ii.) HIV incidence was 27 times higher in the sexual health clinic attending population compared to the general population. This has implications for using surveillance data to make inferences about the general population. To note is that this disparity was significantly smaller among key risk groups with incidence 4-5 times higher among sexual health clinic attending MSM compared to MSM in the general population and only 3-4 times higher among sexual health clinic attending black African heterosexuals compared to black Africans in the general population.

iii.) To expand PHE's routine annual HIV data outputs by presenting population-based HIV incidence estimates for all risk groups and geographies and, where possible, also presenting estimates by age. This will supplement the CD4-back-calculation method which currently only provides estimates for MSM. In the context of a declining epidemic, and with the aim to reach zero infections by 2030, this will enable HIV prevention resources to be targeted effectively and equitably. It is the only method currently available which is able to generate these estimates annually alongside the HIV official statistics.

9.1.2 Enhanced behavioural surveillance of MSM with recent HIV infection

To address the aim:

iii.) explore if recent HIV infection data can enable the collection of additional behavioural information facilitating the application of more conventional infectious disease control measures

In Chapter 8 I conducted the pilot for the enhanced behavioural surveillance of MSM with recent infection. Here I demonstrated that collecting behavioural data directly from patients through the clinic for surveillance purposes was feasible to an extent. However, as with any initiative of this nature, obtaining high coverage was challenging and, more often now particularly for research, monetary incentives are offered to the healthcare service providers to cover potential additional costs, which is likely to become or is in fact already the new standard. Most of the data I collected on behaviours reflected data collected elsewhere in behavioural studies which are described in section 8.2.2. The idea that this type of surveillance could capture new risk behaviour trends prompted the use of the open-ended question '*How do you think you got HIV*'. However, although this field was well completed, it did not yield good information on new behaviours as most men's comments were sparse. I believe qualitative research (206, 247, 260-262) such as interviews would have been a better approach to obtain these insights, providing the opportunity for in-depth information through prompting, and enabling a review of what questions would have been appropriate for a quantitative study, if there were to be further interest in determining the prevalence of new risk behaviour.

The notion that the enhanced surveillance initiative could further feed into improved HIV infection control was based on the potential for real-time information on where participants with incident HIV met their sexual partners. Nearly all men had met sexual partners through internet sites or mobile phone apps, and two thirds indicated they visited bars, clubs or saunas. Information on which apps had been used was well completed but information on which venues were visited, less so. Grindr was by far the most used mobile phone app. With regards to designing interventions, using mobile apps would seemingly have the furthest reach. Of note is that many bars, clubs and saunas are already linked in with outreach groups that work towards increasing awareness of HIV and in some instances offer HIV testing e.g. on certain nights of the week.[3] In addition, home testing and home sampling services are increasing.(191)

Of note was that the enhanced behavioural surveillance initiative was not able to provide or generate any information which could improve targeted prevention initiatives or in fact improve individual patient management. Partner notification is already standard of care for all people newly diagnosed with HIV, and for MSM in particular, focussing on those who are likely to have been infected in the last 4-6 months may not be particularly helpful if there was a recent history of very high partner numbers. Interestingly, the UK is the only country that feeds back the recent infection results of patients to clinicians and clinicians may discuss the results with patients if they wish. In 2012, a survey was undertaken among HIV specialist clinicians by a specialist registrar undertaking a placement in the HIV team at PHE, which explored the role of RITA in patient management and clinicians' views on the usefulness. Although the response rate to the survey was low (36%) most clinicians (80%) felt confident in interpreting the results and nearly all (93%) claimed to discuss these with patients particularly in the context of a possible seroconversion illness. Some (36%) were concerned

[3] https://spectra-london.org.uk/event/hiv-testing-free-condoms-portsea-sauna-13/2018-08-16/, https://www.mesmac.co.uk/news/base-sauna-testing-times, http://express.dean.st/sti-and-hiv-testing/

that the results could create anxiety among patients however no adverse effects were reported. In the US, the HIV incidence assay in use at the time was not approved by the Food and Drug Administration (FDA) and was therefore not to be used as a clinical, diagnostic test. Noteworthy is the FRR of the HIV incidence assays which must be taken into consideration when interpreting results at the individual level. In addition, the legal system in the US differs from that in the UK with lawsuits much more common, likely contributing to the reluctance to use this information for individual patient management.

However, whilst this type of enhanced surveillance may have less potential for infection control in terms of pinpointing to sites or venues where many new HIV infections may have been acquired, or improving patient management, there is potential for it to monitor the extent of exposure participants may have had to interventions before seroconverting. This is now of particular interest in the landscape of the combination prevention initiatives having the effect of reducing HIV infections and the wider spread use of PrEP. As mentioned in Chapter 8, based on my pilot feasibility study, PHE is now (in 2018) rolling out national enhanced surveillance of all HIV seroconversions. The new enhanced surveillance termed SHARE (Surveillance of HIV Acquired Recently: Enhanced) is being conducted in two parts; for each patient diagnosed with evidence of a recent HIV seroconversion, clinicians will be asked to return a short online notification form consisting of approximately 10 questions capturing information on the patients' HIV testing and PrEP use history. Secondly, clinicians will be asked to invite patients to complete a short questionnaire (online or on paper) on similar topics to the feasibility study, such as HIV testing and sexual behaviours and STIs in the 6 months prior to diagnosis (indicating risk), however with more focus on the knowledge, access and use of PrEP during this period. The aim will be a quantitative output accompanying the national figures on the number of new HIV diagnosis where, of the people known to have a recent seroconversion, each will be classified into one of the following:

- Seroconverter with PrEP history, possible PrEP failure: patient has a history of PrEP use since last negative HIV test, reports high adherence.
- Seroconverter with PrEP history, unlikely PrEP failure: patient has a history of PrEP use since last negative HIV test, reports insufficient adherence or having stopped using PrEP.
- Seroconverter with no PrEP history, PrEP offered but declined: patient has no history of PrEP use, was offered in the past but declined.
- Seroconverter with no PrEP history, no PrEP opportunity known: patient has no history of PrEP use and does not report ever having been offered PrEP.

These data will be able to directly feed into understanding the demand for, and need of, HIV prevention initiatives and in particular, show if there is a higher need among certain groups. It will also provide additional information regarding the circumstance of each new infection which will become increasingly crucial to reach the 'zero new infections'(258) target by 2030.

Key findings and outputs of the enhanced surveillance pilot:

- Collecting data directly from patients is resource intensive and it is difficult to obtain high coverage. Incentives for clinic staff and or patients would have likely obtained a better response. However, the questionnaire has now been revised for a different purpose and is being used to explore how each new infection may or may not relate to expose of combination prevention interventions, in particular PrEP. The new questionnaire collects data from both clinicians and patients to account for a potential low response rate from patients.
- The design of the questionnaire did not allow for any new insights to be generated with regards to new, previously unknown HIV risk practices. A qualitative research approach may have been more appropriate for collecting data for this purpose.

- Internet apps were the most popular way for men to meet sexual partners and consequently using these apps would likely have the furthest reach for HIV-related health promotion activities.
- Recent infection testing data were not able to improve individual patient management

9.2 Other uses of serological HIV incidence data

The RITA data have also been opportunistically utilised in other studies; as mentioned previously in this chapter the data were used to recruit patients to the UK Register of Seroconverters which has been the basis for a number of studies.(208, 247, 263) Another study by the VRD at PHE was determining the prevalences of transmitted HIV-1 drug resistance which was confined to MSM with recent infection.(264) Following on from this is work on

i.) the surveillance of transmitted drug resistance against integrase inhibitors,
ii.) investigation of the sources and clinical significance of minority drug resistant variants in recently infected patients, and
iii.) inferring the multiplicity of founder strains during the acute and chronic phases of HIV infection (personal communication Tamyo Mbisa, Acting Head of the Antiviral Unit, VRD).

In addition, the data have been used to select patients into clinical trials, e.g. the Short Pulse Anti-Retroviral Therapy at Seroconversion (SPARTAC) trial which assessed if a short course of ARV therapy in primary HIV infection could delay disease progression (265, 266), and for educational purposes, reviewing the extent to which primary HIV infection is unrecognised.(267) These opportunistic applications should be taken into consideration on reviewing whether the programme should be continued, as collecting these specimens as

part of routine surveillance rather than a research study may be more cost effective. In addition, it provides an ongoing supply which can be used to monitor changes over time.

9.3 Cost considerations

The major drawback of the serological incidence testing is the cost, which has in part prompted this review of the utility and value added. The set-up of the programme by my predecessors took an immense amount of effort to convince clinicians and laboratory staff of the merit of RITA, and two years of newsletters, roadshows and follow up resulted in 50% coverage at which it stagnated. However, no further efforts to increase the coverage were made due to budget constraints. A survey among HIV specialist clinicians in 2012 showed most (92%) felt confident in discussing results with patients and considered recent infection testing standard of care (82%) although the survey response rate was only 36%.(215) Noteworthy is that, during the course of this thesis, the US ceased its programme of serological HIV incidence testing as it was not considered cost-effective.(268) Costs to consider include the set up costs, which in some instances may involve the purchasing of expensive laboratory equipment if the platform for testing is not already present. The Abbott AxSYM HIV 1/2/g0 EIA Avidity is the modified use of commercial HIV diagnostic equipment which was in use at PHE in 2009. PHE now uses the SEDIA HIV-1 Lag Avidity EIA, which was commercialised in cooperation with CDC. Aside from the contents of the testing kit, other equipment necessary (as outlined in the kit insert) include a spectrophotometer, a micro well plate washer, incubators, a vortex mixer, a reagent reservoir to name of few. Many of these items may be standard in a national infectious disease laboratory but their use must none-the-less be considered in the overall cost. The serological incidence testing also entails the collecting, posting, processing and storage of serum specimens. Overall, not including the start-up expenses, an individual avidity test was costed at approximately at £20 per test (personal communication Gary Murphy, Joint Scientific Lead, Clinical Services, PHE), which included the laboratory staff time and the internal and external quality control

procedures. This cost could be affected by the batch sizes, required turnaround time, assay failure rate, and shipping expenses. With 4,561 tests undertaken in 2012, this would have incurred a cost of £91,220. Over the five-year study period, considering a total of 18,535 tests undertaken, this incurred would have an estimated cost of £370,700. Considering this is additional to the cost of my time/salary and the input of other experts involved in analysing the data (a commitment required for the application of any HIV incidence model) this programme may be viewed as expensive compared to other methods.

9.4 Strengths and weaknesses

Strengths

Overall strengths of my research are that I explored a variety of methods to examine the utility of the serological incidence data. The caveats around each specific analysis are outlined within the results Chapters. The estimates for HIV incidence were the most significant contribution to the field of UK HIV epidemiology considering the few other studies available (95, 96, 256). A strong point of the thesis was to have been able to contemporaneously put findings into the public domain with other countries that had similar epidemics allowing comparisons.(133, 199, 224) Data on the proportions of recent infection diagnosed are routinely reported in PHE's annual HIV publication. The work I undertook in Chapters 6 and 7 to covert these data into incidence estimates now supersedes this and the statistical programme I have set up can easily be re-run to routinely produce updates on these findings.

Strengths of using the serological data for incidence estimation are that i.) only the data collected through routine surveillance activities are needed and only data for the years of interest are required (versus data for the total epidemic which is need in some back calculation models), ii.) HIV incidence estimates can be generated for all transmission risk groups and other sub-populations, iii.) HIV incidence estimates using these data are more

accurate for recent years compared to other models based on the width of the variance around the estimates iv.) a higher level of granularity is achievable enabling HIV incidence estimates by an increased number of demographic and geographic breakdowns which will become increasingly important as the epidemic declines and v.) the data can be used for behavioural and other research studies relating to primary infection as incident infection is identified at the time of diagnosis.

Whilst in general, the use of routinely collected data to answer research questions has numerous limitations (e.g. information is restricted to what is routinely collected, missing data, and the type of population sampled) it is a relatively quick and cheap approach compared to primary data collection. National population-based surveys are likely to achieve estimates which are closer to the true values, however as explained in the introduction, these studies are expensive and resource intensive particularly in low incidence settings.

Weaknesses

Weaknesses of the thesis are that it was not able to account for all of the changes which have occurred in this fast-moving field. Firstly, the assay used in this study has been discontinued and is its successor has yet not been fully evaluated in the UK context. The newer assay has slightly different attributes (e.g. lower false recency rate and a shorter mean duration of recency) however these have been more rigorously assessed by the CEPHIA group. With the decline in new diagnoses in more recent years, it will be of interest to examine whether the estimates from the new serological incidence data reflect the supposed changes in incidence and if the estimates from the new and old assay are in fact comparable.

General weaknesses of the serological incidence data are that i.) appropriate use of the assay relies on good characterisation of its performance; research is still ongoing examining how key parameters such as the mean duration of recency may vary in subpopulations(268)

ii.) the assay had a misclassification rate; minimising this relies on good treatment and or CD4 and viral load data iii.) the HIV incidence estimates require accurate and complete information on testing history data and iv.) a significant amount of (both labour and financial) resource is required.

Secondly, and related to the above point of a fast-moving field, is the development of other HIV incidence estimation models. With the availability of more estimates which seem plausible using cheaper approaches, the value of the serological incidence test data may decrease. Consequently, any conclusions on the utility of these data are extremely time sensitive.

Lastly, regarding exploring the use of these assays to improve or facilitate the application of more traditional infectious disease control measures, as mentioned in section 9.1.2, qualitative research approaches may have been more suitable for the identification of new risk behaviours. Although, this is not a feasible model for routine surveillance. Overall, the pilot was a good basis for the design of other enhanced surveillance initiatives however the value of the individual data components, e.g. where men met their partners to identify clusters, would have benefitted from a greater sample size which would in turn have required more time and resource.

9.5 Recommendations and further research

This appraisal of the public health utility of tests for recent infection with HIV in the UK setting has shown that the data are informative in describing the state and direction of the epidemic. Given that there are very few estimates for HIV incidence in the UK general population, the serological HIV incidence testing programme may be considered to have an important role in continuing to provide insights. With the newly widespread availability of

PrEP, having robust HIV incidence estimates will be crucial for understanding the impact both at the national and local levels.

The techniques for handling missing data enable the production of robust estimates despite only half of new HIV diagnoses having undergone recent infection testing. There is a cost benefit consideration regarding the scale up of testing; currently all sexual health clinics and laboratories are offered the service of testing specimens for recent infection. The cost of testing is absorbed by PHE aside from the posting of specimens to the VRD at PHE. Obtaining complete coverage could imply more than a doubling of the cost as active follow up is likely to be required needing additional resources. Another approach may be developing a framework for sentinel surveillance; however, during an era of steep declines in the number of new diagnoses and infections, and thus considerable change over time, specifying sentinel sites which would yield representative data may be particularly challenging and also vary significantly over short space of time. In the context of the 'getting to zero' 2030 target (258), and determining if incidence is and remains less than 1 per 1000 in the key populations, there may be a need to focus on those perhaps less likely to be linked into the bigger clinics which are often based in the larger cities with high numbers of attendances and who may consequently have less exposure to preventions initiatives.

Finally, as described in more detail earlier, there may be an opportunity for improving the information on seroconverters which forms the basis of the model applied in Chapter 7 by combining information on testing history and RITA in such a way that recent infections can be defined by either one of these. This would require an adaptation to the CDC's model. As the recent cases were defined by serological incidence tests and weighted by the testing history, work would have to be undertaken on how to weight cases defined only by the testing history data.

In summary, my recommendations are:

- In an era of a steep decline in new HIV diagnoses and likely HIV infections, to continue the serological incidence testing until at least one other method for determining incidence timely and at regular intervals is available in order to corroborate results.
- Not to publish the proportion of recent HIV infection diagnosed due to the difficulties in interpreting these data. The data do not reflect incidence, only a subset of people who seroconverted shortly before their HIV diagnostic test.
- To routinely publish the HIV incidence estimates based on the serological incidence test data alongside estimates of the back-calculation model and to present for the first time, annual figures on the number of new infections for non MSM groups, by region. Local level estimates may guide local authorities on how to allocate funding for HIV prevention services.
- Not to spend additional resources on further scaling up of serological incidence testing to increase the coverage of the programme; the application of techniques for handling missing data are sufficient to obtain robust estimates. However, this may need to be reviewed if the proportion of missing data increases or the number of incident cases in some subpopulations is so low that they do not allow for further stratification.
- Work on adapting Karon et al.'s incidence estimation model to allow for incorporation of testing history data as the definition of a recent HIV case where serological test data are missing to reduce the amount of data needing to be imputed.

9.6 Concluding statement

In summary, I conclude that the serological HIV incidence data applied to case-based surveillance in the UK setting provides considerable public health utility, enabling the only

timely estimates of HIV incidence for a range of subpopulations. The granularity in new infections will become increasingly valuable in the context of a declining epidemic. In addition, it has the potential to inform a number of current HIV prevention policies, such as the number of people that should have access to PrEP and monitoring the impact of other combination prevention interventions in real time.

The data show that in the period of study, HIV incidence was largely stable for all risk groups. Repeating the analyses for the most recent years will shed light on whether the recent reduction in new diagnoses is a reflection of a reduction in transmission, and in particular if this is across all risk groups, ages and regions.

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Appendix 1. Questionnaire for enhanced surveillance in MSM with recent HIV infection

18. How many partners with whom you had sex with **without a condom** in the **6 months BEFORE** your diagnosis are contactable? _____

*If **none**, please go to Question 23.*

19. How would you be able to contact them? (Please tick all that apply)

Text ☐1 Phone ☐2 Through an app or website ☐3 Email ☐4

Social networking site (e.g. facebook) ☐5 Back at the place I met them (e.g. bar/club/sauna) ☐6

Other (please specify) _____

20. How many partners with whom you had sex with before your diagnosis have you *already* told of your status? _____

21. In total, how many of these sex partners do you *plan* to tell? _____

22. Which do you think would be the best method to contact your sexual partners about your status? (Please tick all that apply)

I would contact them myself	☐1
Through a health advisor/clinic staff	☐2
Anonymously online/through an app	☐3
I wouldn't contact them	☐4
Other, please specify _____	

23. How do you think you acquired HIV? (For example, when, with whom and how.) Please describe the situation.

Thank you for completing this questionnaire.

Please fold the questionnaire back up and then place it inside the envelope.

PLEASE SEAL THE ENVELOPE.

Public Health England

CONFIDENTIAL

Investigation into gay and bisexual men with recently acquired HIV infection

Date of completion

This questionnaire is completely anonymous: we do not wish to know your name or any other form of identification.

The information you provide will help us better understand HIV infection and how to prevent it.

Please ☑ the box or write in your answer. Please try to answer all the questions.

1. Would you describe yourself as: Gay/homosexual ☐1 Bisexual ☐2 Transsexual ☐3 Straight/heterosexual ☐4 Other (please specify) _____

2. What is the first half your postcode? (e.g. N4)_____

3. How old are you now? _____

4. What is your country of birth? _____

5. Are you: White ☐1 Black African ☐2 Black Caribbean ☐3 Black Other ☐4 South East Asian ☐5 Asian (Indian/Pakistani/Bengali) ☐6 Mixed/Other ☐7 (please specify) _____

6. On this occasion why did you decide to get an HIV test? (Please tick all that apply)

Found out regular partner was positive	☐1
Found out casual partner was positive	☐2
I was told (notified) by clinic or partner that I had been at risk	☐3
I felt unwell (e.g. rash, fever, feeling unwell)	☐5
I test regularly	☐6
To check my status after a recent risk	☐7
Offered by clinic as part of sexual health check	☐8
Partner requested test/agreed with partner to be tested	☐9
Split condom	☐10
Advised by GP/other doctor	☐11
Any other reason (please specify) _____	

7. **BEFORE** you were diagnosed with HIV had you ever had a ***negative HIV test***?

No ☐2 Yes ☐1 →

If no, please go to Question 8.

If yes: Where was your most recent test?

Name of clinic/hospital (or home if home test)_____

Date (mm/yyyy) __ __/__ __ __ __

How many tests did you have in the year **BEFORE** you were diagnosed? _____

Please turn over

8. Have you ever taken **PEP** (post-exposure prophylaxis drugs taken **AFTER** sex to reduce the risk of HIV infection) or **PrEP** (pre-exposure prophylaxis drugs taken **BEFORE** sex to reduce the risk of HIV infection).

How many times **PEP** _____

How many times **PrEP** _____ →

*If yes to **PrEP**, where did you get the tablets? (i.e clinic or friend)*
_____

9. In the **year BEFORE** you were diagnosed, had you had a sexually transmitted infection (STI)?

No ☐2 Yes ☐1 →

If yes, which of the following did you have?
Gonorrhoea ☐1 Chlamydia ☐2 Syphilis ☐3 LGV ☐4
Other (please specify) _____

↓ *If **no**, please go to Question 10.*

10. Have you previously been diagnosed with Hepatitis C?

No ☐2 Yes ☐1 →

If yes, when were you first diagnosed?
Date (mm/yyyy) __ __ / __ __ __ __

↓ *If **no**, please go to Question 11.*

11. In the **6 months BEFORE** your HIV diagnosis, how many men did you have sex with (anal or oral)?
Number _____

12. In the **6 months BEFORE** your HIV diagnosis, how many men did you have anal sex with **without a condom**? Number_____

13. In the **6 months BEFORE** your HIV diagnosis, with how many men did you have receptive (bottom, passive) anal sex **without a condom**? (Please estimate if not sure)

Number _____ →

Of these, how many did you know were:
HIV positive? _____ HIV positive and on treatment? _____
HIV negative _____ I didn't know their status _____

14. In the **6 months BEFORE** your HIV diagnosis, with how many men did you have insertive (top, active) anal sex **without a condom**? (Please estimate if not sure)

Number _____ →

Of these, how many did you know were:
HIV positive? _____ HIV positive and on treatment? _____
HIV negative _____ I didn't know their status _____

15. Did you meet any of the men you had sex with in the **6 months BEFORE** your HIV diagnosis through any of the following? (Please tick all that apply)

☐1 Bars/clubs/saunas
If yes, please specify which ones _____

☐1 Internet/mobile phone apps
If yes, please specify which sites/apps (e.g., Squirt, BBRT, GrindR) _____

☐1 Backroom
☐1 Sex party in the UK
☐1 Sex party abroad
☐1 Cruising ground
☐1 Escort service
☐1 Sex abroad
☐1 Other (please specify) _____

16. In the **6 months BEFORE** your diagnosis, did you do any of the following?

Fisting ☐1 Rimming ☐2 Group sex ☐3 Sharing of sex toys ☐4 Water sports ☐5 Scat play ☐6
None of these ☐7
Other (please provide details) _____
_____

17. In the **6 months BEFORE** your diagnosis, did you ever take any recreational drugs **during or before sex**?

Yes ☐1 No ☐2 → *If no, please go to Question 18.*

↓

If yes: In the **6 months BEFORE** your diagnosis, which of the following did you take during or before sex? (*Tick **all** that apply*)

Amphetamine (speed) ☐1 Ecstasy (MDMA) ☐2 G,GHB,GBL ☐3 Mephedrone (m-cat) ☐4
Cannabis/marijuana ☐5 Cocaine (coke) ☐6 Amyl Nitrates (poppers) ☐7 Ketamine (K) ☐8
Crystal meth (ice, glass) ☐9 Crack (rock, stones) ☐10 Viagra/Kamagra/Cialis ☐11

Other non-prescribed (please specify) _____

Did you inject any of these? Yes ☐1 No ☐2

If yes, which? _____

Please turn over

Appendix 2: Information materials for enhanced surveillance in MSM with incident HIV infection

Public Health England

Dear Colleagues,

Re: Enhanced surveillance of MSM with evidence of incident HIV infection

The public health monitoring of incident HIV-1 infection has been an integral part of the routine surveillance of HIV diagnoses in the UK since 2008. With the ability to detect and distinguish recently acquired from long-standing HIV infections, conventional outbreak investigation approaches have become appropriate as a measure to control HIV.

In 2012, there was a 14% increase in new HIV diagnoses in London (PHE surveillance data). HIV testing data indicate this rise is not entirely contributable to changes in HIV testing or reporting. Anecdotal evidence (Lancet 2013) supports that more than expected cases of HIV are currently being diagnosed in the London region, reflecting changes in transmission.

Public Health England intends to roll out enhanced surveillance of individuals with recently acquired HIV infection. In association with 56 Dean Street, we will collate information on incidents of HIV exposure to inform prevention and control initiatives. This will be undertaken in the clinic setting, is a voluntary initiative and recently infected MSM will be invited to complete a short anonymous questionnaire on recent risk behaviours and their contacts.

For information, under the Statutory Instrument 1438 (2002), in the Health Service (Control of Patient Information) Regulations 2002, confidential patient information may be processed with a view to monitoring and managing outbreaks of communicable disease, incidents of exposure to communicable disease and recognising trends in diseases and risks. The processing of confidential patient information for these purposes may be undertaken by Public Health England or other authority in communicable disease surveillance.

Although the health advisers at Dean Street will be leading on this with identifying those MSM that fulfil the inclusion criteria, we welcome your assistance with this enhanced surveillance and believe the information collected will provide invaluable insights into these incident HIV infections.

If you have any questions or would like further clarification, then please contact either myself, Dr Alan McOwan or members of the PHE HIV AIDS reporting team (please see details below).

Yours sincerely

Dr Valerie Delpech
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Public Health England
E valerie.delpech@phe.gov.uk

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HIV and AIDS Reporting Section
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Public Health England

Patient information leaflet

Investigation into gay and bisexual men with recently acquired HIV infection

This is an information leaflet for patients considering taking part in the anonymous questionnaire survey of risk factors for recent HIV infection in gay and bisexual men.

Thank you for considering whether you would like to be part of an important initiative that seeks to understand current behavioural factors and circumstances around why gay and bisexual men become infected with HIV. Chelsea and Westminster Hospital is collaborating with Public Health England in a confidential, anonymous survey to better understand this and we hope you may be able to assist.

From your recent HIV test we know you are now HIV positive. We also know you probably acquired your HIV infection in the last six months. We know this either because of a previous negative test or from the result of a blood test, routinely done with the HIV test known as the Avidity or RITA test. This blood test specifically looks to see how long a person may have been infected with HIV; in your case it showed you were recently infected and most likely within the last six months.

We are inviting all gay and bisexual men who likely acquired their HIV infection within the last six months to complete a brief anonymous questionnaire that should take no longer than 10 minutes. We do not collect any information that can identify you, and nobody at the clinic will see your completed questionnaire. The questionnaire is to be completed while you are at the clinic and returned to the clinic staff in a sealed envelope.

With your help we will gain a much better understanding of the current risks and behaviours (sexual and lifestyle) that contribute to men becoming infected with HIV. We are keen also to better understand the motivations for testing and other circumstantial factors that may influence behaviours. We would also value your views on informing and contacting partners. The information you provide will assist us and those involved with HIV prevention efforts and we hope you will take part.

Please remember, this survey is completely anonymous (and voluntary) and we will not be able to identify you. Please also be reassured that your care will not be affected if you choose not to take part. If you do decide to participate, you do not have to answer any questions you prefer not to.

Please let the clinic staff know if you would like to complete the questionnaire, or alternatively, if you have further questions you would like answered before deciding. When you complete the questionnaire, please put it in the envelope provided, seal it, and return it to clinic staff /reception.

With very best wishes,

Dr XXX XXXXXX and the HIV/AIDs Reporting Team at Public Health England

Public Health England

PHE RITA SURVEY: Information sheet for clinic staff

Investigation into MSM with recently acquired HIV infection

This one year joint investigation between Guy's and St Thomas's and Public Health England will commence from January 2014 to December 2014

Aim of the investigation:

- To greater understand factors and circumstances associated with recently acquired HIV infections in MSM and so assist with HIV prevention initiatives and interventions

Who is eligible?

- All MSM newly diagnosed with HIV that have evidence of recent infection, including:
  - A RITA test indicating recent HIV infection, OR/AND
  - A negative HIV test within the last 6 months, OR/AND
  - A p24 antigen positive result and HIV antibody negative

What to do:

- All MSM that fulfil the above criteria, please invite them to take part in this confidential, anonymous investigation
- Discuss the investigation with them, reassure them about confidentiality, and hand them the information leaflet
- Once they have read the information sheet, ask if they would be willing to complete the confidential questionnaire (should take no longer than 10 minutes)
- If they agree, give them the questionnaire (and pen) and an envelope. Tell them once they have finished, to place the completed questionnaire in the envelope, seal it and return it to the reception staff.
- IMPORTANT – you need to add in the notes that the patient has completed the RITA questionnaire. If the patient asks to complete it at the following visit, this needs to be documented in notes and the questionnaire given at next visit.
- IMPORTANT - If the patient refuses, put the empty questionnaire in the envelope, seal it, and write 'REFUSED' on the envelope and give to reception. Document refusal in the patient notes. [This is so that the patient is not asked twice and we can estimate response rates].

Reassure them that the questionnaire is completely anonymous and no clinic numbers or patient identifiers are collected

Dr XXXX XXXXX will collect the sealed envelopes. A member of the HIV & AIDS Reporting Team at Public Health England will arrange to collect these at regular intervals.

If you have any questions, please ask Dr XXXX XXXX or Adamma Aghaizu (at PHE) on 0208 327 6838 or Adamma.Aghaizu@phe.gov.uk

Thank you for your help with this investigation

Appendix 3. Justification for research ethics exemption for the pilot of enhanced surveillance of MSM with incident infection

Public Health England

HIV/STI Department
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Valerie Delpech
Consultant Epidemiologist/Head of HIV and AIDS Reporting Section
HIV/STI Department
Public Health England
61 Colindale Avenue
London
NW9 5EQ

17 October 2013

Dear Valerie,

Re: Survey of Individuals with Recently Acquired HIV: Pilot Project – justification for research ethics exemption

Thank you for the letter seeking guidance from me, in my capacity as the Associate Caldicott Guardian, on the above mentioned pilot study you are proposing to undertake.

On reviewing the information you have provided to me and the discussions we had, this pilot seeks to develop a long term surveillance system to monitor recently acquired HIV and to established an enhanced surveillance system for new HIV infections associated with injecting club drug use among men who have sex with men. The data you will be using is derived from information already collected in GUM clinics. You will be collecting anonymous data that will be analysed alongside other routinely collected HIV data.

Public Health England (PHE), under its powers already has approval to use anonymous HIV data collected from GUM clinics. This proposed surveillance system will be conducted in the same way as all the other surveillance systems currently maintained by PHE Colindale, in the HIV/STI Department.

Since this is surveillance, it is covered under existing permissions to process information for surveillance, where patient identifiable information is not collected. You do not need to apply for Section 251 of the NHS Act 2006 specific approval.

Kind Regards,

[redacted]

Fortune Ncube
Consultant Epidemiologist/Associate Caldicott Guardian

SURVEILLANCE AND OUTBREAK REPORTS

Recent infection testing algorithm (RITA) applied to new HIV diagnoses in England, Wales and Northern Ireland, 2009 to 2011

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In 2009, Public Health England (PHE) introduced the routine application of a recent infection testing algorithm (RITA) to new HIV diagnoses, where a positive RITA result indicates likely acquisition of infection in the previous six months. Laboratories submit serum specimens to PHE for testing using the HIV 1/2gO AxSYM assay modified for the determination of HIV antibody avidity. Results are classified according to avidity index and data on CD4 count, antiretroviral treatment and the presence of an AIDS-defining illness. Between 2009 and 2011, 38.4% (6,966/18,134) of new HIV diagnoses in England, Wales and Northern Ireland were tested. Demographic characteristics of those tested were similar to all persons with diagnosed HIV. Overall, recent infection was 14.7% (1,022/6,966) and higher among men who have sex with men (MSM) (22.3%, 720/3,223) compared with heterosexual men and women (7.8%, 247/3,164). Higher proportions were among persons aged 15–24 years compared with those ≥50 years (MSM 31.2% (139/445) vs 13.6% (42/308); heterosexual men and women 17.3% (43/249) vs 6.2% (31/501)). Among heterosexual men and women, black Africans were least likely to have recent infection compared with whites (4.8%, 90/1,892 vs 13.3%, 97/728; adjusted odds ratio: 0.6; 95% CI: 0.4–0.9). Our results indicate evidence of ongoing HIV transmission during the study period, particularly among MSM.

Introduction

With over 6,000 new human immunodeficiency virus (HIV) diagnoses in 2011 in the United Kingdom (UK) [1] and a steady increase in the number and proportion of new diagnoses among men who have sex with men (MSM), as well as an increase among UK-acquired infections among heterosexual men and women [2], controlling the HIV epidemic continues to be a public health priority. To ensure public health interventions are implemented efficiently and effectively, an accurate, regular assessment of the epidemic is needed.

HIV incidence, the rate of new infections, is considered to be the most valuable measure for describing the current dynamics of the epidemic. Determining the rate of new infections remains challenging as there is a prolonged asymptomatic period and therefore, in the absence of screening, diagnosis can be delayed for several years. One approach is to use positivity for biomarkers to distinguish recently acquired from long-standing HIV infections from a single sample [3]. Some institutions have incorporated biomarker-based assays as part of the routine surveillance of HIV, such as the Institut de Veille Sanitaire in France [4], and the Centers for Disease Control and Prevention in the United States [5,6]. A technical guide on how to implement testing for recent infection has been developed by the European Centre for Disease Prevention and Control [7].

In 1998, Public Health England (PHE), formerly the Health Protection Agency, introduced the use of a biomarker for the estimation of recent HIV infection among MSM attending sentinel sexual health clinics. This technology has since been applied to distinct HIV incidence research studies and sentinel surveillance sites [8,9]. In 2009, a biomarker testing programme was rolled out in England, Wales and Northern Ireland, offering testing to individuals newly diagnosed with HIV [10]. In the UK, the epidemic is concentrated in two key risk populations: (i) MSM who are mostly white and acquired HIV in the UK; and (ii) heterosexual men and women of black African ethnicity, of whom a large proportion acquired HIV abroad.

In this article, we review the implementation of the first three years of the programme and examine factors

associated with biomarker test results indicative of recent infection among persons newly diagnosed with HIV infection.

Methods

Surveillance of recently acquired HIV infections

PHE collates national data on all new diagnoses of HIV, AIDS and deaths among people living with HIV along with demographic and epidemiological information for individuals aged over 15 years. Since 2009, laboratories in England, Wales and Northern Ireland have been sending specimens from persons newly diagnosed with HIV to the Virus Reference Department at PHE Colindale for testing using a recent infection testing algorithm (RITA) to identify HIV infections archetypal of a recent infection. Results are linked to the new HIV diagnoses database using pseudo-anonymised data on the diagnosis site, soundex (scrambled surname code) [11], date of birth and sex. Samples taken from the patient more than four months after the initial diagnosis are excluded from analyses due to the reduced likelihood of these being a recent infection.

The RITA classifies new diagnoses with an avidity index <80% as positive (a likely recent infection) unless other available clinical information, which completes the algorithm, indicates a likely long-standing infection, i.e. a CD_4 count <200 cells/mm^3 at diagnosis, a report of an AIDS-defining illness within a year of diagnosis or history of antiretroviral treatment. A RITA-positive result is indicative of likely acquisition of infection around six months before diagnosis. In this paper, we refer to RITA-positive diagnoses as 'recent infections'. The avidity assay results are returned to the clinician via local laboratories; at patient level, clinicians interpret the avidity results alongside other test results and in context of information in case notes.

Laboratory testing

Testing is carried out using the AxSYM assay HIV 1/2 gO (Abbott, United States) modified to determine antibody avidity, as described elsewhere [12]. This assay indirectly measures the HIV antibody–antigen bond strength or 'avidity', which is typically weaker during the initial stages of the infection [13]. Test results are reported as an index, with 80% used as a positive cut-off value; results between 75% and 85% are retested and the mean of the two results is used.

Statistical analysis

Data management and analyses were performed using Microsoft Access 2007 and STATA 12.0 (Stata Statistical Software: Release 12, United States). To examine characteristics of individuals with recent infection, we stratified by exposure group (MSM, heterosexual men and women and other) and performed single- and multivariable analyses using logistic regression including any variables in the final model where a hypothesis test on the regression parameters resulted in $p<0.2$.

Results

Testing coverage and representativeness

Between 2009 and 2011, there were a total of 18,134 new HIV diagnoses in England, Wales and Northern Ireland. Over this period, 10,088 samples were received for avidity testing, of which 6,966 (69%) were linked to a new diagnosis report and taken within four months of the diagnosis date. Avidity testing coverage was therefore 38% for the new 18,134 diagnoses over the three-year period as a whole, increasing from 24% (1,479/6,234), from 41 laboratories, in 2009 to 52% (3,069/5,894), from 83 laboratories, in 2011. Coverage was broadly similar across subpopulations apart from slightly more testing among individuals from London and individuals of black Caribbean and other black ethnicity, and less testing among people who inject drugs (PWID); however, numbers were small among PWID (Table 1). The mean age of individuals tested for recent infection was 35.6 years (standard deviation (SD): 10.5) for MSM, 36.6 years (SD: 10.5) for heterosexual women and 41.3 years (SD: 10.5) for heterosexual men, similar to all individuals newly diagnosed in these risk groups: 36.2 years (SD: 10.7) among MSM, 36.4 years (SD: 10.1) among heterosexual women and 41.2 years (SD: 10.9) among heterosexual men.

Recent infections among new HIV diagnoses

After reclassifying individuals whose samples had an avidity score <80% and a CD_4 count <200 cells/mm^3 (n=61), diagnosis of an AIDS-defining illness (n=5) or antiretroviral treatment before or at the time the sample was taken (for example, pre- or post-exposure prophylaxis) (n=44) as having long-standing infections, the overall proportion of recent infection was 14.7% (1,022/6,966) (Figure 1). The highest proportion of recent infection was among MSM, 22.3% (720/3,223) compared with 7.8% (247/3,164) among heterosexual men and women, 5.6% (6/108) among PWID and 10.4% (49/471) among 'other'. The proportion was slightly higher among heterosexual women (8.1%, 153/1,892) compared with heterosexual men (7.4%, 94/1,272) and the proportions were similar across the categories for all three years (data not shown).

Among MSM, higher proportions of recent infections were observed among younger individuals, with the highest among those aged 15–24 years compared with those aged 50 years and over (31.2%, 139/445 vs 13.6%, 42/308) (Table 2). Among MSM, the proportions of recent infections were similar across ethnicities, apart from among black African MSM where it was lower (13.9% (10/72) compared with 22.3% (575/2,584) among those who were white. The proportions of recent infections were similar among MSM born in the UK and abroad; however, it was slightly lower among MSM reported as having acquired their infection abroad than among those reported as having acquired their infection in the UK (17.4%, 179/1,027 vs 24.6%, 541/2,196). Multivariable analyses showed younger age (15–24

Table 1

Proportion of new HIV diagnoses tested for recent infection in England, Wales and Northern Ireland, 2009–2011

Characteristic	% coverage (n tested/N diagnosed)		
	2009	2010	2011
Total	**23.7 (1,479/6,234)**	**40.3 (2,418/6,006)**	**52.0 (3,069/5,894)**
Transmission route			
Men who have sex with men	26.3 (656/2,496)	41.6 (1,063/2,558)	57.5 (1,504/2,617)
Heterosexual men	21.8 (272/1,248)	38.3 (447/1,166)	48.1 (553/1,149)
Heterosexual women	23.1 (434/1,878)	41.2 (692/1,678)	51.7 (766/1,481)
People who inject drugs	15.2 (20/132)	35.9 (46/128)	36.8 (42/114)
Other	20.2 (97/480)	35.7 (170/476)	38.3 (204/533)
Age group in years			
15–24	24.7 (163/661)	40.9 (259/633)	56.4 (345/612)
25–34	23.8 (502/2,106)	40.6 (797/1,964)	54.7 (1,070/1,956)
35–49	24.0 (638/2,660)	39.8 (1,033/2,594)	50.3 (1,258/2,499)
≥50	21.8 (176/807)	40.4 (329/815)	47.9 (396/827)
Ethnicity			
White	22.5 (693/3,076)	39.3 (1,148/2,917)	53.9 (1,670/3,100)
Black African	23.1 (480/2,082)	40.5 (747/1,845)	49.8 (826/1,659)
Black Caribbean	31.6 (75/237)	52.0 (102/196)	59.6 (99/166)
Black other	31.3 (40/128)	50.0 (64/128)	64.2 (61/95)
Indian/Pakistani/Bangladeshi	26.2 (28/107)	34.1 (46/135)	45.6 (52/114)
Other	27.0 (163/604)	39.6 (311/785)	47.5 (361/760)
Country of birth			
United Kingdom	20.7 (460/2,218)	42.1 (879/2,087)	56.3 (1,128/2,004)
Abroad	25.4 (1,019/4,016)	39.4 (1,545/3,919)	49.9 (1,941/3,890)
Probable country of infection			
United Kingdom	27.5 (654/2,378)	44.5 (1,073/2,411)	59.4 (1,425/2,397)
Abroad	21.4 (825/3,856)	37.4 (1,345/3,595)	47.0 (1,644/3,497)
Region of diagnosis			
London	33.5 (937/2,801)	44.8 (1,217/2,714)	59.8 (1,559/2,607)

HIV: human immunodeficiency virus.

years) (adjusted odds ratio (AOR): 1.8; 95% CI: 1.2–2.8 and 25–34 years AOR: 1.6; 95% CI: 1.1–2.3) and the UK as the probable country of infection (AOR: 1.5; 95% CI: 1.2–1.8) were associated with a likely recent infection.

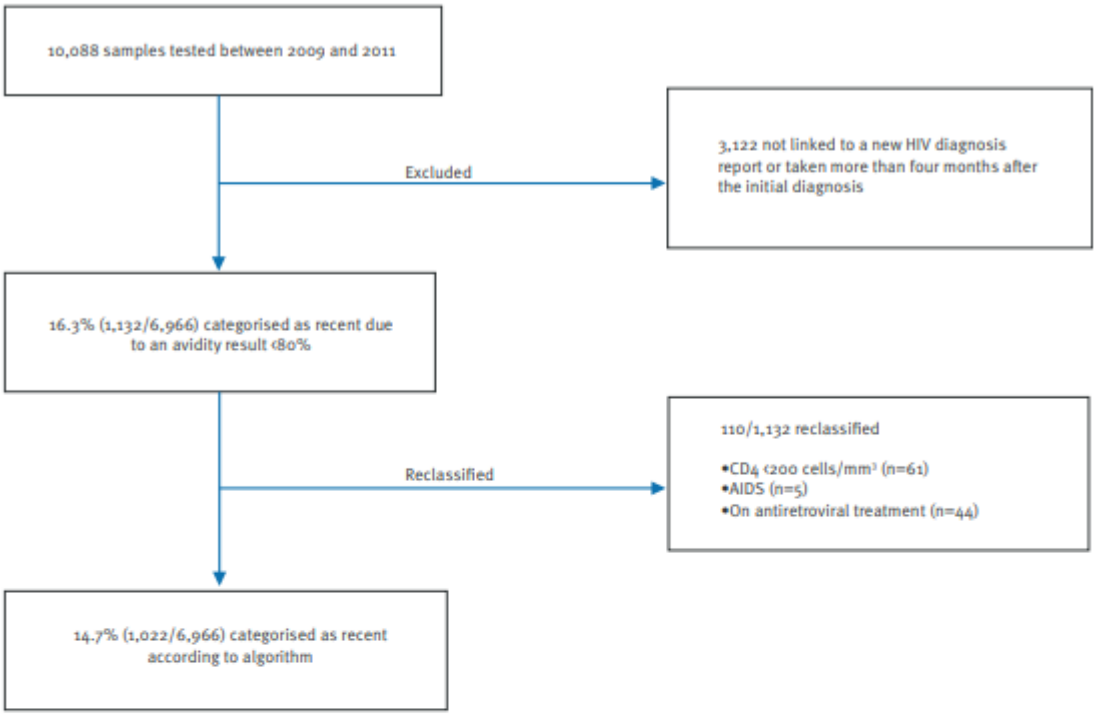
Among heterosexual men and women, the highest proportions of recent infection were among 15–24 year-old women (19.5%, 38/195) and 25–34 year-old men (6.4%, 15/234). Lower proportions were observed among persons born abroad (6.4%, 163/2,554 vs 13.8%, 84/610) and those reported to have acquired their infection abroad compared with in the UK (5.5%, 126/2,302 vs 14.0%, 121/862). Of the four heterosexual men and women of Chinese ethnicity tested for recent infection, none were recently infected and only one among the Indian/Pakistani/Bangladeshi group (n=46), but it should be noted that the numbers were small. Black African heterosexual men and women had a considerably lower proportion of recent infections (4.8%, 90/1,892) compared with those who were white (13.3%, 97/728); individuals in the 'black other' group had the highest proportion (14.8%, 12/81). Multivariable analyses showed ethnicity and country of infection to be associated with a recent infection: black Africans were less likely (AOR: 0.6; 95% CI: 0.4–0.9), whereas those of 'black other' ethnicity (AOR: 2.4; 95% CI: 1.1–5.3) and those with the UK as the probable country of infection (AOR: 1.7; 95% CI: 1.3–2.4) were the most likely to be recently infected.

Relationship between CD4 count and recent infection status

There was a strong association and a significant positive trend between CD4 counts >200 cells/mm³ and recent infection classifications. Among MSM, only 11.4% (68/595) of individuals with a CD4 count between

FIGURE

Flowchart of samples included in analyses and categorised according to the recent infection testing algorithm (RITA), England, Wales and Northern Ireland, 2009–2011



AIDS: acquired immunodeficiency syndrome; HIV: human immunodeficiency virus.

>200 and ≤350 cells/mm³ (≤350 cells/mm³ is the definition of a late diagnosis, at which point antiretroviral treatment should have started [14]), were classified as likely to have acquired their infection recently compared with 43.5% (37/85) with a CD4 count >1,000 cells/mm³. Among heterosexual men and women, this was slightly lower, with the proportion of recent infection 5.8% (38/660) among those with a CD4 count between >200 and ≤350 cells/mm³ and 31.9% (23/72) among those with a CD4 count >1,000 cells/mm³. A recent infection diagnosis was more likely if the individual had a CD4 count >1,000 cells/mm³, compared with those with a CD4 count between >200 and ≤350 cell/mm³ (AOR for MSM: 6.0, 95% CI: 3.7–9.9; AOR for heterosexual men and women: 7.6, 95% CI: 4.2–13.7).

Discussion

This study, covering the first three years of the implementation of a RITA to national surveillance of HIV diagnoses, indicates a high level of ongoing transmission among key populations in England, Wales and Northern Ireland during the study period. Our findings indicate that MSM remain the group at greatest risk of HIV infection, with one in five men diagnosed likely to have acquired their infection recently. As may be expected, younger age, high CD4 count and the UK being the probable country of infection were associated with likely recent acquisition of infection. Nevertheless, a substantial number of recent infections were seen also among MSM aged 50 years and over. Of note, there were no substantial differences by ethnicity or country of birth, indicating high levels of transmission regardless of these characteristics.

Among heterosexual men and women, the proportions of recent infection were lower than in MSM, particularly among those born abroad. Younger age, high CD4 count and the UK being the most probable country of infection were also associated with a likely recent infection in this group. There was considerable variation by ethnicity, with black Africans less than half as likely to have recently acquired infection at the time of diagnosis compared with those who were white. Interestingly, the 'black other' group, representing possibly those

Table 2

Characteristics of persons in England, Wales and Northern Ireland newly diagnosed with HIV and classified as having recently acquired HIV, 2009–2011

Characteristic	% tested of all new diagnoses (n/N)[a]	Men who have sex with men		Heterosexual men and women		Other	
		% recent (n/N)[b]	Adjusted odds ratio (95% CI)	% recent (n/N)[b]	Adjusted odds ratio (95% CI)	% recent (n/N)[b]	Adjusted odds ratio (95% CI)
Total	**38.4 (6,966/18,134)**	**22.3 (720/3,223)**	–	**7.8 (247/3,164)**	–	**9.5 (55/579)**	–
Age group in years							
15–24	40.2 (767/1,906)	31.2 (139/445)	**1.8 (1.2–2.8)**	17.3 (43/249)	1.6 (0.9–2.8)	9.6 (7/73)	1.2 (0.1–14.9)
25–34	39.3 (2,369/6,026)	25.9 (311/1,199)	**1.6 (1.1–2.3)**	9.2 (92/996)	1.1 (0.7–1.8)	13.8 (24/174)	3.8 (0.4–34.3)
35–49	37.8 (2,929/7,753)	17.9 (228/1,271)	1.0 (0.7–1.5)	5.7 (81/14,217)	0.8 (0.5–1.3)	9.1 (22/241)	5.0 (0.6–44.5)
≥50	36.8 (901/2,449)	13.6 (42/308)	1.0	6.2 (31/502)	1.0	2.2 (2/91)	1.0
Ethnicity							
White	38.6 (3,511/9,093)	22.3 (575/2,584)	1.0	13.3 (97/728)	1.0	11.1 (22/199)	1.0
Chinese	41.9 (26/62)	28.6 (6/21)	1.8 (0.6–5.4)	0.0 (0/4)	–	0.0 (0/1)	–
Other Asian	42.9 (146/340)	20.0 (15/75)	1.0 (0.5–1.9)	10.6 (7/66)	1.2 (0.5–3.1)	20.0 (1/5)	–
Black African	36.7 (2,053/5,586)	13.9 (10/72)	0.8 (0.4–1.6)	4.8 (90/1,892)	**0.6 (0.4–0.9)**	5.6 (5/89)	0.4 (0.1–1.8)
Black Caribbean	46.1 (276/599)	17.9 (14/78)	0.6 (0.3–1.2)	10.3 (19/185)	0.9 (0.5–1.6)	7.7 (1/13)	1.2 (0.1–12.3)
Black other	47.0 (165/351)	21.3 (13/61)	0.8 (0.4–1.6)	14.8 (12/81)	**2.4 (1.1–5.3)**	8.7 (2/23)	0.7 (0.1–6.5)
Indian/ Pakistani/ Bangladeshi	35.4 (126/356)	33.3 (23/69)	1.3 (0.8–2.4)	2.2 (1/46)	0.2 (0.02–1.4)	0.0 (0/11)	-
Other	38.0 (663/1,747)	24.3 (64/263)	1.1 (0.8–1.5)	13.0 (21/162)	1.2 (0.7–2.2)	10.1 (24/238)	0.7 (0.2–2.4)
Country of birth							
United Kingdom	39.0 (2,461/6,309)	23.5 (410/1,747)	1.1 (0.9–1.4)	13.8 (84/610)	1.1 (0.7–1.7)	7.7 (8/104)	0.5 (0.2–1.5)
Abroad	38.1 (4,505/11,825)	21.0 (310/1,476)	1.0	6.4 (163/2,554)	1.0	9.9 (47/475)	1.0
Probable country of infection							
United Kingdom	43.9 (3,152/7,186)	24.6 (541/2,196)	**1.5 (1.2–1.8)**	14.0 (121/862)	**1.7 (1.3–2.4)**	10.6 (10/94)	1.0 (0.4–3.0)
Abroad	34.8 (3,814/10,948)	17.4 (179/1,027)	1.0	5.5 (126/2,302)	1.0	9.3 (45/485)	1.0
Region of diagnosis							
London	45.7 (3,713/8,122)	22.7 (405/1,782)	–	7.8 (125/1,603)	–	11.3 (37/328)	–
Outside London	32.5 (3,253/10,012)	21.9 (315/1,441)	–	7.8 (122/1,561)	–	7.2 (18/251)	–
CD4 count (cells/mm³) at diagnosis[c]							
>200 to ≤350	39.0 (1,318/3,379)	11.4 (68/595)	1.0	5.8 (38/660)	1.0	11.4 (68/595)	1.0
>350 to ≤500	41.7 (1,355/3,252)	23.1 (186/804)	**2.3 (1.7–3.1)**	9.9 (48/487)	**1.6 (1.0–2.5)**	23.1 (186/804)	1.7 (0.5–6.6)
>500 to ≤750	40.8 (1,260/3,088)	36.0 (284/789)	**4.4 (3.3–5.9)**	20.4 (86/422)	**3.6 (2.4–5.5)**	36.0 (284/789)	3.1 (0.8–11.1)
>750 to ≤1,000	42.4 (435/1,027)	39.9 (110/276)	**5.1 (3.6–7.3)**	24.8 (33/133)	**5.1 (3.0–8.6)**	39.9 (110/276)	3.6 (0.8–16.4)
>1,000	42.8 (166/388)	43.5 (37/85)	**6.4 (3.9–10.7)**	31.9 (23/72)	**7.1 (3.8–13.0)**	43.5 (37/85)	4.8 (0.7–33.3)

CI: confidence interval; HIV: human immunodeficiency virus.

Values in bold blue are where p<0.2. Cells with dashes are where the value is not applicable.

[a] Number tested for recent infection/number diagnosed.

[b] Number of recent infections/number tested for recent infection.

[c] CD4 data not available for all samples; the number of new diagnoses with CD4 count <200 cells/mm³ was 4,621, of which 1,714 were tested for recent infection.

that identify as black British, had the highest odds of a likely recent infection at the time of diagnosis.

There are several limitations to our study. Firstly, the cut-off used for the avidity assay (80%) is based on a longitudinal seroconversion panel mean [15] with a duration of recency of six months for 58% of individuals and less than a year for 88% [16]. It is therefore likely that the proportions presented are an underestimate due to the limited sensitivity of the assay. Furthermore, the specificity of the test is not well understood, and thus the extent to which the algorithm may misclassify cases. In a separate study, we examined the number of recent infection classifications when applying the algorithm to 1,270 specimens from persons known to have been infected for more than a year. We found that the proportion misclassified, termed the false recent rate [17], was 1.3% (17/1,270). This implies that in the study presented here, up to 91 (8.8%) of recent cases may have had an infection for more than a year, resulting in the overall proportion of recent infection 13.4% (931/6,966). Also, it should be noted that CD4 information was not available for 10% (718/6,966) of cases, among whom the proportion of recent infections was 11.4% (82/718).

Secondly, HIV diagnoses are subject to testing patterns and therefore the absolute numbers and proportions need to be considered in the context of testing frequencies. Sexual health clinic data show MSM test more frequently than heterosexual men and women [1] and we undertook a recent study demonstrating regular testers are more likely to be diagnosed close to the time of infection [18]. Therefore, the higher proportions of recent infection among MSM will be partly attributable to the difference in testing patterns. Further study is needed to evaluate the extent to which lower proportions of recent infection among heterosexual men and women are due to infections acquired abroad or barriers to testing. Nevertheless, a substantial proportion of the recent infections in this group were reported to have been acquired in the UK, which is in line with findings of other studies [2,10].

Thirdly, as coverage of testing for the three years combined was only 38%, there is potential for selection bias. However, we found no major differences when we compared the demographic variables of those tested to all persons newly diagnosed (Table 1).

We found a positive association between recent infection and high CD4 count, both indicators of early-stage disease. Studies have shown that the mean CD4 count before seroconversion among MSM to be about 1,000 cells/mm³, about 780 cells/mm³ six months after infection and about 670 cells/mm³ a year after infection, though with wide variations within and between individuals [19]. Among HIV-negative African populations, observations of median CD4 counts varied from 640 cells/mm³ in Ethiopia [20] to 1,160 cells/mm³ in Uganda [21,22]. Particularly among individuals with HIV infection, it is not uncommon for CD4 counts to double or halve within eight weeks of an initial count, with an average variation of 25% from the mean over this period [23]. Therefore, there is considerable uncertainty in the expected CD4 counts within the first six months or year of infection, which may explain why the proportion of likely recent infection is not higher among those with CD4 counts similar to persons who are HIV negative.

It is known that CD4 counts can drop during seroconversion [24]; if below 200 cells/mm³, according to the algorithm used in this study, individuals would be reclassified as having a long-standing infection (n=61), potentially slightly underestimating the proportion of recent infection.

Along with France and the United States, the UK is one of the first countries to apply a RITA to routine case-based surveillance data. The UK uses the AxSYM assay modified for the determination of antibody avidity, whereas BED capture enzyme immunoassay (BED-CEIA) is currently the assay of choice in the United States [5] and enzyme immunoassay for recent infection (EIA-RI) in France [4]. Each of these tests has a different mean duration of recency, making direct comparisons difficult. The coverage of testing was higher in France (77% between 2003 and 2006) and lower in the United States (17% in 2006) [4,25]. All three countries have found the highest proportions of likely recent infection among MSM. In France, this proportion was 43% among MSM, compared with 16% among heterosexual men and women and lower among those with sub-Saharan nationality compared with those who were French nationals (8% vs 34%) [4,25]. In the United States, incidence estimates based on test for recent infection data showed that 53% of incident infections were among MSM and 45% among persons of black ethnicity [25].

In conclusion, routine surveillance of recent infection with HIV using a biomarker among those diagnosed is feasible in countries where case-based surveillance of HIV infection is in place. Our findings indicate that transmission is high and ongoing in England, Wales and Northern Ireland, and confirm that MSM are disproportionately affected by new infections. Such findings suggest prevention efforts to reduce HIV transmission among MSM should be aimed at all ages and ethnic backgrounds, irrespective of country of birth. Modelling studies illustrate interventions with the greatest impact need to target MSM with recent, undiagnosed infections [26,27] and the RITA could be key in identifying persons in their networks through targeted partner notification. Further work is needed to evaluate RITA as a tool for accelerated partner notification. Better characterisation of HIV incidence assays is currently underway by the Consortium for the Evaluation and Performance of HIV Incidence Assays, a Bill and Melinda Gates-funded project [28].

Although the surveillance data in this study may not reflect HIV incidence in the population, they have been instrumental in demonstrating sustained high rates of recent transmission among persons diagnosed. The next steps are to convert these data into population-based HIV incidence estimates. This will entail applying a sampling frame that accounts for the variation in testing patterns among subpopulations diagnosed and the probability that a person is diagnosed in the recent period of their infection [25,29].

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Conflict of interest

None declared.

Authors' contributions

All authors contributed to the design of the study. AA led on the data analysis and drafting of the manuscript supported by VD, GM, JT, DD, AC and HW. All authors commented on drafts of the manuscript and approved the final version.

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RESEARCH ARTICLE

HIV incidence among sexual health clinic attendees in England: First estimates for black African heterosexuals using a biomarker, 2009-2013

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Abstract

Introduction

The HIV epidemic in England is largely concentrated among heterosexuals who are predominately black African and men who have sex with men (MSM). We present for the first time trends in annual HIV incidence for adults attending sexual health clinics, where 80% of all HIV diagnoses are made.

Methods

We identified newly diagnosed incident HIV using a recent infection testing algorithm (RITA) consisting of a biomarker (AxSYM assay, modified to determine antibody avidity), epidemiological and clinical information. We estimated HIV incidence using the WHO RITA formula for cross-sectional studies, with HIV testing data from sexual health clinics as the denominator.

Results

From 2009 to 2013, each year, between 9,700 and 26,000 black African heterosexuals (of between 161,000 and 231,000 heterosexuals overall) were included in analyses. For the same period, annually between 19,000 and 55,000 MSM were included. Estimates of HIV incidence among black Africans increased slightly (although non-significantly) from 0.15% (95% C.I.0.05%-0.26%) in 2009 to 0.19% (95% C.I.0.04%-0.34%) in 2013 and was 4-5-fold higher than among all heterosexuals among which it remained stable between 0.03% (95% C.I.0.02%-0.05%) and 0.05% (95% C.I.0.03%-0.07%) over the period. Among MSM incidence was highest and increased (non-significantly) from 1.24% (95%C.I 0.96–1.52%) to 1.46% (95% C.I 1.23%-1.70%) after a peak of 1.52% (95%C.I 1.30%-1.75%) in 2012.

surveillance data collected by Public Health England.

Competing interests: The authors have declared that no competing interests exist.

Conclusion

These are the first nationwide estimates for trends in HIV incidence among black African and heterosexual populations in England which show black Africans, alongside MSM, remain disproportionately at risk of infection. Although people attending sexual health clinics may not be representative of the general population, nearly half of black Africans and MSM had attended in the previous 5 years. Timely and accurate incidence estimates will be critical in monitoring the impact of the reconfiguration of sexual health services in England, and any prevention programmes such as pre-exposure prophylaxis.

Introduction

In England, the HIV epidemic is concentrated in two populations, black African men and women who acquired their infection heterosexually, many of whom were born abroad, and men who have sex with men (MSM). New HIV diagnoses, often used as a proxy for monitoring epidemic trends, have remained stable over the last five years at around 6,000 cases each year, down from a peak of over 7,000 in 2005.[1] Among black African heterosexuals, new HIV diagnoses have decreased over the ten year period from 3663 in 2004 to 1113 in 2013 (observed figures) whilst among MSM it increased from 2415 in 2004 to 3,058 in 2013. In parallel, the number of black Africans and MSM testing in sexual health clinics has increased (from 37,701 in 2009 to 46,457 in 2013 and 58,698 in 2009 to 102,553 in 2013, respectively).[2]

Disentangling how much the change in new HIV diagnoses is due to changes in testing or transmission requires accurate estimates of incidence. No estimates of HIV incidence exist for heterosexuals in the UK. National estimates for MSM indicate that incidence has remained stable or increased only slightly over the ten year period. These were derived using models based on serial prevalence estimates [3], back calculations of CD4 cell count data [4] or simulations of risk behaviours [5].

Models for MSM cannot be adapted for heterosexuals since behavioural data are lacking and the assumptions concerning migration are inappropriate, in particular for ethnic minority populations. Although new HIV diagnoses have been decreasing among heterosexuals, mainly due to fewer diagnoses from persons born abroad [1], they still account for approximately half of all new diagnoses. Of note, it is estimated that half of heterosexuals born abroad diagnosed with HIV acquired their infection in the UK.[1]

Many countries are now turning towards the use of biomarkers for recent HIV infection to estimate incidence. These have the potential to produce timely results at relatively low cost.[6–12] Ongoing debate regarding the accuracy of these tests[13,14] prompted a Bill and Melinda Gates funded initiative known as the Consortium for the Evaluation and Performance of HIV incidence Assays (CEPHIA) to evaluate and publish accurate performance characteristics of these assays.[15,16] Public Health England (PHE) first introduced testing for recent HIV infection in sentinel sexual health clinics in 1999 [17] which subsequently developed into a national programme to be offered to all newly HIV diagnosed persons in England in 2009.[18] In England sexual health clinics remain the most important setting for HIV testing for MSM and heterosexual men as well as heterosexual women alongside antenatal testing.[1] About half of all black African men and women and MSM living in the UK have had an HIV test at a sexual health clinic in the past 5 years (46% of black African women, 44% of black African men, 52% of MSM). [19] Thus a significant fraction of new infections is likely to be diagnosed in these

clinics providing a highly efficient place to encounter incident infections. This study provides a unique opportunity to examine HIV incidence in sexual health clinic attendees by combining comprehensive testing data from all sexual health clinics with incidence biomarker data. In particular, for the first time, estimates for black African communities and heterosexuals overall are calculated.

Methods

Data sources

New HIV diagnoses. PHE collates national data on all diagnoses of new HIV, AIDS and AIDS-related deaths along with demographic and epidemiological information for persons aged over 15 years in the UK from clinics and laboratories. Information collected includes sexual orientation, age, gender, ethnicity, country of birth, probable country of infection, place of diagnosis, diagnosis date and HIV type. Information on antiretroviral therapy (ART) and viral load are collected prospectively, annually, through surveys of persons attending clinics for HIV care.[1]

HIV testing data. Since 2008, the Genitourinary Medicine Clinic Activity Dataset (GUMCAD) collated at PHE has collected data on all attendances and services delivered at sexual health clinics in England including HIV tests, age, gender, sexual orientation ethnicity and country of birth.[20] In England, all attendees of sexual health clinics should be offered a HIV test and coverage is high (70% of attendees were tested in 2013, 77% of heterosexual men, 66% of women and 86% of MSM).[2]

Laboratory methods. Testing for recent HIV infection is performed centrally at PHE. During the study period the AxSYM assay HIV 1/2 gO (Abbott, United States) was used, modified to measure antibody avidity [21], which is typically weaker during the initial stages of infection [6]. An antibody avidity index value of less than 80% was the cut-off for recent infection. Avidity results were linked to new HIV diagnosis reports on sex, date of birth, soundex (scrambled surname code) [22] and diagnosis site [18]

A recent infection testing algorithm (RITA) was used to minimise misclassification; cases classified as recent by the assay were reclassified as long-standing infections if the patient had an AIDS-defining illness within a year of diagnosis, or a CD4 count<50 cells/mm^3 at diagnosis, or the patient had had prior ART (indicated either by information on treatment or a viral load <400 copies/mL; CD4 and viral load data available for 94% of cases where avidity<80%). We used 181 days as the mean duration of recent infection (MDRI) for the assay (personal communication Daniela De Angelis).

The coverage of testing for recent infection increased from 25% of all new HIV diagnoses in 2009, to 50% in 2013 and we found that those tested for recent infection were broadly representative of all persons newly diagnosed by the demographic variables available; in 2013 the coverage was 52% (1100/2101) among heterosexuals, 60% (1704/2838) among MSM, 56% (1429/2543) among persons aged <35 years, 51%(1582/3087) among those ≥35 years and 58% (1529/2659) in London versus 50% (1483/2975) outside London.

The false recent ratio. Currently, all available biomarkers assays misclassify a fraction of longstanding infections as recently acquired.[23] We estimated the proportion false recent, also termed the false recent ratio (FRR), in our population by identifying the number of cases defined by our RITA as recently infected among a subset of patients known to have been diagnosed more than a year previously. These specimens were from patients who had transferred their care from one clinic to another and were therefore not diagnosed for the first time at the latter clinic which sent a specimen for recent infection testing (excluded from the main analyses).

Statistical methods

All data are fully anonymised at the time of analysis. A serial cross-sectional study design was used to estimate HIV incidence examining the number of incident infections among a population tested for HIV using [24]:

$$lr = \frac{\mathrm{R} - \in \mathrm{P}}{(1 - \in)\mathrm{wN}}$$

Where:

lr = Annual rate

R = the number of recent infection cases

$\in$= the False Recent Ratio (FRR)

P = the number of HIV positive people tested for recent infection

W = the window period/MDRI

N = the number of people that tested negative for HIV

Biomarker data were used to determine the number of recent infections (R). As not all new diagnoses were tested for recent infection (50% in 2013), we used HIV testing data from GUMCAD to extrapolate a corresponding number of persons tested for HIV each year (T_R) and number of persons that tested negative (N). In GUMCAD, for each risk group, we calculated the total number of HIV tests per diagnosis (diagnosis rate) and used this as a multiplier for the number of positive cases (P):

$$T_R = P_R\left(\frac{T_G}{P_G}\right)$$

Where:

T_R = the number of people that tested for HIV (corresponding to P_R)

P_G = the number of HIV positive people observed in GUMCAD

T_G = the number of people that tested for HIV in GUMCAD

To obtain the number of negative HIV tests (N), we subtracted the number of positive tests (which here equates to the number of recent infection tests) (P) from the number of HIV tests (T_R). Each clinic attendee was considered only once each year (the first test) despite possible multiple attendances and tests. Patients diagnosed for the first time at a given clinic each year and with no evidence of previous HIV-related care were considered newly diagnosed.

Annual incidence estimates are presented separately for black African heterosexuals, heterosexuals overall and MSM, and separately for those attending clinics in London where half of all new HIV infections are diagnosed.[1]

Confidence intervals were derived using the delta method approximation recommended in the WHO guidance for use of biomarker assays to estimate incidence.[24] Briefly, the 95% C.I.

was calculated using the following:

$$I = \pm 1.96 x I_r C_v$$

Where the coefficient of variation (Cv) was calculated using:

$$C_v = \sqrt{\frac{1}{P}\left(\frac{N+P}{N} + \frac{(P-R)R[1+\frac{\varepsilon}{1-\varepsilon}]^2}{[R-\frac{\varepsilon}{(1-\varepsilon)(P-R)}]^2}\right) + \frac{\sigma_w^2}{w^2} + \frac{\sigma_\varepsilon^2(P-R)^2}{(1-\varepsilon)^4[R-\frac{\varepsilon}{(1-\varepsilon)(P-R)}]^2}}$$

with

σ_w = the standard deviation of the mean RITA distribution

σ_ε = the standard deviation of the FRR

Inferences of trends over time were made based on the width of the variances around the annual estimates.

All data were managed and analysed in Stata 13.0 (Stata Statistical Software: Release 13, United States).

Results

Number of HIV tests, diagnoses and the proportion of recent infection

For each year between 2009 and 2013, 144 (of 206), 141 (of 206), 136 (of 209), 150 (of 209) and 125 (of 222) sexual health clinics in England submitted specimens for recent infection testing, representing between 56% and 72% of all sexual health clinics in England (2013 data only until September 1st after which a different assay was used). A total of 19,008 new HIV diagnoses were reported by participating clinics, with similar numbers each year (Table 1). The annual number of HIV tests per diagnosis increased from 162 in 2009 to 215 in 2013 and was much higher among heterosexuals overall (increasing from 236 in 2009 to 424 in 2013) compared to black African heterosexuals (increasing from 22.1 in 2009 to 55.0 in 2013) and MSM (increasing from 26.3 in 2009 to 41.4 in 2013). The decrease in diagnosis rate coincides with an increase in HIV tests among the participating clinics (Table 1).

After applying the RITA algorithm, the proportion of recent infection among samples tested was 9.8% (145/1478) in 2009, increasing to 19.3% (321/1665) in 2013. The proportion of recent infection differed by risk group and increased in all sub-groups over this period; among black African heterosexuals from 1.7% (8/440) to 4.4% (11/256); among heterosexuals overall from 5.3% (36/681) to 8.4% (46/546) and MSM, among whom it was highest, from 14.5% (103/715) to 27.3% (265/970) (Table 1).

The false recent ratio (FRR)

Of 580 available specimens from persons known to have had an infection for more than a year (not included in the main analyses), 38 were classified by the assay as recent (avidity index<80%). Of these, 27 were correctly reclassified by the RITA algorithm (24 had evidence of prior ART, an additional two had a viral load <400/copies/mL and one had AIDS within a year) yielding a 1.9% (11/580) (95% C.I. 1.0%-3.4%) FRR.

Table 1. Estimated annual HIV incidence in sexual health clinics in England, by transmission risk group 2009–2013.

Risk group		All attendees					All					Heterosexuals					Black Africans					MSM				
Year		2009	2010	2011	2012	2013*	2009	2010	2011	2012	2013*	2009	2010	2011	2012	2013*	2009	2010	2011	2012	2013*	2009	2010	2011	2012	2013**
GUMCAD	N tests taken[a]	699487	694800	739446	774212	530240	518494	561970	633006	667166	447302	23813	26613	29178	33031	23113	49634	51403	65443	71152	53053					
	N new diagnoses[b]	4328	4117	4250	3889	2424	2197	1947	2045	1795	1056	1076	961	953	742	420	1698	1636	2010	1941	1280					
	Tests per diagnosis[c]	1616	1688	174	1991	2146	236	288.6	309.5	371.7	423.6	22.1	27.7	30.6	44.5	55	26.3	31.4	32.6	36.7	41.4					
	N tested[d]	1478	2230	2724	2700	1665	681	1083	1180	1050	546	440	660	671	985	256	715	997	1428	1497	970					
RITA	N avidity <80%[e]	217	337	483	593	400	64	90	112	114	77	22	39	41	44	26	145	233	356	452	307					
	N recent applying RITA[f]	173	286	426	507	353	49	68	89	81	56	16	28	30	29	16	117	206	327	494	283					
	% recent[g]	11.7%	12.8%	15.6%	18.8%	21.2%	7.2%	6.3%	7.5%	7.7%	10.3%	3.6%	4.2%	4.5%	4.96%	6.3%	16.4%	20.7%	22.9%	27%	29.2%					
	N recent after FRR applied[h]	1449	2436	3742	4357	3214	361	474	66.6	61	45.6	7.7	15.5	17.3	17.9	11.1	1034	1871	2959	3756	2646					
	% recent after FRR[i]	9.8%	10.9%	13.7%	16.9%	19.3%	5.3%	4.4%	5.6%	5.8%	8.36%	1.7%	2.3%	2.6%	3.1%	4.4%	14.5%	18.7%	21.0%	25.1%	27.3%					
Estimated	N tests taken for RITA[j]	238873	376343	457941	537599	357343	160717	312590	365255	390364	231275	9738	18277	20544	26942	14088	18795	31326	46494	58876	40304					
	N negative tests[k]	237595	374113	457217	534889	355678	160036	311507	364075	389214	231275	9298	17617	19873	25457	14088	18080	30329	45066	53379	39234					
	Estimated incidence[l] (95% CI)	**0.13%** (0.10%-0.16%)	**0.14%** (0.12%-0.17%)	**0.17%** (0.15%-0.20%)	**0.19%** (0.16%-0.21%)	**0.20%** (0.17%-0.23%)	**0.05%** (0.03%-0.07%)	**0.05%** (0.02%-0.07%)	**0.04%** (0.03%-0.05%)	**0.03%** (0.02%-0.05%)	**0.04%** (0.03%-0.06%)	**0.18%** (0.05%-0.39%)	**0.19%** (0.04%-0.34%)	**0.19%** (0.05%-0.33%)	**0.15%** (0.05%-0.26%)	**0.17%** (0.05%-0.30%)	**1.24%** (0.96%-1.52%	**1.34%** (1.10%-1.58%)	**1.44%** (1.22%-1.67%)	**1.52%** (1.30%-1.75%)	**1.46%** (1.25%-1.70%)					

[a] data from GUMCAD,

[b] = data from New HIV Surveillance,

[c] = a/b,

[d,e,f] = data from the recent HIV infection testing programme after applying the RITA algorithm

[g] = f/d,

[h] = f-(FRR* d),

[i] = h/d

[j] = e+d,

[k] = j-d,

[l]applying the WHO formula[24]

* until August 31st (different assay used after this date)

** False Recent Rate = 1.9%

https://doi.org/10.1371/journal.pone.0197939.t001

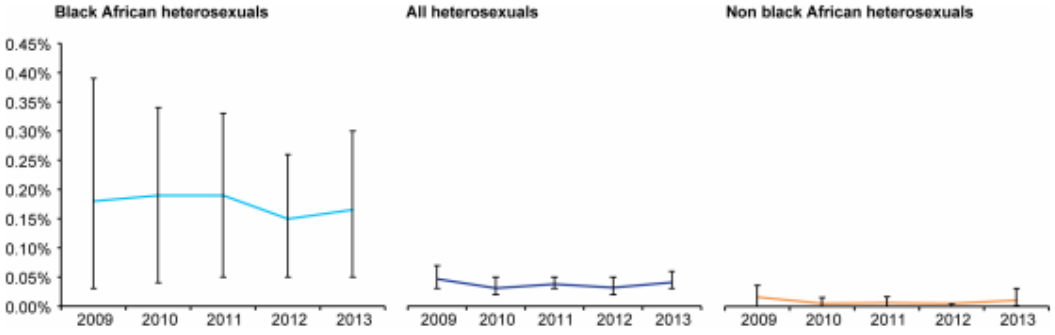

Fig 1. Trends in annual HIV incidence among heterosexual sexual health clinic attendees in England 2009–2013.

https://doi.org/10.1371/journal.pone.0197939.g001

Estimated HIV incidence among sexual health clinic attendees by risk group and age

Using an MDRI of 181 days, we estimated annual HIV incidence among sexual health clinic attendees to have increased from 0.13% (95%C.I 0.10%-0.16%) in 2009 to 0.20% (95% C.I. 0.17%-0.23%) in 2013. Annual incidence increased slightly but non-significantly from 0.15% in 2009 (95% C.I 0.05%-0.26%) to 0.19% in 2013 (95% C.I. 0.05%-0.33%) among black Africans and was approximately 4–5 times higher each year compared to heterosexuals overall, among whom it was stable over the period at between 0.03% (95% C.I. 0.02%-0.05%) and 0.05% (95% C.I. 0.03%-0.07%) (Fig 1). For heterosexuals, we examined these data by gender and country of birth however the number of recent infection cases in these sub populations was extremely small resulting in very wide and unstable variance estimates. In London, where approximately 30–40% of HIV tests were undertaken each year (219614 (31%), 232398 (33%), 244525 (33%), 270491 (35%) and 193875 (37%) in 2009, 2010, 2011, 2012 and 2013, respectively), HIV incidence was broadly similar to the rest of England among black Africans and heterosexuals overall (Fig 2).

HIV incidence among MSM was highest and rose non-significantly from 1.24% (95%C.I. 0.96%-1.52%) to 1.46% (95% C.I. 1.23%-1.70%) (Fig 3). Among MSM in London, estimates

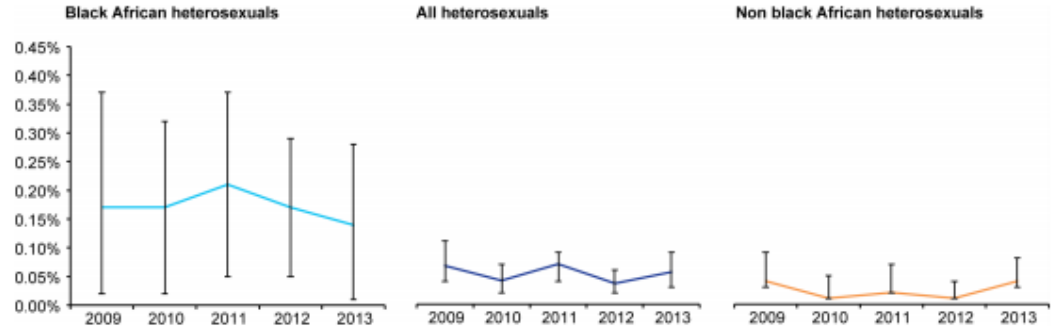

Fig 2. Trends in annual HIV incidence among heterosexual sexual health clinic attendees in London, 2009–2013.

https://doi.org/10.1371/journal.pone.0197939.g002

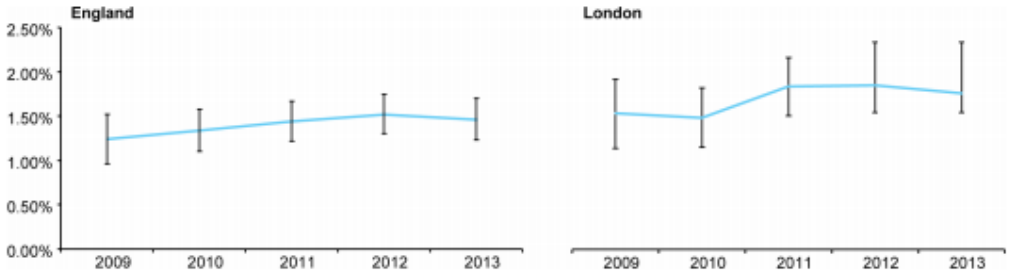

Fig 3. Trends in annual HIV incidence among MSM sexual health clinic attendees by region 2009–2013.

https://doi.org/10.1371/journal.pone.0197939.g003

were slightly but not significantly higher. Analysis by age showed little difference in incidence by age among heterosexuals (data not shown due to small numbers and consequent unstable variances); among MSM the increase in incidence occurred in all age groups with highest rates among those aged 25–34 years followed by those aged 35–50 years (Fig 4).

Conclusion

Principal findings

This is the first study to provide estimates of annual HIV incidence among a representative sample of sexual health clinic attendees and importantly, the first estimates among heterosexual men and women of black African ethnicity, one of the largest sub-populations living with HIV in the UK. The study uses unique methodology combining information from new diagnoses case reports, recent infection biomarkers and HIV testing in sexual health clinics with minimal sampling biases in demographics. We estimate 2 per 1,000 incident HIV cases among all sexual health clinic attendees annually in 2013. Incidence was 1.7 per 1000 for black African heterosexuals, approximately four-fold higher than the 0.4 per 1000 in heterosexuals overall. HIV incidence was highest among MSM at 14.6 per 1000.

The findings suggest a slight increase in annual HIV incidence among MSM over the period, although this was not statistically significant. Of note is that the variance estimates here may be slightly wider than they would be if no RITA data had been missing as the calculations here are based on a smaller sample. The HIV diagnosis rate and the proportion of recent

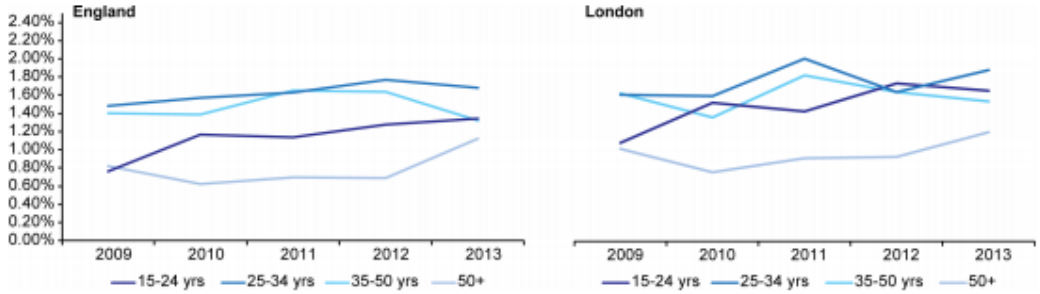

Fig 4. Trends in annual HIV incidence among MSM sexual health clinic attendees by region and age 2009–2013.

https://doi.org/10.1371/journal.pone.0197939.g004

infection diagnosed ranged widely between risk groups reflecting both the variation in testing patterns and underlying HIV prevalence and incidence in these populations. The much lower proportion of recent infection among black Africans may also be due to a larger fraction having likely acquired their infection prior to arriving to the UK.

Our approach provides estimates with improved precision compared to other estimation methods [2–4], because here, the HIV status is known for the whole population of study. This approach is particularly effective for estimating incidence among all risk groups allowing comparison. Using a biomarker circumvents the need for sexual behavioural and migration data as identifying incident infection is based on testing specimens in real time in conjunction with routinely collected clinical data such as viral load and CD4 cell counts.

Comparisons with other studies

There are no previous studies which have attempted to estimate HIV incidence for the black African community in England or indeed heterosexual populations whilst several estimates exist for MSM. A previous study using biomarkers in sentinel sites among MSM participants of an unlinked anonymous HIV prevalence serosurvey in England and Wales between 1995 and 2005, found a higher rate of HIV incidence (2.45% in 2001 based on 317 recent infection diagnoses).[25] However in this study, incidence is likely to have been overestimated as the assay specific FRR was not accounted for and likely longstanding specimens were not excluded as part of an algorithm. Further, comparing findings is difficult as a different assay was used.

More recent studies estimated HIV incidence among MSM in the general population at national level, one based on back calculations of HIV diagnoses and CD4 cell count [4] and the other on simulations of risk behaviours [5]; Birrel et al's model estimated 2,300–2,500 new HIV infections among MSM in 2010, which would equate to an incidence rate of 0.4%. Similarly, a stochastic model found from 2006–2010 HIV incidence was 0.53 per 100 person years. [5] A Bayesian evidence synthesis model found that HIV incidence was between 0.5% and 1% among MSM in 2007.[3] Annual incidence estimates among MSM attending sexual health clinics in this study were approximately three-fold higher than estimates among all MSM confirming that sexual health clinic attendees are a higher risk group of HIV acquisition and likely to benefit from HIV prevention initiatives such as pre-exposure prophylaxis (PrEP).

The lack of population-based estimates for black Africans in the literature makes such a comparison difficult and hence we are unable to assess the potential bias among the sexual health clinic attendees of this population.

Limitations

Epidemiological data from sexual health clinics are influenced by population-level testing patterns creating sampling bias, due to the non-random nature of attendance. For example, patients with a seroconversion illness may be more likely to present for HIV testing, termed the 'seroconversion effect'. [26] Test-seeking behaviours may also have changed over time due to changes in national HIV testing recommendations; currently, recommendations are for black Africans to test for HIV and to test after every new partner; for MSM they are to test annually or more frequently, e.g. also after every new sexual partner.[1] Motivated and frequent testers have a higher probability of being diagnosed during the earlier stages of infection, therefore potentially inflating the estimated incidence. We observed a large increase in testing over the five year period which likely identified more recent infections, but potentially diluted our incidence estimates due to more low risk persons testing, as demonstrated by the increasing number of tests per diagnosis.

Secondly, sampling bias may occur due to incomplete coverage of recent infection testing (approximately half of new HIV diagnoses). Clinicians could also be more inclined to send specimens for recent infection testing from patients who report a recent risk exposure. However, we previously explored the representativeness of persons tested for recent infection comparing them to all persons newly diagnosed and found no differences in age, ethnicity or country of birth.[18] Although recent infection is associated with some demographic characteristics [18], we acknowledge that similar demographic characteristics may not mean similar risk. In addition the width of the variance estimates is likely to have been overestimated contributing to the difficulty in determining trends over time.

Thirdly, clinical data for the algorithm were not available for 6% of cases with avidity<80%. This may imply the number of recent cases and incidence is overestimated. However we consider our data on treatment status to be complete, capturing most cases with low viral load or CD4 count.

Fourthly, certain patient characteristics may affect the performance of the assay; for example it is known that the HIV subtype affects the FRR [16], and that the MDRI may vary for different population groups (the estimate used here was measured only among MSM). We believe HIV subtype variation is unlikely to have a huge effect on our estimates as the composition of our population regarding transmission risk was similar to the specimens used to calculate the FRR (45% MSM, 49% heterosexuals, 6% other e.g. PWIDs or not reported; see section on FRR). To note, subtype B is mostly diagnosed in the UK (40% overall, 89% among MSM), followed by subtype C (34%).[27] Among heterosexuals subtype C is the most common (50.6%) followed by B (14.8%).[27] Data for the FRR by subtype for other incidence assays show the FRRs for subtypes B and C to be similar for the Limited Antigen Assay ((SEDIA BioSciences) (0.5% FRR for subtype B and 1.3% for subtype C) but vary more significantly for other assays.[16] No such data are available for the assay used here which is no longer commercially available. We undertook sensitivity analyses around the FRR and MDRI and found that increasing the FRR by 1%, from 1.9% to 2.9% or adding 40 days to the MDRI, increasing it by 20% from 181 to 221 days, or both, did not result in estimates outside the variance of those presented here. However, to note is that our FRR is based on diverse subtypes and the MDRI on subtype B, which may imply the FRR estimate is higher than appropriate for the MSM group. This would result in an underestimate of incidence in this subpopulation.

Lastly, patient records in GUMCAD can only be uniquely linked within and not between clinics. Therefore a patient could be coded as newly diagnosed in more than one clinic which would underestimate the number of HIV tests per diagnosis and inflate incidence estimates. Currently, it is estimated that approximately 10% of patients use multiple clinics, of which a subset may be newly diagnosed patients.

Implications

Testing for recent HIV infection enabled these first estimates for HIV incidence among black Africans among a representative sample of sexual health clinics and showed they remain disproportionately at risk of infection in England. To note is that the sexual health clinic attending population is unlikely to be representative of the general population. However, in this setting, for all population groups, HIV incidence has not decreased over the last half decade despite ongoing prevention and HIV testing initiatives.[28] Interpreting the trend (or lack of) in incidence is difficult as, this may be influenced by an insufficient sample size given the number of new infections.

This may call into question the value of incidence tests; although we have been able to derive incidence estimates with considerable precision, only large changes in incidence over time can

be reliably observed due to sample size restrictions and the background prevalence of HIV. A group at the South African Centre for Epidemiological Modelling and Analysis (SACEMA) have published a tool which countries can use to determine the sample sizes required to detect a reduction in incidence over two time points.[29] Using this tool and the characteristics of our assay, estimated incidence and number of HIV tests, we would need to observe a change in incidence greater than 20% to correctly infer a reduction to 5% significance and 80% power (assuming 5% prevalence among MSM and 1% among all attendees). In the absence of any drastic interventions, a reduction to this extent is only likely to be observed over an extended period.

Further, use of antiretrovirals including PrEP can compromise biomarkers [16] However, patients taking PrEP are encouraged to test for HIV every three months at a sexual health clinic and seroconverters will therefore be detected through the genitourinary surveillance system without the need for a biomarker. [30,31]

Our findings shed light on the rates of new infections in black Africans and compare these across sub-populations in the UK for the first time, which is timely, given the recent reconfiguration of sexual health services in the England. In 2013, the commissioning of sexual health services in England was split from HIV care; sexual health and sexually transmitted infection prevention services are assigned to local authorities and HIV treatment and care is funded nationally by NHS England. In addition, providers are moving towards online models for service provision (https://www.sh24.org.uk/) which will result in fewer sexual health clinics and the expansion of home sampling and home testing. As of current, the National Institute for Health and Care Excellence (NICE) guidance recommends HIV testing to be routinely offered to all sexual health clinic attendees, antenatal services, termination of pregnancy services and drug dependency programmes and expanded testing is to be undertaken in areas where more than 2 in 1000 population have been diagnosed with HIV. Our data show a significant scale up of HIV testing in recent years, up to doubling among MSM attending sexual health clinics. With the number of HIV tests required per HIV diagnosis among key risk groups (black Africans and MSM) approximately a tenth that of other heterosexuals (~1 in 40 compared to 1 in 400 in 2012) targeted HIV testing remains efficient and cost effective. This is further supported by the observed stable HIV incidence over the period despite increased testing. It will be crucial to monitor the impact of structural changes to the delivery of sexual health services on HIV testing rates among different sub-populations and importantly, HIV incidence among these groups.

With black African men and women most likely to be diagnosed late [1] more work is needed to improve HIV testing rates in this group and promote regular testing. Stigma remains a huge barrier towards testing and successful prevention efforts in this population. [32] Although a large proportion of infections are acquired in the UK, the Mayisha II study showed nearly half of black African men and women travelled to their country of origin in the previous five years and 40% of men and 22% of women acquired a new sexual partner when abroad.[33] An association between travelling to their country of origin and high sexual risk such as larger numbers of partners and history of a sexually transmitted infection diagnosis was also one of the findings. More work is needed to develop innovative, targeted prevention programmes reaching black Africans at risk, including persons who recently travelled as well as those engaging in other more established high risk behaviours such as unprotected sex with casual, concurrent, and high numbers of, sexual partners.

Applying the 0.17% annual incidence estimate among black Africans to the 67,337 who attended sexual health clinics in 2013 equates to 115 persons with incident infections. Using a CD4 back-calculation model and date of entry into the UK, we estimate that approximately 500 black African heterosexuals acquired their infection each year in the UK [34] over the 5 years (equating to 30% of all newly diagnosed black Africans). As such, this would imply that

about one in five (115/500) persons of black African ethnicity who acquire HIV in the UK each year are detected in sexual health clinics in the same year. Given that this is only a small fraction of estimated incident infections in this group, better methods are needed to track new infections in this population. Although there are no population-based incidence estimates for black Africans, in the 2011 UK census, it was estimated that there were 989628 black Africans living in England and Wales [35] (479799 men; assuming 3% are MSM (n = 14394) would approximate a heterosexual population size of 975234). Five hundred incident infections would thus approximate a population-based incidence rate of 0.05%.

For MSM, where population-based HIV incidence estimates are available, considering a 1.5% incidence among MSM attending sexual health clinics and 92037 MSM in total attended a clinic in England in 2013 [2], this would equate to 1381 MSM with incident HIV infections having attended a clinic in that year. Based on Birrel et al.'s estimates of between 2300–2500 new infections each year, this implies over half (55%) of all MSM with incident infections attend sexual health clinics and are diagnosed within a year of their infection. Community-based behavioural studies show higher risk MSM are often linked into sexual health services and are more likely to be diagnosed with a sexually transmitted infection. As such, PrEP coupled with behaviour change interventions are likely to be highly appropriate for this healthcare seeking population. Strategies to better inform and provide access to prevention strategies including PreP among other individuals at high risk of HIV infection in the UK need to be developed.

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18th Annual Conference of the British HIV Association, Birmingham 2012 (Oral presentation)

Recently acquired HIV infections: an overview of surveillance in the UK

Background: Recent HIV infections are indicative of ongoing transmission. Testing for recent infection with HIV was introduced as part of routine national surveillance in 2009. Here, we report the results of the first two years of national monitoring in England and Northern Ireland.

Method: Cross-sectional analyses of surveillance data from over 90 laboratories and 50 clinics in England and Northern Ireland. The data incorporate results from an HIV antibody assay modified for the determination of HIV using an avidity test, and clinical data including initial CD4 count, simultaneous AIDS diagnoses and antiretroviral therapy.

Results: Coverage of testing increased from 26% in 2009 to 46% of all new diagnoses reported until end June 2011. Socio-demographic characteristics linked to samples received were similar to those of all newly diagnosed. Between 2009 and 2011, the overall proportion of recent HIV infections was 15% which was highest in the lower age groups with 25% and 20% among those 15-24 and 25-34 versus 12% and 8% among those 35-44 and over 50 years, respectively. Recent infections were highest among men who have sex with men (MSM) (23%), followed by heterosexuals (10%) and people who inject drugs (4%). One in three MSM aged less than 35 years acquired their infection recently compared to one in seven over 50. The highest proportions of recent infections among heterosexuals were in women aged 15-24 (20%) and men aged 25-34 (15%). Half of all recent infections were diagnosed in London.

Conclusion: One in four MSM and one in ten heterosexuals diagnosed with HIV between 2009 and 2011 had a probable recent infection indicating high levels of ongoing transmission. Further work is being carried out to estimate HIV incidence and understand the data in context of testing patterns.

Annual conference, British Association for Sexual Health and HIV, 2015 (Oral presentation)

HIV incidence among people who attend sexual health clinics in England in 2012: estimates using a biomarker for recent infection

Introduction: In England, 80% of HIV diagnoses are in sexually transmitted infection (STI) clinics. Since 2009, Public Health England offered testing for recent HIV infection.

Aim: To estimate HIV incidence among STI clinic attendees in 2012.

Methods: The AxSYM avidity assay, modified to determine antibody avidity, was conducted on aliquots of newly diagnosed persons and results linked to the national HIV database. An incident case was defined as avidity<0.8, no antiretroviral treatment or AIDS and viral load≥400 copies/mL at diagnosis. The number of persons tested for HIV was assessed using the Genitourinary Medicine Clinic Activity Dataset. We estimated and adjusted for a 1.9%(95% C.I. 1.0%-3.4%) false recent rate and used 202 days as the mean duration of recent infection to calculate incidence rates.

Results: Of 212 STI clinics in England, 150(71%) submitted specimens for recent infection testing, comprising 3,930 persons newly diagnosed; 50% were MSM. The number of HIV tests/diagnosis was 210 for all clinic attendees, 38 for MSM, 403 for all heterosexuals and 46 for black African heterosexuals. HIV incidence was 0.15% (95%C.I 0.13-0.18%) for all attendees, 1.22% (95%C.I 1.07-1.42%) for MSM, 1.41% (95%C.I 1.21%-1.66%) for MSM in London, 0.03%(95%C.I 0.02-0.04%) for heterosexuals and 0.13%(0.05-0.22%) for black African heterosexuals.

Discussion/conclusion: Testing for recent HIV infection combined with routinely collected clinical data provides robust and timely national estimates of HIV incidence. HIV incidence among MSM and black African heterosexuals attending STI clinics was 40 and nine times higher respectively than among all heterosexuals, and exceeds the WHO-defined elimination threshold of 0.1%.

Fourth Joint Conference British Association for Sexual Health and HIV (BASHH), British HIV Association (BHIVA), 2018 (Poster presentation)

Preventive and risk behaviours among MSM recently infected with HIV: results of a pilot cross sectional survey in England

Background: For the first time since the mid-80s, HIV diagnoses among men who have sex with men (MSM) have fallen in five of the largest clinics in London. The PrEP Impact trial will roll out PrEP for 10,000 deemed to be high risk persons. Here, we explore the circumstances in which men report to have acquired their incident HIV infection and review if men anticipated their risk and took measures to reduce these.

Methods: Self-administered survey distributed to MSM diagnosed with incident HIV infection (identified either through testing history, a p24 antigen positive HIV antibody negative test or a Recent Infection Testing Algorithm (RITA)) across 7 clinics in London, Manchester and Sheffield in 2014. Men were asked about behaviours in the 6 months preceding diagnosis and, using an open ended question, how they believed they had acquired HIV.

Results: Of the 51 MSM recruited, 20 were born abroad (mainly Europe) and most (44) were white. The median age was 32 years (range 20-57). Half (24) reported PEP (17) or PrEP (3) use in the previous 6 months. Nearly all men (n=47) reported a specific event which they attributed their HIV infection to; these could be broadly categorised using four themes:

i) men who had been aware when they had engaged in high risk UAI, (n=17; UAI with casual partners and or multiple partners);
ii) men reporting to have attempted to negotiate safe sex but that their ability to do so had been compromised, (n=6;UAI due to drug induced disinhibition (4), lack of opportunity to negotiate safe sex in group sex situation (1), and rape (n=1);
iii) men who reported attempting to protect themselves but that this was unsuccessful (n=21; split condom (7), believing partner had an undetectable viral load (2), dipping (5), serosorting (6), oral sex only (1)
iv) men who believed transmission to have been from a regular partner (n=3), however the majority of these also indicated other risks such as >1 UAI partner, an STI or chemsex.

Conclusion: In a group of MSM who had recently acquired HIV, while there were high levels of risk behaviour shortly before diagnosis, half reported having taken active steps to prevent infection implying at risk men may self-select for PrEP. All men in this random sample would have been eligible based on the current recruitment criteria.