How is the epidemiology of heterosexually-acquired HIV infection evolving, particularly among black Africans, in England, Wales and Northern Ireland?

CITY UNIVERSITY LONDON

Brian Rice

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City University London

School of Health Sciences

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THE FOLLOWING PARTS OF THIS THESIS HAVE BEEN REMOVED:

Appendix II: HIV and Aids Reporting section notification forms.

pp 179-180:	CIDSC Laboratory report of new HIV diagnosis.
pp 181-183:	Clinicians report of new HIV diagnosis, first AIDS diagnosis and deaths.
pp 184-187:	The Survey of Prevalent HIV Infections Diagnosed (SOPHID) metadata files.

Contents

Table of contents

List of tables

List of figures

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Declaration

I, Brian Rice, confirm the work presented in this thesis is my own.

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Abstract

In the United Kingdom (UK), an estimated 107,800 people were living with HIV in 2013, of whom 55% were heterosexual men and women. Black African men and women accounted for the majority of heterosexuals living with HIV in the UK in 2013. In this PhD by prospective publication my research question is "*How is the epidemiology of heterosexually-acquired HIV infection evolving, particularly among black Africans, in England, Wales and Northern Ireland?*". I conducted a quantitative analysis of national surveillance datasets and undertook literature searches. Most of my analysis was based on data from the three national HIV surveillance systems which constitute the HIV and AIDS Reporting System (New HIV Diagnoses database; Survey of Prevalent HIV Infections Diagnosed; CD4 Surveillance Scheme). I published the results of my analyses in six peer-reviewed papers between 2007 and 2014. My key findings were as follows: over the last decade an increasing proportion of black African heterosexuals born abroad but diagnosed with HIV in the UK acquired HIV whilst living in the UK; outward migration from the UK may explain why some black African heterosexuals were lost to follow-up from HIV care; the proportion of black African heterosexuals diagnosed late with HIV has not changed substantially; the uptake of HIV testing among black African heterosexuals has increased over time but remains low compared with that among MSM. To minimize the risk of HIV transmission and to maximise the benefits of earlier detection my key recommendation is to promote regular HIV testing among black African women and men in a range of healthcare and community settings in E,W&NI, particularly in primary care.

Abbreviations

AIDS: Acquired Immunodeficiency Syndrome

ECDC: European Centre for Disease Prevention and Control

E,W&NI: England, Wales and Northern Ireland

HARS: HIV and AIDS Reporting System

HPA: Health Protection Agency

HIV: Human Immunodeficiency Virus

IMD: Index of Multiple Deprivation

IPS: International Passenger Survey

LFS: Labour Force Survey

LSOA: Lower Layer Super Output Area

LTIM: Long Term International Migration

MSM: Men who have sex with men

Natsal: National Survey of Sexual Attitudes and Lifestyles

NHS: National Health Service

ONS: Office for National Statistics

PHE: Public Health England

PWIDs: People who inject drugs

SOPHID: Survey of Prevalent HIV Infections Diagnosed

UK: United Kingdom

UK-THRED: UK Tuberculosis & HIV Research Epidemiology & Development group

UNAIDS: Joint United Nations Programme on HIV/AIDS

UNESCO: The United Nations Educational, Scientific and Cultural Organisation

USA: United States of America

1. Introduction

Summary

In this chapter I provide a background to the research and analysis conducted for my thesis. I summarise the epidemiological characteristics of the Human Immunodeficiency Virus and comment on research focusing on heterosexually-acquired HIV in England, Wales and Northern Ireland. I describe the proposed structure of the doctoral thesis which will include six papers published in peer-reviewed journals.

1.1 Background to my thesis

My involvement in HIV epidemiology began in 2002 when I joined the HIV and STI Department of the Public Health Laboratory Service (later to become the Health Protection Agency and then Public Health England) as an HIV scientist. Until that time, the majority of HIV diagnoses had been among men who have sex with men (MSM) (1). However, in my first year as an HIV scientist, in 2002, the HIV surveillance team (of which I was a member) observed there had been an increase in HIV diagnoses among heterosexuals since 1999 (1). This increase triggered my interest in the epidemiology of heterosexually-acquired HIV in the United Kingdom (UK). Prior to describing the proposed structure of my doctoral thesis I provide background information on the epidemiology of HIV in England, Wales and Northern Ireland (E,W&NI).

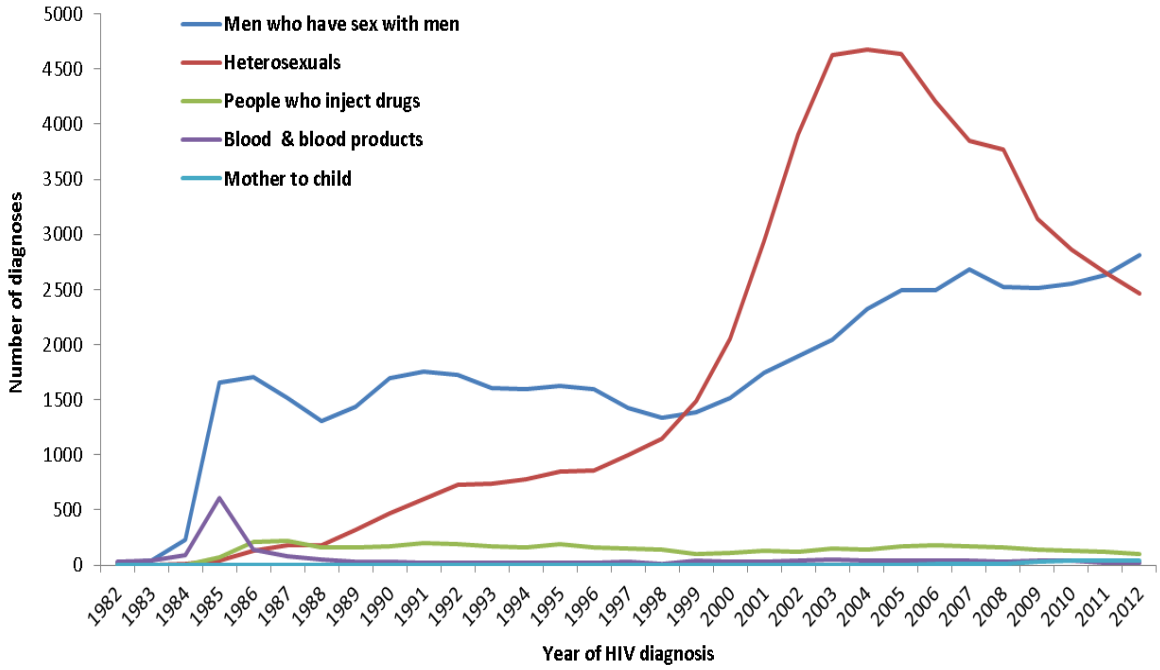
1.1.1 Early years of the HIV epidemic in E,W&NI

In July 1982, the first cases of AIDS were reported in the UK. Since these initial reports, 133,767 people have been diagnosed with HIV in E,W&NI (up to the end of 2013) (1).

In the early years of the HIV epidemic (1980s) in the UK, HIV diagnoses were predominately among MSM, people who inject drugs (PWIDs), and recipients of blood and blood products (figure 1.1). The introduction during the 1980s of needle and syringe programmes, and opiate substitution therapy, were successful in maintaining HIV diagnoses among PWIDs at a low level (2). The introduction in 1985 of the routine screening of blood donations for HIV greatly diminished the risk of transmission from blood transfusions and blood products (3, 4). Among MSM, however, an average of

1,570 men were diagnosed with HIV every year in E,W&NI between 1985 and 1998 (range: 1,302 in 1988 to 1,755 in 1991) (figure 1.1). During that period of time MSM accounted for the majority of new HIV diagnoses reported annually in E,W&NI.

Figure 1.1: HIV diagnoses among adults (aged ≥15 years at diagnosis) in E,W&NI by probable route of infection, 1982 to 2012



Source: Public Health England (1)

In these early years, the potential for HIV transmission through heterosexual sex in the UK was unclear. It was questioned whether "*AIDS*" in the UK would remain confined to PWIDs and MSM (5), and whether HIV could actually be transmitted between two heterosexual partners through sexual contact (6). However, early evidence for the sexual transmission of HIV between heterosexual partners emerged in other European countries and in sub-Saharan Africa.

Among confirmed "AIDS" cases in France in 1982, some people were identified for whom the only risk factor was living in Equatorial Africa (ie there was no history of homosexual contact, nor travel to the USA or Haiti) suggesting that heterosexual contact was the route of transmission (7). In Belgium in 1984, HIV infection was reported among previously healthy patients originating from Central Africa for whom there was no evidence of an underlying immunosuppressive disease and no history of

blood-product transfusion, homosexuality, or intravenous-drug abuse raising the possibility of heterosexual transmission (8). The authors of a study conducted in the Democratic Republic of the Congo (then known as Zaire) in 1983 argued that a new epidemiological stage of HIV/AIDS was emerging in Central Africa with significant transmission among large heterosexual populations, implicating heterosexual transmission (9). The authors of a survey conducted in Zambia in the early 1980's also concluded that HIV infection was prevalent in Africa and was transmitted heterosexually (10). A study of female "*prostitutes*" in 1984 in Rwanda reported a high risk of HIV infection (then referred to as HTLV III) among these women (11).

A study in Edinburgh between 1985 and 1986 reported a 15% HIV "*infection rate*" among persons with no HIV risk factors other than having had heterosexual sex with a PWIDs (12). In London, early evidence of HIV being acquired heterosexually was presented among attendees of a sexual health clinic in 1987 having routine serological tests for syphilis. Among heterosexual patients at the clinic HIV prevalence was 1% both among women (4/412) and men (4/377) (13). Two of the eight HIV-positive heterosexuals had a history of injecting drug use (13). However, the remaining six had no identifiable risk factors that would have warranted their inclusion in an HIV risk group (13).

To gain a better understanding of risk factors for heterosexually-acquired HIV, heterosexuals reported to national HIV surveillance in E,W&NI were categorised as first or second generation transmission (14). First generation transmission was defined as having a partner who was infected by a route other than heterosexual transmission, mainly bisexual men and PWIDs. Second generation transmission was defined as having a partner who themselves acquired HIV heterosexually.

Behavioural interviews were conducted among those assigned to the second generation transmission group for whom the only reported risk for infection was heterosexual contact in the UK with a partner who themselves acquired HIV heterosexually. The purpose of these interviews was twofold: (i) confirm risk information was correct; (ii) identify additional risk factors for HIV transmission. These interviews found that, as compared with heterosexuals in the general population, HIV-diagnosed heterosexual men assigned to the second generation transmission group had an earlier sexual debut, and diagnosed heterosexual men and women were significantly more likely to report

having never used a condom (15). The sub-categorisation of heterosexuals ceased in 2002, and interviews with HIV-diagnosed heterosexuals who acquired their infection from a partner who themselves acquired HIV heterosexually ceased in 2011.

Between 1986 and 1991, there was a steady increase in both the number of newly diagnosed persons acquiring HIV through first generation and second generation heterosexual transmission (14). The proportion of HIV diagnoses in E,W&NI attributable to the two heterosexual categories combined increased from 4% in 1986 to 23% in 1991 (14). By 1996, this proportion had increased to 27% (16).

Figure 1.1 shows the number of heterosexuals diagnosed annually with HIV in E,W&NI increased steadily from 35 in 1985 to 1,150 in 1998. Over this time period, heterosexuals accounted for one quarter (24%) of all adults (aged ≥15 years at diagnosis) newly diagnosed with HIV in E,W&NI (1).

1.1.2 The HIV epidemic in E,W&NI from 1999 onwards

Between 1999 and 2012, approximately six out of ten HIV diagnoses in E,W&NI were among heterosexuals (1). In 1999, the annual number of HIV diagnoses in E,W&NI among heterosexuals exceeded for the first time that among MSM (figure 1.1). Between 1999 and 2004, diagnoses of HIV among heterosexuals increased rapidly from 1,489 to 4,679 before declining year on year to 2,465 in 2012 (figure 1.1). During this same period of time, the number of MSM diagnosed with HIV increased steadily (from 1,387 in 1999 to 2,814 in 2012) (figure 1.1). These contrasting trends resulted in the annual number of HIV diagnoses among MSM once again exceeding that among heterosexuals in 2012, the first time it had done so since 1998.

The rapid increase in HIV diagnoses between 1999 and 2004 triggered my interest in heterosexually-acquired HIV. However, it was the difference between diagnosed heterosexuals and MSM that attracted my attention. Whereas the majority of MSM diagnosed with HIV in E,W&NI between 1999 and 2012 were of white ethnicity and were born in the UK, the overwhelming majority of heterosexuals diagnosed with HIV were of black African ethnicity and were born abroad, mainly in sub-Saharan Africa (1). It was this finding that first got me thinking about the potential impact of migration both to and from the UK on the evolving epidemiology of heterosexually-acquired HIV infection in E,W&NI.

1.1.3 HIV among heterosexuals in E,W&NI

In the UK (Scotland included) in 2012, an estimated 98,400 people of all ages were living with HIV (including diagnosed and undiagnosed) (3). Of these, 52,900 (54%) were heterosexuals (31,700 women and 21,200 men). African born men and women accounted for the majority (60%; 31,800) of heterosexuals living with HIV in 2012 (3).

The estimated 52,900 heterosexuals living with HIV in the UK in 2012, equates to a prevalence of <1.5 per 1,000 of the total population. However, in black Africans, among whom heterosexual sex is the predominant route of infection, the prevalence of HIV is elevated. Among black African women, the estimated prevalence in 2012 was 51 per 1,000, and among black African men 26 per 1,000 (3). The estimated prevalence of HIV among black African women in 2012 was higher than that in MSM (47 per 1,000) (3).

Among the estimated 31,700 heterosexual women living with HIV in 2012, 24% were undiagnosed (3). The corresponding figure among the 21,200 heterosexual men was 30%. The level of undiagnosed HIV among heterosexual women and men in 2012 was higher than that among MSM (18%) or PWIDs (14%) (3).

In 2012, 6,028 adults were newly diagnosed with HIV in E,W&NI (1). Among those for whom probable route of infection was reported, 45% were heterosexuals (1). Among heterosexuals newly diagnosed with HIV in 2012 in the UK, 57% of women and 65% of men were diagnosed late (diagnosed with a CD4 cell count <350 cells/mm^3 and beyond the point treatment should have been commenced) (3). Among MSM the figure was 34%, while among PWIDs it was 64% (3).

Elevated levels of undiagnosed HIV and late HIV diagnosis among heterosexuals are of public health concern. In relation to undiagnosed HIV, data from the United States of America (USA), suggests that nearly half of all new HIV infections derive from the one in five people living with HIV who remain undiagnosed (17). The proportion of infections resulting from people living with undiagnosed HIV is likely to increase as the quality of HIV care improves among those diagnosed (17). This is because the majority of people with diagnosed HIV in receipt of antiretroviral therapy achieve virological suppression (<50 copies/mL) within a year of beginning treatment (18). Those who achieve virological suppression can almost eliminate their risk of sexually transmitting HIV (19). In relation to late HIV diagnosis, among heterosexuals diagnosed with HIV in

England and Wales between 2000 and 2004, those diagnosed very late (CD4 cell count <200 cells/mm3) were nine times more likely to die in the year following diagnosis than those diagnosed earlier (20).

1.2 Research on heterosexually-acquired HIV infection in E,W&NI

In 2008 I submitted my application for a research degree to City University London to examine the epidemiology of heterosexually-acquired HIV in E,W&NI in greater detail. As part of my application, I conducted a literature search on the epidemiology of heterosexually-acquired HIV in E,W&NI. My search highlighted a gap in the literature as little had been published on this subject prior to the submission of my application.

I was only able to identify three papers published in peer-reviewed journals up to 2008 which focused on the epidemiology of heterosexually-acquired HIV in E,W&NI. In 2003, a paper describing the epidemiology of HIV infection among African communities in the UK (the majority of whom acquired HIV heterosexually) was published (21). In 2005, a research letter presenting the annual number of heterosexuals diagnosed with HIV in the UK was published (22), and a year later a paper on late HIV diagnosis and mortality among heterosexuals in England and Wales was published (20).

The relative absence of published papers on HIV among heterosexuals in E,W&NI may have been explained by research having focused on the group most likely to acquire HIV in the UK, namely MSM. Until recently it was thought the overwhelming majority of heterosexuals acquired their HIV infection abroad (23, 24). On the other hand, among MSM, the rate of HIV transmission within the UK has been and remains high (3). In the years leading up to my registration for a PhD, a substantial body of research on HIV among MSM in the UK had been published (25-34). In comparison, relatively little had been published on HIV among heterosexual men and women in the UK. Clearly there was a gap in the research literature which further motivated me to examine the epidemiology of heterosexually-acquired HIV in E,W&NI.

1.3 Research question and objectives

The overarching research question of my thesis is "*How is the epidemiology of heterosexually-acquired HIV infection evolving, particularly among black Africans, in England, Wales and Northern Ireland?".* To answer this research question, I have formulated six objectives. My objectives are to:

1. analyse epidemiological data and undertake literature searches to highlight who is at risk of heterosexually-acquired HIV in E,W&NI;

2. consider challenges in accurately ascertaining epidemiological trends in heterosexually-acquired HIV, and design new methods to improve precision;

3. explore the quality of HIV care provided to HIV-diagnosed heterosexuals in E,W&NI by examining key indicators of care available from routine HIV surveillance data;

4. examine the impact of migration on the heterosexual transmission of HIV in E,W&NI and consider whether a "*home-grown*" epidemic has developed among both heterosexuals born abroad and those born in the UK;

5. conduct research into HIV tuberculosis co-infection among heterosexuals in E,W&NI and consider the role of testing for HIV in tuberculosis clinics and vice-versa;

6. investigate HIV testing trends among heterosexuals in E,W&NI and why high rates of undiagnosed HIV and late presentation persist in this group.

In objective 4, "*home-grown*" refers to HIV infections acquired in the UK rather than abroad. Among persons born abroad, it also refers to HIV infections acquired post arrival in the UK rather than prior to arrival.

1.4 The thesis

I have written a PhD by prospective publication. My thesis includes six peer-reviewed papers published in national and international journals. I wrote and published five papers after I had registered for my PhD at City University London in 2009; one paper was published shortly before registration. My role and that of the co-authors of the six published papers is described in Appendix i.

The papers are embedded in four chapters where I explore some of the issues raised by the papers. In addition to this Introduction and the four chapters, my thesis includes a Methods and a Conclusions chapter. In table 1.1, I provide a summary of the structure of the thesis and the six peer-reviewed papers.

Table 1.1: Structure of the thesis including the published papers

Chapter title	Peer-reviewed publication
Chapter 1: Introduction	-
Chapter 2: Methods	-
Chapter 3: Trends in heterosexually-acquired HIV in England, Wales and Northern Ireland	Rice BD, Sinka K, Patel B, Chadborn T, Delpech V. The changing epidemiology of diagnosed prevalent HIV infections in England: greatest impact on the London environs. *Epidemiol & Infect* 2007; **135**:151-158. Rice B, Elford J, Yin Z, Croxford S, Brown A, Delpech V. Trends in HIV diagnoses, HIV care and uptake of antiretroviral therapy among heterosexual adults in England, Wales and Northern Ireland. *Sex Transm Dis* 2014; **41**(4): 257-265
Chapter 4: Migration	Rice BD, Elford J, Yin Z, Delpech D. A new method to assign country of HIV infection among heterosexuals born abroad and diagnosed with HIV in the UK. *AIDS* 2012; **26**(15): 1961-1966. Rice BD, Delpech VC, Chadborn TR, Elford J. Loss to follow-up among adults attending HIV-services in England, Wales and Northern Ireland. *Sex Transm Dis* 2011; **38**(8):685-690.
Chapter 5: HIV and tuberculosis co-infection	Rice BD, Elford J, Yin Z, Kruijshaar M, Abubakar I, Lipman M, *et al*. Decreasing incidence of tuberculosis among HIV diagnosed heterosexuals in England and Wales. *AIDS* 2013; **27**(7):1151–1157.
Chapter 6: HIV testing	Rice BD, Delpech V, Sadler KE, Yin Z, Elford J. HIV testing among black Africans living in England. *Epidemiol & Infec* 2012; **141**:1741–1748.
Chapter 7: Conclusion	-

1.4.1 Thesis outline

Chapter 1: Introduction

In this Introduction I present my research question and objectives, and describe the structure of my thesis. To provide background to the thesis, I present a summary of the epidemiology of HIV in E,W&NI between 1982 and 2012 and comment on research focusing on heterosexually-acquired HIV.

Chapter 2: Methods

Five of the peer-reviewed papers are based on the quantitative analysis of data collected through routine national HIV surveillance. For the sixth paper, data collected as part of a community-based survey are analysed. In the Methods chapter, I describe each of the datasets I use and explain my role in collecting, processing and analysing the data for my thesis. I discuss the strengths and weaknesses of the data and describe how data confidentiality is maintained.

Chapter 3: Trends in heterosexually-acquired HIV in England, Wales and Northern Ireland

In Chapter 3, I examine trends in heterosexually-acquired HIV in E,W&NI. The chapter includes two peer-reviewed published papers.

The first of the two peer-reviewed papers, published in *Epidemiology & Infection* in 2007, is called "*The changing epidemiology of diagnosed prevalent HIV infections in England: greatest impact on the London environs*" (35). In the paper, I explore the heterogeneous growth of the HIV epidemic in England between 1997 and 2004. I also present projections for the number of people living with HIV for the period 2005 to 2007, based on observed trends between 1997 and 2004. The second paper, published in *Sexually Transmitted Diseases* in 2014, is called "*Trends in HIV diagnoses, HIV care and uptake of antiretroviral therapy among heterosexual adults in England, Wales and Northern Ireland*" (36). In the paper, I present overall trends in HIV diagnoses and quality of HIV care among heterosexual adults in E,W&NI between 1992 and 2011. For the period 2002 to 2011, I investigate trends among heterosexuals in late HIV diagnoses, first AIDS diagnosis, prompt integration into HIV care, uptake of antiretroviral therapy, and short-term mortality.

In the accompanying text I explore the accuracy of the epidemiological predictions I made in the first paper. I also investigate differences in late HIV diagnosis and quality of HIV care among heterosexuals reported in the second paper as well as examining an observed increase over time in average age at HIV diagnosis.

Chapter 4: Migration

The majority of heterosexual adults newly diagnosed with HIV in E,W&NI are born abroad (3). This raises several questions. What is the role of migration in shaping overall trends in HIV diagnoses among heterosexuals in E,W&NI? Has migration resulted in a wider "*home-grown*" epidemic developing among heterosexuals in E,W&NI? As well as inward migration, does outward migration influence the number of heterosexuals seeking HIV care annually? What are the challenges in accurately assessing the impact of migration on heterosexually-acquired HIV in E,W&NI? How best to define migrants and migration in relation to HIV? In Chapter 4 I consider these questions.

Chapter 4 consists of two peer-reviewed papers plus accompanying text. The first of the two papers, published in *AIDS* in 2012, is called "*A new method to assign country of HIV infection among heterosexuals born abroad and diagnosed with HIV in the UK*" (24). In the paper, I introduce and apply a new technique for ascertaining where HIV was acquired among adults born outside of the UK. The second paper, published in *Sexually Transmitted Diseases* in 2011, is called "*Loss to follow-up among adults attending HIV-services in England, Wales and Northern Ireland*" (37). In the paper, I explore annual patterns of attendance at HIV services among HIV-diagnosed adults between 1998 and 2007. I focus on the extent to which HIV-diagnosed adults are lost to follow-up or attend services intermittently, and investigate predictors of loss to follow-up. I put forward outward migration from the UK as one explanatory factor for loss to follow-up.

In the accompanying text I explore different definitions of migration and migrants both in the general population and in relation to HIV. I examine the impact of inward and outward migration on the epidemiology of heterosexually-acquired HIV infection in E,W&NI, and consider whether a "*home-grown*" epidemic has developed among heterosexuals either born abroad or born in the UK.

Chapter 5: HIV and tuberculosis co-infection

Globally, tuberculosis is the leading cause of illness and death among people living with HIV (38). In 2012, HIV-associated tuberculosis was estimated to have killed 320,000 people worldwide (38). The highest rates of HIV-associated tuberculosis are seen in sub-Saharan Africa countries (38). In the UK, the majority of heterosexual men and women diagnosed with HIV are born in sub-Saharan Africa where the prevalence of both HIV and tuberculosis is high (3).

Chapter 5 consists of a peer-reviewed paper plus accompanying text. The paper, published in *AIDS* in 2013, is called "*Decreasing incidence of tuberculosis among heterosexuals living with diagnosed HIV in England and Wales*" (39). As the title suggests, in the paper I report that the annual tuberculosis incidence rate among heterosexual adults living with diagnosed HIV in England and Wales has declined over time. Despite this decline the tuberculosis incidence rate in the study population remains significantly higher than in the general population of England and Wales. In the paper I highlight missed opportunities for earlier HIV testing.

In the accompanying text I consider HIV tuberculosis co-infection in other European countries and reflect on the role of migration. I also investigate HIV TB service provision both in the UK and elsewhere in Europe.

Chapter 6: HIV testing

Rates of undiagnosed HIV and of late HIV diagnosis are elevated among black African heterosexual men and women in E,W&NI (3). This suggests that uptake of HIV testing is sub-optimal for this population group. Undiagnosed HIV is a driver of HIV transmission (17), and late presentation is a major risk factor for HIV-related morbidity and mortality (20).

Chapter 6 consists of a peer-reviewed paper plus accompanying text. The paper, published in *Epidemiology & Infection* in 2012, is called "*HIV testing in black Africans living in England*" (40). In the paper, I present results from a community-based cross-sectional survey of HIV prevalence, sexual attitudes and lifestyles among black African adults attending commercial and social venues in London, Luton, and the West Midlands in 2004 (41). I present the percentage of participants having tested for HIV in

the previous 24 months or having ever tested. In the paper, I also explore the association between perceived risk of HIV and HIV testing.

In the accompanying text I report on HIV testing among black Africans since 2004 in this country. I also explore late HIV diagnosis and undiagnosed HIV among black Africans, and investigate barriers to, and triggers for, HIV testing among this group.

Chapter 7: Conclusions

In the final chapter of my thesis, I summarise the findings from my six peer-reviewed published papers and the accompanying text in Chapters 3, 4, 5 and 6. I describe what I have discovered that is new and discuss the public health importance and impact of my research. I also describe the methodological innovations introduced through my research, and discuss the strengths and limitations of my analysis. Finally, I make recommendations based on the research contained in my published papers and thesis chapters.

2. Methods

Summary

This thesis is based on an analysis of quantitative data collected through routine national surveillance in E,W&NI and a community-based survey in England. Throughout this chapter I place emphasis on three national HIV surveillance systems which underpin the majority of my analysis. The three systems are the New HIV Diagnoses database, the Survey of Prevalent HIV Infections Diagnosed and the CD4 surveillance system. These three systems constitute the HIV and AIDS Reporting System.

In this chapter, I provide a description of each of the datasets I utilised and provide details on the providers of these data. I outline ethical issues, discuss data confidentiality, and explore the strengths and limitations of using surveillance data for my analysis. I describe my role in relation to HIV surveillance data management and analysis and in developing and introducing new surveillance methodologies. Finally, I provide details of the literature reviews I conducted.

2.1 HIV and AIDS Reporting System in E,W&NI

Most of my analysis is based on data from the HIV and AIDS Reporting System (HARS). The HARS consists of three national surveillance systems: (i) the New HIV Diagnoses database; (ii) the Survey of Prevalent HIV Infections Diagnosed (SOPHID); (iii) the CD4 Surveillance Scheme (42).

Data from HARS are used at the local, regional and national level in E,W&NI to monitor trends in the epidemiological characteristics of adults newly diagnosed with HIV and adults seen for HIV-related care. The data are also used to monitor trends in the diagnosis of AIDS defining illnesses and deaths (HIV and non HIV-related) in HIV-infected adults. The data are utilised by health professionals (including HIV clinicians, public health specialists, and researchers), and HIV professional bodies, charities, and governmental / non-governmental organisations (including the British HIV Association, the All-Party Parliamentary Group on HIV and AIDS, the Terrence Higgins Trust, and the National AIDS Trust).

Health professionals and organisations at the local, regional and national level in E,W&NI use HARS data for the following purposes: evaluate the impact of HIV testing

strategies; assess the quality of HIV care; design strategies to reduce HIV transmission and HIV-associated morbidity and mortality; determine the prevalence of diagnosed HIV; support the commissioning of HIV treatment, care, and prevention services; predict demands on local health and social services. The HARS is hosted at Public Health England.

2.1.1 Public Health England

Public Health England (PHE) is an executive agency of the Department of Health formally established in April 2013 (43). Prior to April 2013, the Health Protection Agency (HPA) was responsible for the national surveillance of HIV in E,W&NI. The HIV and STI Department of PHE is the national centre for the surveillance of HIV and other sexually transmitted infections in E,W&NI (42). The aims of the HIV and STI Department include describing trends in the prevalence and incidence of HIV, monitoring the transmission of HIV in at risk populations, and providing information for planning, targeting and evaluating prevention activities aimed at reducing risk behaviours and interrupting the transmission of HIV.

2.1.2 New HIV Diagnoses database

The New HIV Diagnoses database was established in 1982. The database receives voluntary and confidential reports of new HIV diagnoses, first AIDS diagnoses, and deaths in HIV-infected adults. Data are collected during two six monthly reporting periods (January to the end of June and July to the end of December). The variables collected are listed in table 2.1.

The database is a dual reporting system. Reports are received from sites where adults test for HIV and laboratories conducting HIV diagnostic testing. In 2011, 296 laboratories, genito-urinary medicine clinics, GP practices and other services where HIV testing takes place in E,W&NI reported to the New HIV Diagnoses database.

Table 2.1: HIV and AIDS Reporting System - data variables (as of end 2013)

Information collected	New HIV Diagnoses		SOPHID	CD4 Surveillance
	Laboratory	Clinic		
Date of HIV diagnosis in the UK*	x	x		
Place of HIV diagnosis in the UK*	x	x		
Place where last seen for HIV care*			x	
Postcode of residence**			x	
Clinic ID	x	x	x	
Laboratory ID	x			x
HIV sub-type	x	x		
Previous HIV test history	x	x		
Reason for test		x		
Pregnant at HIV diagnosis		x		
Symptoms		x		
CD4 cell count		x	x	x
Date of CD4 cell count		x	x	x
Viral load		x	x	
Date of viral load		x	x	
Sex*	x	x	x	x
Date of birth (from which age is derived)*	x	x	x	x
Soundex code* ***	x	x	x	x
Initials	x	x	x	
Probable route of HIV infection**	x	x	x	
Probable country of HIV infection**		x		
Ethnicity**	x	x	x	
Country of birth		x		
Year of arrival in the UK		x		
AIDS diagnosis		x	x	
AIDS indicator disease		x		
Date of AIDS		x	x	
Date of death		x	x	
Cause of death		x		
Antiretroviral therapy			x	
Date started ART			x	

* Mandatory fields required for a report to be entered and on which follow-up is conducted if missing

** Key fields on which follow-up is conducted if missing

*** A soundex code is a four character coding of an adults surname (the initial letter followed by three numbers)

Testing laboratories are encouraged to report new HIV diagnoses using either the laboratory report paper form or the Microsoft Excel laboratory report worksheet (forwarded via secure email on a six monthly basis). Sites conducting HIV testing (for example, genitourinary medicine clinics, infectious disease units, primary care services, and private healthcare facilities) are encouraged to report new HIV diagnoses, first AIDS diagnoses, and deaths in HIV-infected adults using either the clinician HIV report paper form or the Microsoft Excel clinician report worksheet. The laboratory and clinician HIV report forms are presented in Appendix ii.

Having entered all reports received to the end of June or December on the system, the New HIV Diagnoses dataset is archived. Data entry is suspended and validations are conducted to create a dataset representing all diagnoses to the end of the reporting period.

2.1.3 Survey Of Prevalent HIV Infections Diagnosed

The SOPHID is a cross-sectional survey of all adults with diagnosed HIV infection who attend for HIV-related care within the National Health Service (NHS) in E,W&NI in a calendar year. The survey began in 1995 and is funded by the Department of Health and the London Specialised Commissioning Group. The survey is run twice a year (January to the end of June and July to the end of December) in London, Brighton, Hastings and Eastbourne, and annually (January to the end of December) in the rest of E,W&NI.

Following the end of a survey period, reports of adults seen for HIV-related care are forwarded to PHE in electronic batches using the Microsoft Excel SOPHID report worksheet (forwarded via secure email). In 2011, 216 sites providing HIV care (for example, NHS HIV outpatient clinics and infectious disease units) reported to SOPHID. In table 2.1 I list the variables collected. The annual cross-sectional surveys are linked to create a cohort of adults seen for HIV care. I describe the method for linking surveys in section 2.6.1. In Appendix ii, I present the SOPHID metadata file.

2.1.4 CD4 Surveillance Scheme

The CD4 Surveillance Scheme monitors national trends in immunosuppression among HIV-infected adults. This is done through the collection and analysis of CD4 cell counts reported to PHE by laboratories across E,W&NI which perform CD4 T-lymphocyte counts and are registered with the National External Quality Assessment Scheme for

Leukocyte Immunophenotyping (44). Data are reported electronically bi-annually, quarterly, or monthly to suit individual laboratories using the Microsoft Excel CD4 surveillance report worksheet. In 2011, 64 laboratories reported to the CD4 Surveillance Scheme. The variables collected through CD4 surveillance are listed in table 2.1.

2.1.5 Data linkage within HARS

In all three national surveillance systems no names are collected or held. Instead, a soundex code in combination with sex and date of birth provides a unique identifier for each adult reported to HIV surveillance. A soundex code is a four character coding of an adults surname (the initial letter followed by three numbers) (45). The code is created by applying an algorithm that encodes the first three consonants after the initial letter to numbers ranging between one and six (for surnames that contain less than three consonants zeros are added). The unique identifier is used to link records within and between the three national surveillance systems, a process that is integral to routine data processing and management. As I indicate in table 2.1, soundex code, sex and date of birth are all mandatory fields (fields that must be completed for a record to be entered on to HARS).

2.2 Additional data sources

I used two additional datasets held at PHE for my analysis: (i) Enhanced Tuberculosis Surveillance; (2) Mayisha II study. I also used information from national death registrations and the Index of Multiple Deprivation.

2.2.1 Enhanced Tuberculosis Surveillance

Enhanced Tuberculosis Surveillance commenced at the beginning of 1999 in England and Wales, and the start of 2000 in Northern Ireland. The main objective of Enhanced Tuberculosis Surveillance is to provide detailed demographic, clinical and microbiological information on pulmonary and extra pulmonary tuberculosis diagnoses in E,W&NI (46). Testing sites (for example, tuberculosis clinics, chest clinics, primary care services, and private healthcare facilities) are encouraged to report all new diagnoses of tuberculosis via a web-based system. Information is received from all tuberculosis diagnosing sites in E,W&NI, and the data are held at PHE.

To promote data quality, an annual data audit is undertaken based on criteria suggested in the 2007 Department of Health TB Toolkit for planning, commissioning and delivering high-quality services in England (47). Local and national data audits and evaluations are conducted on data quality, system user satisfaction, and mechanisms for implementing data quality improvement. The completeness of key fields is regularly reviewed.

Key fields include name, date of birth, sex, place of diagnosis, ethnicity, country of birth, previous tuberculosis treatment history, start of tuberculosis treatment, previous diagnosis of tuberculosis, sputum smear status (pulmonary cases only), site of disease, and treatment outcome. For my analysis of HIV and tuberculosis co-infection, the following Enhanced Tuberculosis Surveillance fields were used: surname (converted by the tuberculosis surveillance team at PHE to a soundex code); date of birth; sex; place of tuberculosis diagnosis; date of tuberculosis diagnosis.

2.2.2 Mayisha II study

The Mayisha II study was a community-based survey of sexual attitudes and lifestyles among black African communities in England (London, Luton, and the West Midlands) conducted by the HPA (now PHE) in 2004 (41, 48, 49). The study was supported by a grant from the Medical Research Council, and approved by the Trent Multi-centre Research Ethics Committee, following a successful feasibility and acceptability pilot study in 2004 (49). Fieldwork was conducted in community-identified social and commercial venues (including bars, clubs, universities, churches, shops, barbers, hairdressers and community events) in London, Luton, and the West Midlands between August and December 2004.

The study consisted of a cross-sectional community-based survey and a nested qualitative study. For my analysis, I focused on the community-based survey. The survey included an anonymous self-completion questionnaire (available in English and French) of 24 questions relating to demographics, health service use, and sexual behaviour and attitudes, and an optional oral fluid sample (using an OrasureTM device) for anonymous testing for HIV antibodies. Samples were forwarded to, stored and tested at the HPA for anti-HIV-1/2 antibodies.

The following fields from the Mayisha II study were included in my analysis: current HIV status (as reported by the participant and confirmed by a laboratory test result); HIV test history (whether previously tested for HIV and, if so, when and where the test was conducted); sex; age; country of birth; length of time living in the UK (for participants born abroad); highest level of formal education achieved; condom use at last sexual intercourse; number of sexual partners in the past 12 months; if ever diagnosed with a sexually transmitted infection other than HIV; perceived risk of catching HIV. Variable completion in the Mayisha II study was high.

2.2.3 National death registrations

Deaths among people living with diagnosed HIV are reported directly by clinics to the New HIV Diagnoses database and SOPHID. These reports are supplemented by national death registrations from the Office of National Statistics (ONS) (50). The ONS is the executive office of the UK Statistics Authority, an independent body operating at arm's length from government as a non-ministerial department, directly accountable to Parliament (51). National death registrations are received from the ONS via monthly, quarterly and annual files.

Monthly files, which are received by PHE soon after the end of the month, include deaths where HIV and/or AIDS were recorded on the death certificate. Monthly files also include causes of death that are unusual in non HIV-infected individuals (for example Kaposi's sarcoma or *Pneumocystis* pneumoni).

Quarterly files, which are received by PHE soon after the end of the quarter, contain all deaths in persons aged ≤60 years reported that quarter, regardless of when the death occurred. This means that adding together four quarterly files in a year does not equate to the number of deaths in a given year (for example, some deaths occurring in 2011 will not be reported until 2012 or later, while some deaths for earlier years will have been reported during 2011).

Annual files contain all deaths in persons aged ≤60 years occurring within a calendar year. To ensure annual files are accurate and include underlying cause of death (a field not included in the quarterly file), there is an eighteen month reporting delay. Underlying cause of death is not part of the public death certificate and may be used to

record HIV status for persons where the family has objected to such information being made public.

Augmenting deaths reported directly to the two national HIV systems with ONS death registrations (through data linkage on soundex code, sex and date of birth) helps ensure deaths among HIV-infected patients who have died in the community and/or of a non-HIV-related event are also identified. The Births and Deaths Registration Act (1836) makes it a legal requirement for all deaths to be registered in the UK (52).

2.2.4 The Index of Multiple Deprivation

The Index of Multiple Deprivation (IMD) is part of the English Indices of Deprivation (53). The English Indices of Deprivation is calculated by The Department for Communities and Local Government, a UK ministerial department which has calculated local measures of deprivation in England since the 1970s (54).

In 2010, the English Indices of Deprivation used 38 separate indicators organised across seven distinct domains of deprivation. These indicators were subsequently combined, using appropriate weights, to calculate the IMD. The IMD is used to rank every Lower Layer Super Output Area (LSOA) in England according to their relative level of deprivation (an LSOA is an aggregation of postcodes and typically contains a population of around 1500 people; LSOAs were developed by the ONS to produce areas of consistent size and stable boundaries) (55). Adults seen for HIV care in England, and reported to SOPHID, are assigned to an LSOA based on their postcode of residence. According to their LSOA, adults are assigned an IMD score.

2.3 Ethical issues and data confidentiality

For all PHE surveillance systems strict attention to confidentiality is maintained at every stage of data collection, analysis and storage. The HIV systems held at PHE are designed to directly support the public health surveillance of HIV infection in E,W&NI. Therefore, it is required that all fields collected within these systems add value to surveillance outputs. Limited patient identifiers are collected to aid the identification and removal of duplicate records and to link records across surveys and systems.

The NHS Trusts and Primary Care Trusts (Sexually Transmitted Diseases) Directions 2000 (56), enables PHE to collect HIV data without consent for surveillance and

prevention services from NHS trusts. Through National Information Governance Board for Health and Social Care approval under section 251 (57), PHE is legally covered to collect HIV data without consent from outside of trusts. The Patient Information Advisory Group approved the 2001 application from the Public Health Laboratory Service (predecessor to the HPA and PHE) for the use of patient data (including HIV data) without consent (58). Approval is renewed each year by the National Information Governance Board for Health and Social Care through the section 251 annual review process.

Statutory Instrument 2002 No. 1438 in The Health Service (Control of Patient Information) Regulations 2002 provides the legal basis for the handling of HIV data (59). Public Health England is registered under the Data Protection Act 1998 (registration number Z7749250) to handle data for diagnostic, public health and other purposes (60). All records are kept securely in compliance with the Caldicott Guidelines (61). All PHE staff have a legal duty to keep patient information confidential.

All personal health information is stored at PHE on secure servers and all databases are password protected. Access to disaggregate HARS data is strictly limited to those directly involved in the collation of the data.

2.4 Strengths and limitations of HIV surveillance data for my thesis

The majority of my analysis is based on data from HARS. There are both advantages and disadvantages in using established, pre-collected data to answer my research question.

In E,W&NI, HIV care through the NHS is open access and free at point of contact, and all NHS sites providing HIV care, and all HIV diagnostic laboratories, are encouraged to report to HARS. Recognising the need for clinician co-operation, regular contact is made with reporting sites, and both routine and bespoke site-specific outputs are made available by PHE. Recognising the need for clinicians to focus on the medical needs of their patients the collection of risk behaviour information in HARS is kept to a minimum.

2.4.1 Advantages of using HARS data

An evaluation by internal and external stakeholders conducted in 2007 and 2008 of all HIV and STI national surveillance systems in E,W&NI considered the utility of HARS data. The evaluators concluded that the three components of HARS provided important and vital HIV statistics used to describe the HIV epidemic in the UK, and that the data were both comprehensive and valid (62).

Comprehensive

Only laboratory confirmed cases of HIV are reported to the New HIV Diagnoses database. For a record of a newly diagnosed adult to be included in the database their site and date of diagnosis, soundex code, sex, and date of birth must be present. To reduce underreporting, both laboratories and clinics are encouraged to report a new diagnosis of HIV, and reporting sites that either have not reported, or have reported fewer patients than might be expected based on previous reports, are identified and contacted. To further minimise underreporting, SOPHID records identified as new HIV diagnoses during the specified year are linked to the New HIV Diagnoses database. Records in SOPHID without a match in the New HIV Diagnoses database are added to the latter system.

SOPHID receives data from all NHS sites providing HIV care. For a record of an adult seen for HIV care to be included in SOPHID their site and date seen for care, soundex code, sex, date of birth, and place of residence must be reported. Reporting to SOPHID is directly linked to funding allocation of local HIV services. Non-reporting NHS sites that might be providing HIV-related care are identified and contacted. Sites that either have not reported, or have reported fewer patients than might be expected based on previous reports, are subsequently contacted.

All laboratories carrying out CD4 cell counts in E,W&NI registered with the National External Quality Assessment Scheme for Leucocyte Immunophenotyping are invited to participate in the CD4 surveillance scheme (44). The NEQAS list is regularly checked to identify and invite new laboratories carrying out CD4 cell counts.

The reporting of a first AIDS diagnosis at time of an HIV diagnosis is likely to be comprehensive as HIV and AIDS diagnoses can be reported to the New HIV Diagnosis database jointly via the same electronic or paper form. The reporting of deaths among

HIV-infected persons is also likely to be comprehensive as notifications reported directly by clinics to the New HIV Diagnoses database and SOPHID are supplemented by death notifications from the ONS.

Valid

All HIV data received by PHE are checked for duplicate records and missing or inaccurate information. Through routine data linkage within and between the New HIV Diagnosis database and SOPHID duplicate records are identified and removed from final amalgamated datasets. Missing and inaccurate information are identified through routinely run validation checks.

Validation checks are applied to individual records (for example, sex is male if route of infection is sex between men), and to records pertaining to the same adult reported over time to a single system (for example, ethnicity is consistently reported over time). Validation checks are also applied to records pertaining to the same adult reported to two or more systems (for example, if an adult is reported as having died to the New HIV Diagnoses database a validation check is conducted to see whether they were subsequently reported to SOPHID as having been seen for HIV care).

Data linkage within and between the national surveillance systems is conducted to populate missing information (for example, probable route of infection is reported to SOPHID but not to the New HIV Diagnoses database) and update inaccurate information where possible (for example, an adult reported to multiple annual SOPHIDs was reported as white to all but one survey). Where information is still missing or inaccurate, follow-up is undertaken with clinicians, health advisors, or data managers for all key / mandatory fields (see table 2.1).

Available

The data, which underpin the majority of my analysis, are not only comprehensive and accurate but also readily available for analysis. It would not have been feasible for me, singlehandedly, to assemble a comparable dataset for the purpose of my thesis.

2.4.2 Disadvantages of using HARS data

Fixed variables with limited range

To promote reporting and encourage clinician co-operation the HARS dataset is kept to a minimum (see table 2.1 for a list of variables collected). To facilitate regular reporting from all HIV diagnostic sites and sites providing HIV care across E,W&NI the HARS dataset is standardised and fixed. The HARS data I use for my analysis are therefore limited and inflexible. Although the data facilitate simple trend analysis at the national and sub-national level they do not provide insight or context for these trends.

Overestimating heterosexually-acquired HIV

Information on probable route of HIV infection has been described as being key to understanding the epidemiology of HIV (63). In relation to describing how the epidemiology of heterosexually-acquired HIV infection is evolving in E,W&NI, accurate information on probable route of HIV infection is crucial. The assignment of route of infection through surveillance, however, has been accused of both underestimating and overestimating heterosexual HIV transmission.

The potential for underestimation arises from the rigid and cautionary approach to assigning heterosexually-acquired HIV (6, 64, 65). The potential for overestimation arises from some MSM being misclassified as heterosexuals due to social stigma (66, 67).

In E,W&NI, probable route of infection is assigned through national HIV surveillance according to a hierarchy of risk. Heterosexual sex is at the lowest level of this hierarchy. To illustrate how the hierarchy is applied we may consider a newly diagnosed adult male reported by a clinic as having injected drugs and having had unprotected sex both with men and women. Based on current estimates of HIV prevalence, the primary route of infection for this adult male would be sex between men. Injecting drug use would be his secondary factor and sex with a woman his third. In the USA, where probable route of HIV infection is also applied hierarchically, it has been argued that the rigidity of assignment results in heterosexual HIV transmission being underestimated (6).

I would argue that it is unlikely that the figures I present in this thesis represent an underestimation of HIV diagnoses among heterosexuals in E,W&NI. The hierarchical

approach to HIV risk assignment would result in heterosexually-acquired HIV potentially being underestimated if it was applied regularly. In the seven years I was jointly responsible for coding probable route of infection on new HIV diagnoses reports I rarely applied hierarchical assignment in relation to potential heterosexual transmission. This was because few new HIV diagnoses reports presented heterosexual sex and one or more other probable route of infection.

It is likely that the figures I present in this thesis represent an overestimation of HIV diagnoses among heterosexuals in E,W&NI because of misclassification. For example, in Italy, where probable route of HIV infection is also assigned according to a hierarchy of risk, national HIV surveillance data were linked to data from the Italian Cooperative Group on AIDS-Related Tumours (67). Comparing probable route of HIV infection between the two systems, a lower level of concordance was observed among heterosexual men than among PWIDs or MSM (67). The results of the study led to the proposition that there was a pervasive tendency for some men to conceal their having sex with other men leading to heterosexual transmission being overestimated (66). In Florida, an in-depth case review of 168 people reported in 1989 and 1990 as having acquired "*AIDS*" heterosexually resulted in 50 having their risk reclassified (68). The majority were reclassified as PWIDs or MSM (68).

A potential explanation for why some PWIDs or MSM may be misclassified as having acquired HIV heterosexually is social stigma. It has been argued that the level of misclassification of route of infection among MSM will depend, in part, on the strength of social stigma in a country (67).

As a marker of social stigma in the UK, 6% of 2,092 lesbian, gay and bisexual people in England, Scotland and Wales responding to an online interview in 2012 reported that they expected to be treated worse than heterosexual people when accessing routine or emergency hospital treatment (69). Among gay people from black and minority ethnic backgrounds the figure was 12% (69). Related to this, it has been suggested some healthcare workers in the UK assume all black and minority ethnic people are heterosexual (70). These findings suggest the misclassification of probable route of infection among MSM may be limited overall but higher among black and minority ethnic groups.

Exclusion of heterosexuals living with undiagnosed HIV

Data from HARS relate only to persons diagnosed with HIV. In the UK, an estimated one in four heterosexuals living with HIV in the UK remain undiagnosed (3). Therefore, the numbers I present in this thesis relating to diagnosed heterosexuals systematically underestimate the true number of heterosexuals living with HIV.

Underreporting of AIDS diagnoses

In section 2.4.1, I suggested that the reporting of first AIDS diagnoses at the time of HIV diagnosis is likely to be comprehensive. Reports of first AIDS diagnoses subsequent to HIV diagnosis, however, are likely to be under-reported as no procedures are in place to encourage such reporting.

2.5 My role in HIV surveillance and monitoring

I have been employed within the HIV and STI department of PHE for two periods: April 2002 to May 2005 and September 2006 to the present day. During the first of these two periods I was the Lead Scientist for SOPHID. Between September 2006 and January 2011 I was Senior Scientist for New HIV Diagnoses. From January 2011 to the present day I have been a Principal HIV Scientist.

2.5.1 Lead Scientist for SOPHID

As Lead Scientist for SOPHID I was responsible for developing methodological changes concerning the surveillance of adults seen for HIV care. I was also responsible for designing and implementing audits of data quality, for maintaining the confidentiality of patient information, for coordinating all aspects of database management, and for disseminating results from the survey. I supervised a team of three scientists and administrators.

I introduced a number of methodological changes to the system which improved data comprehensiveness and validity, and facilitated analysis for this thesis. The methodological changes I introduced included linking the annual cross-sectional surveys to create a cohort of adults seen for HIV care, establishing a new secure document gateway for transferring electronic data, and introducing enhanced and timely data quality checks.

2.5.2 Senior Scientist for New HIV Diagnoses

In my role as Senior Scientist I oversaw all activities surrounding the national reporting of new HIV and AIDS diagnoses and deaths in HIV-infected individuals. I supervised a team of seven scientists and administrators. I introduced a number of methodological changes which facilitated analysis for this thesis. I introduced new methods of receiving, checking and conducting follow-up on new diagnoses to improve the quality, completeness and consistency of these data. I also introduced methodological changes to promote integration between the New HIV Diagnoses system and SOPHID.

In addition to my responsibilities for HIV surveillance, I was responsible for the safe storage and handling of Mayisha II study data, and for outputs generated from these data. I was also responsible for a number of HIV and STI departmental surveillance audits, reviews and evaluations. In 2007 and 2008 I was the departmental lead for an evaluation conducted by internal and external stakeholders of all HIV and STI national surveillance systems.

2.5.3 Principal HIV Scientist

As a principal HIV scientist I am responsible for cross-system operational support and scientific leadership on the development and management of routine, integrated surveillance outputs, and for ensuring consistency in data analysis methodologies, data presentation policies and surveillance operating procedures. As a scientific lead for HIV prevention monitoring, I represent the UK on a number of international advisory groups. These include the Joint United Nations Programme on HIV/AIDS (UNAIDS) Monitoring and Evaluation Reference Group Indicator Working Group (71), and the European Centre for Disease Prevention and Control (ECDC) advisory group to monitor the Dublin declaration on Partnership to Fight HIV/AIDS in Europe and Central Asia (72). As an advisory group member I helped successfully argue for the inclusion of migrants in the monitoring of the Dublin declaration.

I am / have been a co-applicant or work package lead on a number of European wide projects. These include the ECDC tendered project "*Migrant health: Sexual transmission of HIV within migrant groups in the EU/EEA and implications for effective interventions*" (73), the ECDC tendered project "*Revised HIV/AIDS surveillance in*

Europe, including collection of data about country of HIV infection" (74), and the European Union project "*Joint Action on Improving Quality in HIV Prevention*" (75).

2.6 My role in bespoke HIV data linkage and assigning country of HIV infection

2.6.1 Creating a cohort of adults seen for HIV care using SOPHID

I created with a colleague (Dr Valerie Delpech) a cohort of adults seen for HIV care using SOPHID. This was done by linking records across the 1998 to 2007 annual cross-sectional SOPHIDs on full identifiers (soundex code, sex, date of birth, and postcode of residence), and by applying a deterministic matching algorithm written to take into consideration a variety of possible matches based on part identifiers (see table 2.2). Deterministic matching applies a series of rules. Records are assigned as matches or non-matches according to whether the requirements of one of these rules have been met. The algorithm presented in table 2.2 was subsequently amended to also consider an adults clinic identification number. The algorithm is now routinely applied to annual surveys.

By linking the annual SOPHIDs to create a cohort of adults seen for HIV care it was possible to monitor, for the first time, patterns of attendance, loss to follow-up from care, and quality of HIV care provision. I explore these themes in Chapters 3 and 4 of this thesis.

Table 2.2: Data linkage algorithm

Full-matched identifiers	1	Full soundex, DOB and sex
Part-matched identifiers (identify transcription error)	2	Soundex initial, full DOB and sex
	3	Soundex numbers, full DOB and sex
	4	Full soundex, DOB month/year and sex
	5	Full soundex, DOB day/year and sex
	6	Full soundex, DOB day/month and sex
	7	Full soundex, DOB day/month of one record to month/day in another and sex

2.6.2 Data linkage between HIV and tuberculosis surveillance

To link individual level data on persons living with diagnosed HIV (as reported to HARS) with individual level data relating to diagnoses of tuberculosis (as reported to Enhanced Tuberculosis Surveillance) the HIV and tuberculosis surveillance teams at PHE (including myself) developed and applied probabilistic matching. Probabilistic matching considers the frequency and uniqueness of data and accounts for complex typographical errors. Considering soundex code, sex, date of birth, country of birth and residential postcode, the probability of two or more records belonging to the same adult was expressed as a percentage. Based on this percentage, records were assigned as matches, possible matches or non-matches. Possible matches were subsequently reviewed by a member of the research team and assigned as matches or non-matches. Data linkage between the HIV and tuberculosis systems facilitated my analysis for Chapter 5.

2.6.3 Assigning likely country of HIV infection

To identify people most at risk of acquiring HIV heterosexually whilst living in the UK I developed a new method to assign likely country of HIV infection. Assignment was based on CD4 cell count at diagnosis and year of arrival in the UK (data available from the New HIV Diagnoses database), estimated year of HIV infection, and estimated CD4 cell count at HIV infection.

To estimate year of HIV infection, my colleagues Dr Valerie Delpech and Dr Zheng Yin and I applied multilevel linear models with random effects to the square root of CD4 cell counts from date of first count to date of last count for eligible adults diagnosed with HIV between 1996 and 2010. A proxy date of infection was calculated for each adult based on the mid-point between date of last negative HIV test and date of first HIV positive test. An individual's CD4 cell count at infection was estimated by extrapolating the parameters of the multilevel linear models to the proxy dates of infection. I present the results of this analysis in Chapter 4 of this thesis.

2.7 Data analysis

For the purpose of this thesis I analysed, independently and combined, the New HIV Diagnoses, SOPHID, and CD4 surveillance datasets. I analysed Enhanced Tuberculosis Surveillance data in combination with merged HARS data. I analysed death

registrations as part of the New HIV Diagnoses database and IMD rankings as part of the SOPHID dataset. I analysed the Mayisha II dataset, which I cleaned and validated, independently.

Throughout this thesis, I define an adult as aged ≥15 years. The only exception is when presenting data from the Mayisha II study where I define an adult as ≥16 years (41, 48, 49).

2.7.1 Univariate and multivariate analysis

In this thesis, I applied multivariate logistic regression models to test for associations between variables. I include in multivariate logistic regression models explanatory variables found to be significantly associated with outcome variables in univariate analysis (either at the 95% or 99% level as stated in the published papers).

2.7.2 Statistical tests

I compared continuous variables using the Wilcoxon–Mann–Whitney test, and compared rates using the Pearson's χ^2 test. I used the Cochran-Armitage chi-square trend test for time-trend analysis. To model trends over time I applied a linear regression model. I applied longitudinal analysis of the trajectories of CD4 cell counts to model CD4 cell decline over time. Testing values and confidence intervals are, as indicated, either at the 95% or 99% level. I use STATA 8.2, 9.0, and 12.0 (Stata Corp., College Station, Texas, USA) for my analysis. Further information on my statistical analysis is included in each of the published papers.

2.7.3 Geography

Most of my analysis is based on data for E,W&NI (HARS; ONS national death registrations) or England only (MAYISHA II study; Index of Multiple Deprivation). Enhanced Tuberculosis Surveillance commenced at the beginning of 1999 in England and Wales, and the start of 2000 in Northern Ireland. To maximise the number of years included in the analysis for paper 5.1, I focused on England and Wales only. Much of the literature I identified in my computerised literature searches (see section 2.8) refers to the UK as a whole (i.e. includes Scotland). Where appropriate, in this thesis I refer to the UK, E,W&NI, England and Wales, or England only.

2.8 Literature review

In each of the four chapters within which I embed my published papers I identified topics raised in the papers for further exploration To this end, I undertook a computerised literature search around these topics using Ovid MEDLINE and EMBASE by means of City University London's Health and Society E-Resource Databases (76). I applied key terms to search article titles and abstracts for papers published in the English language. Research into HIV is fast moving and this has been particularly true since the widespread introduction of highly active antiretroviral therapy in the late 1990's. It is for this reason that the majority of my computerised literature searches focus on papers published from 2000 onwards. Publications with relevant titles were selected for abstract screening.

I conducted a review of the reference lists of key publications identified through my computerised literature searches. Publications of interest were obtained through title and / or author searches using PubMed Central and Google Scholar (77, 78). To identify grey literature, I conducted manual Internet key word searches using Google. The literature searches I conduct for the purpose of this thesis are presented in Appendix iii.

3. Trends in heterosexually-acquired HIV in England, Wales and Northern Ireland

Summary

In this chapter, I explore trends over time in heterosexually-acquired HIV in E,W&NI. The two published papers in this chapter examined: (i) trends among adults living with diagnosed HIV in England between 1997 and 2004 and (ii) trends in HIV diagnoses and quality of HIV care among heterosexual adults in E,W&NI between 1992 and 2011.

The first paper is called "*The changing epidemiology of diagnosed prevalent HIV infections in England: greatest impact on the London environs*" (35). In the paper I reported an increase in the number of HIV-diagnosed adults living in England between 1997 and 2004 and highlighted differences in this trend across three regions (London; London environs; rest of England). I also presented projections for the number of people living with HIV for the period 2005 to 2007, based on the trends for 1997 to 2004.

The second paper is called "*Trends in HIV diagnoses, HIV care and uptake of antiretroviral therapy among heterosexual adults in England, Wales and Northern Ireland*" (36). In the paper, I reported an increase in the number of HIV diagnoses among heterosexual men and women in E,W&NI between 1992 and 2004, followed by a steady decline to 2011. I also presented evidence for improvements over time in the quality of HIV care among heterosexuals, and report an increase in average age at HIV diagnosis.

In this chapter, I examine the accuracy of the epidemiological predictions I made in the first paper. In relation to the second paper, I examine differences in late HIV diagnosis and quality of HIV care by age, sex and other factors. I also investigate the increase over time in average age at HIV diagnosis.

3.1 Introduction

As described in Chapter 1, approximately six out of ten HIV diagnoses in E,W&NI between 1999 and 2012 were among heterosexuals (1). In this chapter, I investigate trends over time in heterosexually-acquired HIV in E,W&NI. The chapter includes two papers which I published in peer-reviewed journals. In the first paper I examined trends in the number of HIV-diagnosed adults living in England between 1997 and 2004, and made epidemiological predictions for the period 2005 to 2007 based on these trends. In the second paper I explored observed trends in HIV diagnoses and quality of HIV care among heterosexual men and women in E,W&NI between 1992 and 2011.

In this chapter, after summarising the key findings from the two papers I go on to explore the accuracy of the epidemiological predictions I made in the first paper. Considering the results presented in the second paper, I investigate differences in late HIV diagnosis and quality of HIV care by age, sex and other factors among heterosexuals. I also examine the increase over time in average age at HIV diagnosis.

3.2 The published papers

3.2.1 Rice et al., Epidemiology & Infection 2007

The changing epidemiology of diagnosed prevalent HIV infections in England: greatest impact on the London environs

http://www.ncbi.nlm.nih.gov/pubmed/16753075

Summary: Data from the 1997–2004 Surveys of Prevalent HIV Infections Diagnosed were analysed by three geographical areas of residence and treatment to describe the heterogeneous growth of the HIV epidemic in England and provide projections to 2007. Between 1997 and 2004, the number of diagnosed HIV-infected adults resident in England increased by 163 % (14 223 to 37 459). Within the 'London environs' the increase was 360 % (742 to 3411), within the rest of England 219 % (4417 to 14 088) and within London 120 % (9064 to 19 960). By 2004, the London environs had the largest proportion of infections acquired through heterosexual sex (and in particular women) and the most recently diagnosed population. Projections indicate over half of diagnosed HIV- infected adults will live outside London by 2007. The epidemiology of diagnosed HIV infection within the London environs is likely to be a predictor of future trends in England overall.

3.2.2 Rice et al., Sexually Transmitted Diseases 2014

Trends in HIV diagnoses, HIV care, and uptake of antiretroviral therapy among heterosexual adults in England, Wales, and Northern Ireland

http://www.ncbi.nlm.nih.gov/pubmed/24622638

Aim: To examine epidemiological trends among heterosexual adults (Q15 years) in England, Wales, and Northern Ireland (E,W&NI) newly diagnosed as having HIV between 1992 and 2011, or seen for HIV care in 2011.

Methods: Trend analyses of heterosexual adults newly diagnosed as having HIV in E,W&NI in 1992 to 2011 was performed, as well as univariate and multivariate analyses examining the late diagnosis of HIV, integration into care, AIDS, uptake of antiretroviral therapy, and mor- tality in 2002 to 2011. Data are as reported to the national HIVand AIDS Reporting System.

Results: The number of heterosexual adults newly diagnosed as having HIV in E,W&NI increased steadily between 1992 (731) and 2004 (4676), before declining (2631 in 2011). Nonetheless, in 2011, hetero- sexuals accounted for 49% (2631/5423) of all newly diagnosed adults in E,W&NI. Of 38,228 heterosexual adults as having HIV between 2002 and 2011, 72% were black African, of whom 99% were born abroad. Over the decade, there was an increase in the percentage of HIV diag- nosed heterosexuals integrated into care within 28 days of diagnosis (61%Y78%) and in receipt of antiretroviral therapy within 1 year of diagnosis (45%Y52%) and a decline in the percentage with AIDS (16%Y7%; all, P G 0.01). Late HIV diagnoses (CD4 G350 mm3) among heterosexuals exceeded 60% in all years.

Conclusions: Our analyses highlight the impact of migration on the epidemiology of heterosexually acquired HIV in E,W&NI. Although there was evidence of an improvement in clinical care over time, con- tinued high rates of late diagnosis suggest that current testing policies are failing among heterosexuals.

3.3 Research findings from my published papers

The first published paper in this chapter is called "*The changing epidemiology of diagnosed prevalent HIV infections in England: greatest impact on the London environs*" and was published in the journal *Epidemiology and Infection* in 2007 (35). In this chapter, it is referred to as paper 3.1. In the paper, I described how the number of HIV-diagnosed adults living in England increased between 1997 and 2004, and highlighted differences between three regions (London, London environs, and the rest of England). The London environs comprised nine 2001 health authorities, eight of which bordered London (Buckinghamshire, Hertfordshire, North Essex, South Essex, West Kent, East Surrey, West Surrey and Berkshire). The ninth health authority was Bedfordshire, and was included due to its proximity and links to London. In paper 3.1, I also presented projections for the number of people living with HIV for the period 2005 to 2007, based on trends from 1997 to 2004 (the last year for which data were available).

In paper 3.1 I reported a 360% increase between 1997 and 2004 in the number of HIV-diagnosed adults resident in the London environs. In the rest of England and London, increases of 219% and 120% were reported (respectively). Differences in trends among heterosexuals diagnosed with HIV mainly explained these differing patterns. By the end of 2004, the London environs had the largest percentage of diagnosed adults who acquired HIV heterosexually, and the largest percentage increase in the number of diagnoses among black Africans.

Applying a linear progression model to the observed data between 1997 and 2004, I predicted in paper 3.1 that the number of HIV-diagnosed heterosexuals living in London would exceed the number of diagnosed MSM resident in the capital in 2005. This phenomenon had already been observed in the London environs and the rest of England. I also predicted that half of all diagnosed adults would be living in the London environs and the rest of England by 2007 (in 2004, 47% of diagnosed adults in England were living in these two areas combined). Finally, I predicted that the epidemiology of diagnosed HIV infection within the London environs would be a predictor of future trends in England overall.

The second paper in this chapter is called "*Trends in HIV diagnoses, HIV care and uptake of antiretroviral therapy among heterosexual adults in England, Wales and*

Northern Ireland" and was published in the journal *Sexually Transmitted Diseases* in 2014 (36). In this chapter, it is referred to as paper 3.2. In the paper, I presented time trends in HIV diagnoses among heterosexuals in E,W&NI for the period 1992 to 2011. I also explored late HIV diagnosis, first AIDS diagnosis, prompt integration into HIV care, uptake of antiretroviral therapy, and short-term mortality for the period 2002 to 2011. These are considered to be proxies for the uptake of HIV testing and the quality of HIV care.

Following an increase between 1992 and 2004 in the number of heterosexuals diagnosed with HIV in E,W&NI, I reported in paper 3.2 a steady decline in diagnoses between 2005 to 2011. Behind this overall decline was a reduction in the number of diagnoses among black Africans, the majority of whom were born in sub-Saharan Africa.

In paper 3.2 I presented evidence for HIV care among heterosexuals improving over time. The percentage of heterosexuals in the study population diagnosed with AIDS declined between 2002 and 2011. Over the same time period, the percentage of heterosexuals promptly integrated into care or starting antiretroviral therapy within one year of HIV diagnosis increased. The decline between 2010 and 2011 in table 2 of paper 3.2 in the percentage of heterosexuals starting antiretroviral therapy within one year of HIV diagnosis is due to the analysis being conducted only to the end of 2011. For the majority of persons diagnosed in 2011 uptake of antiretroviral therapy was monitored for less than 12 months.

Despite a slight decline over time (which was not statistically significant), the percentage of heterosexuals reported in paper 3.2 as diagnosed late with HIV (CD4 cell count <350 cells/ml) between 2002 and 2011 remained high at 64%. In the paper, a late HIV diagnosis was shown to be strongly associated with short-term mortality (a death within one year of HIV diagnosis). This finding highlights the need for improved HIV testing strategies among heterosexuals in E,W&NI.

In paper 3.2, I also presented evidence of median age at HIV diagnosis increasing between 1992 and 2011. Among men median age at diagnosis increased from 33 to 41 years, and among women from 28 to 36 years.

In the remaining part of this chapter I assess the validity of my predictions in paper 3.1 on future epidemiological trends. Considering the results presented in paper 3.2, I investigate differences in late HIV diagnosis and quality of HIV care by age, sex and other factors. I also explore the increase over time in age at HIV diagnosis. I finally make recommendations based on papers 3.1 and 3.2 and the analysis in this chapter.

3.4 Literature search

The two published papers in this chapter raised a number of issues which I described in the previous section. Using the methods I described in Chapter 2 (section 2.8), I conducted computerised and manual literature searches in relation to these topics. The main topics were: (i) utility of surveillance data to predict HIV trends; (ii) quality of HIV care; (iii) late HIV diagnosis; (iv) older age at HIV diagnosis. Appendix iii lists details of the searches conducted for this chapter. The identified papers provide the foundation for the rest of this chapter.

3.5 Predicting future epidemiological trends

In paper 3.1, I extrapolated national HIV surveillance data for England for the period 2001 to 2004 to provide estimates for 2005 to 2007. Ten years later, it is possible to look back and reflect on the accuracy of my estimates. At the time of this analysis the SOPHID cohort did not exist and therefore I was not able to follow individuals over time.

3.5.1 Reasonable approximations

Two predictions which I made in paper 3.1 were more or less borne out. In paper 3.1 I predicted an increase in the number of heterosexuals living with diagnosed HIV in England from 18,554 in 2004 (observed figure) to 28,053 in 2007. The number of heterosexuals living with diagnosed HIV in England did in fact increase between 2004 and 2007 (as I had predicted) but the actual number in 2007 was 26,520 rather than the 28,053 I predicted (1). Why did my predicted number slightly exceed the actual number?

The predictions presented in paper 3.1 were based on the assumption that observed trends in the number of people seen for HIV care up to 2004 would continue. Overall trends in the number of people seen for HIV care are influenced by the annual number

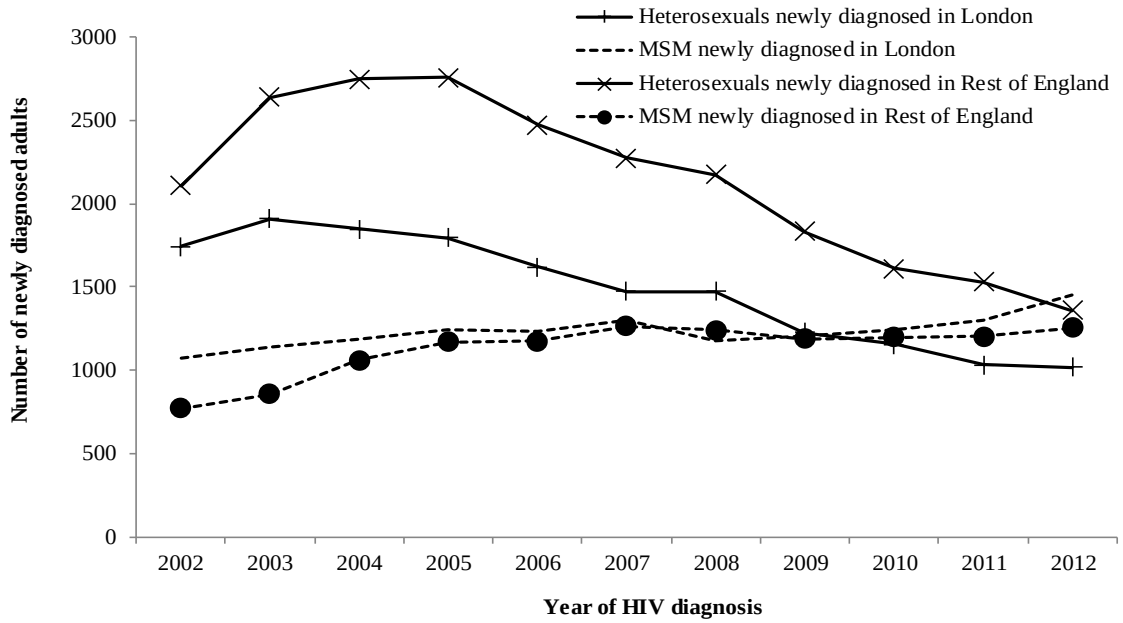
of new HIV diagnoses. My predictions for the years 2005 to 2007 were mainly based on the observed increase in HIV diagnoses up to 2004 continuing. However, as I highlighted in paper 3.2, between 2004 and 2011 there was a year on year decline in the number of new HIV diagnoses among heterosexuals in E,W&NI. This decline led to a slower rate of increase than I had predicted in the annual number of heterosexuals living with diagnosed HIV in England. This slower rate of increase resulted in the observed number of heterosexuals living with HIV in 2007 falling slightly short of my predicted figure, although the difference was small.

I also predicted in paper 3.1 that half of all HIV-diagnosed adults in England would be living outside London by 2007. The number of HIV-diagnosed adults living outside of London actually exceeded the number living in London a year earlier, in 2006 (1). My prediction was based on HIV diagnoses continuing to increase in both areas up to 2007 but with the rate of increase being faster outside of London. Figure 3.1A shows the number of HIV diagnoses among heterosexuals in London actually declined from 2003 onwards. A decline in diagnoses was also observed outside of London but not until two years later, in 2005 (see figure 3.1A). The earlier decline in diagnoses among heterosexuals in London resulted in the number of HIV-diagnosed adults living outside of London exceeding the number living in London one year earlier than I predicted.

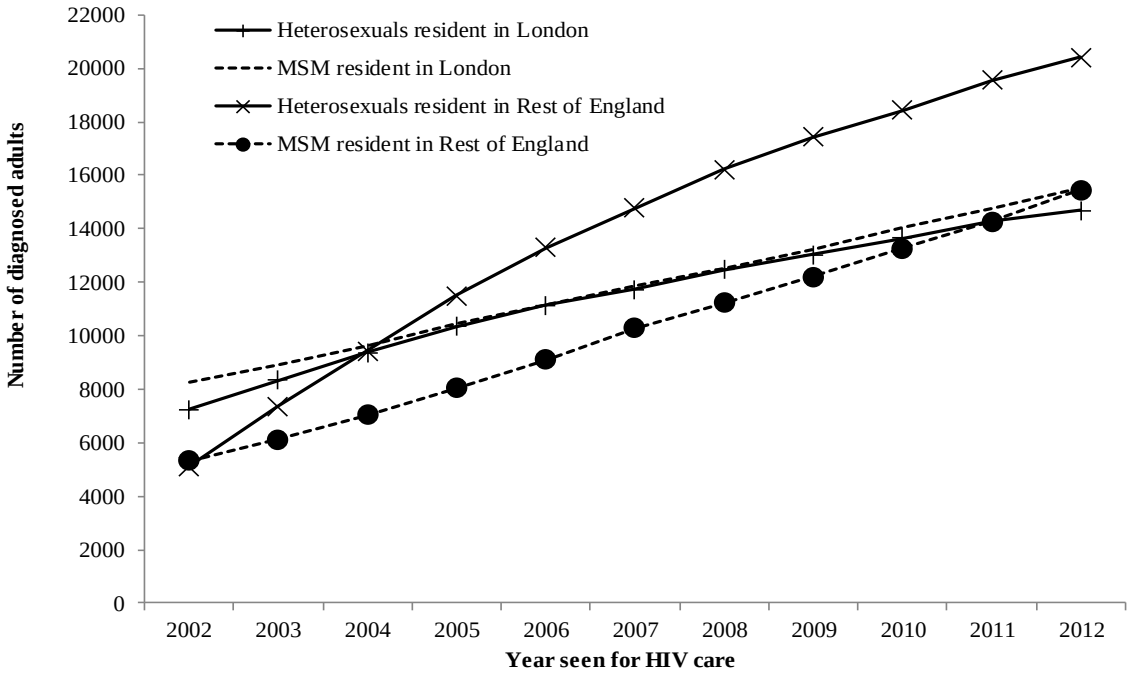
In paper 3.2, I highlighted another potential reason for a divergence between the predicted and observed rates of increase. In paper 3.2, the majority of heterosexuals diagnosed with HIV were shown to be born abroad, mainly in sub-Saharan Africa. In a recent London School of Economics report, it was suggested that between 2001 and 2011 "*poor-country*" migrants, including those from Africa, were increasingly settling in towns on the outskirts of London as settlement within the boroughs of London was becoming ever more financially difficult (79). Also, in 1999 a system of relocating asylum seekers across the UK was introduced (80). It is therefore probable that the voluntary or involuntary movement of foreign born HIV-diagnosed heterosexuals from London to elsewhere in England influenced the observed trends. As neither residency status nor reason for moving residence is collected through national HIV surveillance it was not possible to consider the voluntary or forced movement of diagnosed people in my analysis for paper 3.1

Figure 3.1: HIV-diagnosed heterosexuals and men who have sex with men by place of diagnosis and residence, 2002 to 2012

A. Newly diagnosed adults by area of diagnosis



B. Diagnosed adults seen for HIV care by area of residence



Source: Public Health England (1)

3.5.2 Imprecise approximations

Two predictions I made in paper 3.1 were not borne out. In the first of these two predictions I forecast the number of HIV-diagnosed heterosexuals residing in London to exceed the number of diagnosed MSM in 2005. Figure 3.1B highlights how the observed number of diagnosed heterosexuals resident in London actually remained the same or lower than the number of MSM in all years up to 2012 (2005:10,345 heterosexuals versus 10,421 MSM; 2012: 14,697 heterosexuals versus 15,552 MSM) (1).

In the second prediction I forecast that, as seen in the London environs, heterosexuals, black-Africans, and females would account for an increasing percentage of the HIV-diagnosed population in the rest of England, excluding London. In fact, between 2005 and 2012, the annual percentage of diagnosed adults living in England outside of London who acquired HIV heterosexually, were black African, or were female remained more or less constant (heterosexually-acquired: 56% in 2005 and 59% in 2012; black African: 40% in 2005 and 36% in 2012; female: 37% in 2005 and 35% in 2012) (1).

I suggested in paper 3.1 that my predictive model was particularly sensitive to changes in the pattern of in-migration of HIV-infected people from high prevalence countries. The results I present in paper 3.2 support this suggestion. In paper 3.2, I reported the majority of heterosexuals newly diagnosed with HIV in E,W&NI to be black African, female, and born in sub-Saharan Africa. I also reported a decline in diagnoses between 2004 and 2011 which almost certainly reflects corresponding changes in migration to the UK. A decline in diagnoses among people arriving in the UK from high HIV prevalence countries would translate in to fewer diagnoses among black African and female heterosexuals and explain why my two predictions above were not borne out.

3.5.3 Challenges in predicting future trends

I highlight mixed success for the predictions I made in paper 3.1. I am not alone in failing to predict accurately the future course of HIV. In 1993, it was predicted that the heterosexual transmission of HIV in the UK would increase steadily but at a rate lower than that among MSM and PWIDs (81). In fact, between 1993 and 2003, the annual number of HIV diagnoses among heterosexuals in E,W&NI increased rapidly, among

MSM diagnoses increased steadily, and among PWIDs they decreased (1). In 1986, it was claimed in a book entitled "*The AIDS Cover Up*" there would be 64 million people infected with HIV in the USA by 1990 (82). At the end of 2010, an estimated 872,990 persons were living with diagnosed HIV infection in the USA, of whom approximately one in four probably acquired their infection through heterosexual sex (83).

It has been argued that the utility of HIV surveillance to predict the future course of HIV epidemics among heterosexuals is limited due to the long latency period of infection and misclassification of risk (84). I disagree with this argument. The latency period of HIV can be accounted for by basing predictive models on observed trends in diagnoses, preferably over many years, and monitoring changes in the percentage of people diagnosed late. In addition, the potential impact of misclassification of risk is likely to be small. In Chapter 2 (section 2.4.2), I suggested that the misclassification of risk through national HIV surveillance in E,W&NI was limited. In the UK context, I would argue that changing patterns of migration and health boundary changes limit the utility of surveillance data for predicting the future course of heterosexually-acquired HIV.

Paper 3.2 highlighted the impact of migration on trends of HIV diagnoses among heterosexuals in E,W&NI. Despite acknowledging in paper 3.1 the potential impact of migration on predicted trends I did not apply an adjustment for migration patterns in my analysis. The reason for this was two-fold. At the time of conducting the analysis for paper 3.1 it was not clear there would be a subsequent decline in HIV diagnoses and that this decline would be associated with changing migration patterns. Also, any adjustment would require accurate national and regional estimates of migration patterns both to and from the UK. Such data are not easily available as I discuss in Chapter 4.

There is evidence not only of foreign born people arriving in the UK already infected with HIV, but also acquiring HIV post arrival (24). Predictive models of heterosexually-acquired HIV could be improved if we better understood reasons for ongoing heterosexual transmission of HIV in high prevalence countries from which people migrate to the UK, and the extent to which these remain present after arrival in the UK. Explanations for the ongoing heterosexual transmission of HIV in parts of sub-Saharan Africa from which people migrate to the UK include unequal gender relations, resistance to sexual behaviour change, and regionally specific sexual behaviours and

practices (85, 86). In relation to sexual behaviours and practices, male circumcision (87-90), concurrent sexual partnerships (91-93), and Herpes Simplex Virus2 prevalence (87, 94, 95), have been put forward to explain differential rates of heterosexual HIV transmission in sub-Saharan Africa. I think it would be fair to say that there remains little consensus on why rates of heterosexually-transmitted HIV differ so greatly between countries and populations in sub-Saharan Africa.

The utility of surveillance data in predicting the future course of heterosexually-acquired HIV is also limited by changes to health boundaries. Between 2002 and 2014, there were three major changes to the geographical structure of the NHS. In 2002, health authorities were replaced with primary care trusts and strategic health authorities (96). In 2006, many of these trusts and authorities were combined to create larger health geographies (96). Finally, in 2013, primary care trusts and strategic health authorities were abolished and replaced with clinical commissioning groups, NHS area teams, and NHS commissioning regions (96, 97).

On each occasion health boundaries are amended, national HIV surveillance data are mapped to the new geographies. Mapping to both the previous and new geographies is conducted by linking the postcode of an HIV-diagnosed person's residence and site of HIV care to the Office of National Statistics postcode directory. Once mapping has been completed, older geographies are discarded. As a consequence, it was not possible to explore recent trends in the London environs, and thereby verify the accuracy of my predictions in paper 3.1, as this area was defined by 2001 health authority boundaries which have since been abolished.

3.6 Late HIV diagnosis and quality of HIV care

As described in Chapter 2 (section 2.6.1), I created with my colleagues a cohort of adults seen for HIV care by linking annual cross-sectional SOPHIDs. The creation of a cohort of diagnosed persons facilitated the development of measures of late HIV diagnosis and quality of HIV care. Currently, seven measures of the uptake of HIV testing and quality of HIV care are used in the UK. These seven measures are generally (3)referred to as quality of HIV care indicators and are as listed in table 3.1.

Table 3.1: Quality of HIV care indicators in the UK

Indicator	Monitoring	Measure
Late diagnosis	Timeliness of diagnosis	CD4 cell count <350 cells/ml within 3 months of diagnosis
Linkage to care	Prompt integration into care	CD4 cell count taken within 2 weeks, 1 month and 3 months of diagnosis
Retention in care among new patients	Retention in care	Seen for care after 12 and 24 months of diagnosis
Retention in care among all patients	Retention in care	Seen for care in current and previous year
Viral load outcome	Effectiveness of ART after initiating treatment	Viral load <50 copies/ml within 12 months of commencing ART
ART coverage	Those in need of treatment in receipt of treatment	CD4 cell count <350 cells/ml and in receipt of ART
CD4 outcome	Immune status of adults regardless of treatment status	CD4 cell count ≥350 cells/ml after 12 months in care

Source: Amended from Aghaizu et al., 2013(3) and Delpech et al., 2013 (98)

Quality of HIV care indicators, it has been argued, enable necessary service enhancements by identifying where gaps in care provision are most pronounced (99). Several of the quality of HIV care indicators presented in table 3.1 have been revised and incorporated into British HIV Association quality standards to promote equity of access to care in the UK and to ensure people living with HIV can access the care they need (100).

In paper 3.2, I examined three of the indicators presented in table 3.1. These were: (i) late HIV diagnoses; (ii) linkage to care; (iii) ART coverage. I also examined first AIDS diagnosis and short-term mortality as markers of late HIV diagnosis and quality of subsequent HIV care.

3.6.1 Late HIV diagnosis

A late diagnosis of HIV is associated with increased risk of morbidity and mortality (3, 20, 101-106). In paper 3.2, I report a small decline between 2002 and 2011 in the percentage of heterosexual adults diagnosed late (CD4 cell count <350 cells/ml) from 66% to 61%. This decline was statistically significant ($p<0.01$) in univariate but not in multivariate analysis. Despite this slight decline, heterosexuals remain more likely to be diagnosed late with HIV compared to MSM. In 2012, six out of ten heterosexuals diagnosed with HIV in the UK were diagnosed late compared to one in three MSM (3).

In paper 3.2, late diagnosis was shown to be associated with male sex, older age, non-white ethnicity, and being born or probably acquiring HIV abroad. How can we explain these differences?

The successful provision of HIV screening through antenatal services may partly explain the observed difference in late diagnosis by sex. In 2012, 98% of pregnant women attending antenatal services in the UK agreed to have an HIV test (107). This high rate of screening ensures the majority of HIV-undiagnosed pregnant women attending antenatal services are identified prior to giving birth. Among heterosexual men there is no equivalent setting for the systematic offer of an HIV test.

The authors of a clinic-based study conducted in the USA between 2002 and 2004 concluded that low perceived risk for HIV infection by both patients and health providers potentially explained elevated rates of late HIV diagnosis among older patients (108). It has been argued that persons who present late in general have a low perceived risk of infection (109). In the USA, a low rate of HIV risk perception both among older adults and HIV service providers has been linked with a reduced number of opportunities for HIV testing among persons aged 50 years or above and, therefore, a higher level of late diagnosis in this group (110).

The majority of HIV-diagnosed heterosexuals of black African ethnicity and / or born abroad acquire their infection prior to arrival in the UK (24). Therefore, the associations between late diagnosis and non-white ethnicity and being born or probably acquiring HIV abroad may be due, in part, to some individuals among these groups arriving in the UK with established (but undiagnosed) infection. Other potential explanatory factors include migrant groups in the UK having poor access to healthcare services due to a

range of issues, including a lack of information and fears over privacy (111-115), HIV positive black Africans delaying testing due to them not suspecting their positive status (113), symptom misrepresentation (116), and missed opportunities for earlier diagnosis in setting such as primary care (101) and tuberculosis services (117, 118) (see sections 5.6.2 and 6.7.2). Another likely explanatory factor for the reported association is the considerable level of stigma attached with HIV in African communities in the United Kingdom. Stigma has been reported as a major barrier to accessing HIV testing and other HIV services (114, 115, 119, 120). In section 6.7.1, I discuss how testing strategies targeted at black African communities in the UK may create stigma.

Similar associations with late HIV diagnosis to those presented in paper 3.2 have been reported elsewhere. Among adults attending two south London hospitals for HIV care between 1998 and 2000, black Africans were more likely to present with a lower CD4 cell count than whites and black Caribbeans (121). Among heterosexuals diagnosed in England and Wales between 2000 and 2004, a very late diagnosis (CD4 cell count <200 cells/ml) was shown to be associated with increased age at diagnosis, and acquiring HIV abroad (20). In France (122), Greece (123), and Spain (124), a late diagnosis has been associated with acquiring HIV heterosexually. In Greece a late HIV diagnosis has also been associated with being born outside of Greece, and increased age at diagnosis (123). In Spain, older age, male sex, and being born abroad were predictive factors for a late HIV diagnosis (124).

3.6.2 Linkage to care and ART coverage

The percentage of newly diagnosed heterosexuals in E,W&NI promptly integrated into HIV care (having a CD4 cell count measured within 28 days of HIV diagnosis), or in receipt of antiretroviral therapy within one year of diagnosis, is shown in paper 3.2 to have increased over time. Prompt integration into care is reported in the paper to be associated with recent year of diagnosis, being aged 35 years or above at diagnosis, and white ethnicity. Receipt of antiretroviral therapy within one year of diagnosis is reported to be associated with recent year of diagnosis, being aged 35 years or above at diagnosis, female sex, and late diagnosis. How might we account for these differences?

The association between recent year of HIV diagnosis and the two quality of care indicators most probably reflects changes to guidelines for the treatment of HIV-infected adults and associated improvements in clinical practise. In 2008, British HIV

Association treatment guidelines recommended HIV-diagnosed adults started treatment at a higher CD4 cell count than was previously recommended (from 200 cells/ml to 350 cells/ml) (125). To implement this recommendation it was required that a CD4 cell count at diagnosis be conducted among both symptomatic and asymptomatic adults newly diagnosed with HIV, and that an increased percentage of these adults start antiretroviral therapy within one year of diagnosis.

The associations between older age at diagnosis and the two quality of care indicators (prompt integration into care and receipt of ART) may be explained by the fact that heterosexuals aged 35 years or above are more likely to be diagnosed late than those aged less than 35 years (reported in paper 3.2). As persons diagnosed late are in greater need of timely referral pathways and treatment than those diagnosed promptly a greater proportion of older adults, as compared with younger adults, would be fast tracked.

The association between white ethnicity and prompt integration into HIV care may be explained by the finding that white adults in England are more likely than black African adults to be diagnosed with HIV in a GUM clinic with integrated services (126). The majority of adults diagnosed with HIV outside of a GUM clinic or other HIV services will require referral to these services, thereby resulting in some delay.

The association between female sex and being in receipt of ART within one year of diagnosis is harder to interpret as females were less likely than males to be diagnosed late. The finding may be linked to the role of antenatal services in promoting prompt HIV diagnoses and, where required, treatment among women.

3.6.3 AIDS defining illnesses and deaths

Among HIV-diagnosed heterosexuals both the number of AIDS diagnoses (a diagnosis of an AIDS defining illness) and deaths are reported in paper 3.2 as having declined between 2002 and 2011. Among heterosexuals who died, two-thirds died within one year of HIV diagnosis (referred to as short-term mortality).

In paper 3.2, an AIDS diagnosis was shown to be associated with earlier year of HIV diagnosis, male sex, older age at HIV diagnosis, and being born and probably acquiring HIV abroad. The associations between AIDS diagnosis and male sex, older age, and being born and probably acquiring HIV abroad are most likely explained by late diagnosis, for which the same associations were presented in section 3.6.1. Although

over nine in ten heterosexuals with an AIDS diagnosis were diagnosed late, a late diagnosis was not included as an explanatory variable for AIDS diagnosis in paper 3.2 as both are markers of severe immunosuppression. The association between an AIDS diagnosis and year of diagnosis probably reflects improvements in quality of HIV care over time. In recent years, improvements in prompt entry into HIV care and in maintaining a high CD4 count have been linked with better clinical outcomes (98).

Short-term mortality was shown in paper 3.2 to be strongly associated with late HIV diagnosis and not receiving antiretroviral therapy within one year of HIV diagnosis. These associations are probably explained by the fact that the predicted life expectancy of a person diagnosed with HIV is relatively high if they are diagnosed promptly and have access to a wide range of antiretroviral drugs (127). Persons diagnosed late are more likely to die shortly after diagnosis before they can begin antiretroviral therapy (20, 127). Short-term mortality was also reported in paper 3.2 to be associated with male sex and older age at HIV diagnosis. The strength of the association between short-term mortality and age at diagnosis increased with age. It is likely that this finding is partly explained by higher overall deaths rates in the general population among older age groups (128). The association between male sex and short-term mortality is difficult to interpret.

The results I presented in paper 3.2 are similar to the results of previous analysis of HIV surveillance data. In England and Wales between 2000 and 2004, one third of heterosexuals diagnosed very late with HIV also had an AIDS diagnosis (20). Among heterosexuals diagnosed with a CD4 count ≥200 cells/ml the figure was 4% (20). Among the heterosexuals diagnosed very late, the percentage who died within a year of their diagnosis was nine times higher than among those diagnosed earlier (20).

In paper 3.2, I linked the decline in AIDS diagnoses and deaths with improvements in clinical HIV care. A previous analysis of mortality trends among HIV-diagnosed persons in England and Wales between 1999 and 2008 also linked the observed reduction in deaths among heterosexuals with enhancements in clinical care (129). This analysis however, highlighted the need for further enhancements. Despite the decline in deaths, the mortality rate among HIV-diagnosed heterosexuals in 2008 was reported to be five times higher than that in the general population (129).

3.6.4 Reducing late HIV diagnosis and improving quality of HIV care

In paper 3.2, I reported mixed success in reducing late HIV diagnosis and improving quality of HIV care among heterosexuals in E,W&NI over time. Although I reported a slight decline between 2002 and 2011 in the percentage of heterosexual adults diagnosed late, in 2012 six out of ten heterosexuals were diagnosed beyond the point treatment should have commenced. This proportion is unacceptably high and remains almost double that among MSM.

On the other hand, I also presented evidence of success in paper 3.2. I reported increases over the study period in the percentage of newly diagnosed heterosexuals in E,W&NI promptly integrated into HIV care or in receipt of antiretroviral therapy within one year of diagnosis. I also reported a reduction in the number of HIV-diagnosed heterosexuals diagnosed with an AIDS defining illness or having died between 2002 and 2011.

The authors of a recent study based on national HIV surveillance data concluded that the UK NHS provides high quality HIV care, and that there was no evidence of health inequalities in relation to access to, and retention in, HIV care (98). However, they did find elevated rates of late diagnosis among black Africans. The authors concluded that this was largely a result of adults of sub-Saharan origin having acquired HIV prior to arriving in UK (98). The authors of the study highlighted how their findings were in sharp contrast to similar studies conducted in the USA (98). In the UK, it was estimated that of the 96,000 people living with HIV in 2011 (diagnosed and undiagnosed) half had an undetectable viral load (<50 copies/ml) (130). In the USA, of the estimated 1.1 million people living with HIV in the USA in 2011 only one quarter were estimated to have achieved viral suppression (131). Poorer quality HIV care in the USA as compared to the UK may be explained by differences in national healthcare provision. In the UK, HIV care through the NHS is free and open access whereas in the USA HIV care is largely provided by private organisations. It has been suggested that one of the reasons for a low rate of retention in HIV care among people of black ethnicity in the USA is a lack of health insurance (132).

3.7 Increase in median age at HIV diagnosis

In paper 3.2, I reported median age at HIV diagnosis among heterosexuals as having increased over the study period. Between 1992 and 2011, median age at diagnosis increased from 33 to 41 years among men and from 28 to 36 years among women.

Over the same period of time during which median age at HIV diagnosis increased, the number of HIV diagnoses among heterosexuals born abroad, specifically in sub-Saharan Africa, declined (36). As compared to the overall population, a greater proportion of migrants to the UK are of working-age (16 to 59 years for women and 16 to 64 years for men) (133). If, on average, migrants are younger than the general population, a reduction in the number of migrants and in the number of diagnoses among migrants would lead to an increase in median age among the remaining population diagnosed with HIV.

Based on additional analysis of the data I described in paper 3.2, in table 3.2 I present median age at HIV diagnosis among heterosexuals by year and ethnicity. Median age at diagnosis is shown in table 3.2 to increase not only among black Africans, of whom the majority are born abroad, but also among people of white, black Caribbean and other ethnicity. The majority of people of white or black Caribbean ethnicity were born in the UK. This increase in median age at diagnosis among all ethnic groups suggests the impact of reduced migration on median age at diagnosis is modest, if it exists at all.

Table 3.2: Median age at diagnosis among heterosexual adults (aged ≥15 years at diagnosis) in E,W&NI by ethnicity, 2002 to 2011

	Year of HIV diagnosis									
	2002	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**
Black African	32	33	33	33	33	35	35	36	37	37
White	35	36	36	37	36	39	38	39	40	40
Black Caribbean	32	32	32	34	35	32	37	39	42	43
Other ethnicity	31	32	31	33	33	34	35	35	36	37

Source: Additional analysis of data presented in Paper 3.2

A more likely explanation for the increase in median age at diagnosis is a rise of HIV transmission among older adults. In a previous analysis of national HIV surveillance

data, the overall number of HIV diagnoses in E,W&NI among older adults (aged 50 years or above) was shown to have more than doubled between 2000 and 2007 (104). Of the increasing number of older adults diagnosed with HIV, it was estimated half acquired their infection when aged 50 years or over (104). It has been proposed that an increase in HIV infection among older adults is due to an ageing population, an increased number of older adults starting new sexual relationships, and poor risk perception (110, 134, 135).

Between 1985 and 2010, the median age of the UK population increased from 35.4 years to 39.7 years (136). Over this same time period, the percentage of the UK population aged 65 years or over increased from 15% to 17% (136). Although this percentage growth appears modest, it represents an increase of 1.7 million people aged 65 years or over (136). An increase in the number of older adults in the population will lead to an increase in the number of older people at risk of heterosexually-acquired HIV if sexual risk behaviour remains constant, or increases, in this group.

It has been suggested that an overall increase in sexually transmitted infections among older adults in the UK may, in part, be associated with an increasing number of older adults leaving long-term relationships (135). In the USA, an increase in HIV diagnoses among older adults has been linked with a high number of widowed and divorced people commencing new sexual relationships (134). In Sweden, it has been suggested that an observed increase in sexual activity in older people may partly be due to the general population having more positive attitudes to sexuality in later life (137).

In relation to older men in countries such as the UK and USA, a greater number may now be capable of vaginal or anal intercourse due to the availability of erectile dysfunction medications (134, 135). In relation to older women, they may be more likely than younger women to have unprotected sex due to the greatly reduced chance of pregnancy (134). Age-related thinning and dryness of vaginal tissue may also increase the risk of HIV infection among sexually active older women (134). Unfortunately, evidence for on-going risk of HIV transmission among older adults is not presented by ethnic group.

Another potential explanation for older adults being at increased risk of acquiring HIV is risk perception. In the USA, it has been suggested that although older adults visit their

doctors frequently, they are less likely than younger adults to discuss sexual habits (134).

3.8 Recommendations

In papers 3.1 and 3.2, I explored trends in HIV diagnoses. In paper 3.1 I highlighted the diverse growth of the HIV epidemic between regions of England, and in paper 3.2 presented trends in HIV diagnoses and quality of HIV care among heterosexual adults in E,W&NI.

Based on the analysis of paper 3.1, I recommended local services be responsive to increases and changes in their diagnosed HIV-infected population as described by national surveillance. Since 2008, the British HIV Association has recommended HIV testing be expanded beyond specialised sexual health services in local areas where national surveillance data show diagnosed HIV prevalence (based on SOPHID data) to exceed two per 1,000 population aged 15-59 years (138).

In section 3.5.3 I highlighted how changing migration patterns and health boundaries present challenges when predicting the future course of diagnosed HIV. These challenges can be overcome by exploring methods to adjust for inward and outward migration, and by assessing at which geographical level estimates remain both robust and useful for the planning of HIV services.

To minimize the risk of on-going transmission of HIV within the UK, I argue in paper 3.1 for sustained HIV prevention activities among heterosexual men and women from countries with a high HIV prevalence. In paper 3.2, I conclude that the results presented underscore the need for targeted HIV prevention strategies and making available to black Africans the routine offer of an HIV test in a range of healthcare and community settings, as recommended in the National Institute for Health and Clinical Excellence guidance on HIV testing in 2011 (139).

Research conducted in this country has highlighted on-going heterosexual HIV transmission within the UK among African communities (23, 24). Based on this evidence, the National AIDS Trust called for a holistic HIV prevention strategy to reduce HIV incidence amongst black African men and women in the UK (140). In addition to HIV testing, it was suggested that a holistic HIV prevention strategy include the promotion of free or affordable condoms and lubricant, health promotion and

outreach work, methods to address risks associated with travel to and from countries of origin (see section 4.8.1), and the engagement of faith groups (140).

Evidence is presented in paper 3.2 for improvements over time in the quality of HIV care received by heterosexuals. Caution, however, should be exercised when interpreting these results as they relate to diagnosed heterosexuals only. Had both diagnosed and undiagnosed heterosexuals been considered, the percentage promptly integrated into care or in receipt of ART would have been substantially lower. This point should be made clear when quality of care indicators are presented. The issue of undiagnosed HIV among heterosexuals is discussed in Chapter 6.

In section 3.7, I suggested the increase in median age at HIV diagnosis among heterosexuals is associated with a rise of HIV transmission among older adults, which in turn, is due to an aging population having increased sexual relationships. Research into strategies to reduce HIV transmission among older adults is warranted.

In an editorial accompanying the publication of paper 3.2, two recommendations were put forward in light of the paper's findings (141). Firstly, the authors of the editorial argued for widespread and, where appropriate, repeated HIV testing to facilitate prompt initiation of antiretroviral treatment among those diagnosed positive (141). I believe the British HIV Association recommendation for expanded HIV testing in local areas where diagnosed HIV prevalence exceeds two per 1,000 adult population strikes the right balance between widespread and targeted HIV testing strategies. In relation to repeat testing, to reduce late HIV diagnoses among heterosexuals I believe further research is warranted into the frequency of testing. This research should include community and provider engagement, an examination of the frequency with which the target population engage with healthcare and community settings where HIV testing is offered, the likelihood that a person who previously tested HIV negative will acquire HIV infection (i.e. the incidence), and the cost effectiveness (for example, cost per infection averted, cost per life year gained and cost per quality-adjusted life year gained). Future research should also take into account HIV-related stigma and how best to make testing facilities both accessible and acceptable to heterosexual men and women in this country. Secondly, the authors of the editorial recommended the use of HIV surveillance data to monitor interventions, justify the deployment of prevention strategies available, and make predictions on future benefit (141). I support this recommendation.

Comprehensive and validated surveillance systems can provide routine and accurate risk information which may be used to develop, deploy and monitor prevention and treatment strategies.

4. Migration

Summary

In this chapter, I consider the challenges we face in accurately assessing the impact of migration on the epidemiology of heterosexually-acquired HIV in E,W&NI. For the purposes of this chapter I apply the United Nations Educational, Scientific and Cultural Organisation (UNESCO) definition of migration as the "*crossing of the boundary of a political or administrative unit for a certain minimum period of time*" or the "*territorial relocation of people between nation-states*" (142). The two published papers in this chapter examine: (i) country of HIV infection among migrants living in the UK and (ii) retention in HIV care in E,W&NI.

The first paper is called "*A new method to assign country of HIV infection among heterosexuals born abroad and diagnosed with HIV in the UK*". The paper highlighted difficulties in accurately ascertaining where heterosexual adults who were born abroad and diagnosed with HIV in E,W&NI actually acquired their infection (the majority were born in sub-Saharan Africa and were of black African ethnicity) (24). To address these difficulties, I developed a new method for ascertaining likely country of HIV acquisition among heterosexual adults born abroad.

The second paper is called "*Loss to follow-up among adults attending HIV-services in England, Wales and Northern Ireland"*. In the paper, I examined annual patterns of attendance at HIV services in E,W&NI (37). I identified two phenomena previously not reported at the national level. These were: (i) permanent loss to follow-up to HIV services and (ii) intermittent attendance at services. Outward migration from the UK was put forward as a partial explanation for loss to follow-up.

Both papers relied on a definition of migration which has been adopted by PHE. In this chapter, I explore different definitions of migration and migrants both in the general population and in relation to HIV. I highlight the importance of applying clear and meaningful definitions when ascertaining the impact of migration on heterosexually-acquired HIV. I also examine the impact of migration on the heterosexual transmission of HIV in E,W&NI and consider whether a "*home-grown*" epidemic has developed among heterosexuals either born abroad or born in the UK. I then go on to examine the possibility that outward migration from the UK has contributed to people being lost to

follow-up. Finally I describe the impact of the two published papers to date and make some recommendations.

4.1 Introduction

In Chapters 1 and 3 I highlighted that the majority of heterosexual adults newly diagnosed with HIV in E,W&NI were born abroad. Most of the heterosexual adults born abroad originated from sub-Saharan Africa. In this chapter I examine the impact of migration on the epidemiology of heterosexually-acquired HIV in E,W&NI. The chapter includes two papers which I published in peer-reviewed journals. The first paper examined the country of HIV infection among migrants while the second paper considered retention in HIV care in E,W&NI. In this chapter, after summarising the key findings from the papers I go on to conduct a detailed examination of definitions of migration and migrants. I also consider challenges in assessing the impact of migration on heterosexually-acquired HIV in E,W&NI. Finally I consider the impact of my papers and the two new methods I developed for describing the epidemiology of heterosexually-acquired HIV in E,W&NI.

4.2 The published papers

4.2.1 Rice et al., AIDS 2012

A new method to assign country of HIV infection among heterosexuals born abroad and diagnosed with HIV in the UK

http://www.ncbi.nlm.nih.gov/pubmed/22781226

Objective: To apply a new method to ascertain likely place of HIV infection among persons born abroad and diagnosed with HIV in the United Kingdom (UK).

Design: Analyses of heterosexual adults born abroad, diagnosed with HIV in the UK between 2004 and 2010, and reported to the national HIV diagnoses database.

Methods: Year of infection was ascertained by applying an estimated rate of CD4-cell count decline between an individual's CD4-cell count at diagnosis and estimates of CD4-cell count at infection. A person was classified as having probably acquired HIV while living in the UK if estimated year of infection was later than reported year of arrival in the UK.

Results: Of 10,612 heterosexual adults born abroad included in the analyses, 85% (9065) were of black-African ethnicity. We estimate that 33% (26%-39%) of persons acquired HIV whilst living in the UK. This percentage increased from 24% (16%-39%) in 2004 to 46% (31%-50%) in 2010 ($p < 0.01$). The estimate of 33% is three times higher than national estimates of HIV acquired in the UK based on clinic reports (11%) ($p< 0.01$).

Conclusions: Assigning place of HIV infection using routinely available clinical and demographic data and estimated rates of CD4-cell decline is feasible. We report a high and increasing proportion of persons born abroad who appear to have acquired their HIV infection whilst living in the UK These findings highlight the need for continued targeted HIV prevention efforts, particularly among black-African communities.

4.2.2 Rice et al., Sexually Transmitted Diseases 2011

Loss to Follow-Up among adults attending Human Immunodeficiency Virus services in England, Wales, and Northern Ireland

http://www.ncbi.nlm.nih.gov/pubmed/21844719

Aim: To assess the extent to which human immunodeficiency virus (HIV)-diagnosed adults attending HIV-services in England, Wales, and Northern Ireland are lost to follow-up or attend services intermittently.

Methods: A cohort of HIV-diagnosed adults was created by linking records across the 1998 to 2007 national annual Survey of Prevalent HIV Infections Diagnosed. The records were also linked to the national HIV and acquired immune deficiency syndrome New Diagnoses Database (n = 61,495) and to Office for National Statistics death records. Patterns of HIV-service attendance were analyzed.

Results: On average, 90% of adults attending HIV-services in any one year attended the following year. Nearly 5% of adults attending services in any one year were lost to follow-up, a further 4% subsequently attended services intermittently, whereas less than 2% died. Cumulatively, 19% of adults seen for HIV care between 1998 and 2006 were lost to follow-up by the end of 2007. Factors associated with loss to follow-up included being the following: female; aged 15 to 34 years; black-African or "other" ethnicity; not on antiretroviral therapy; recently diagnosed; and infected outside the United Kingdom.

Conclusions: Although the majority of HIV-diagnosed adults in England, Wales, and Northern Ireland attended HIV-services regularly, cumulatively nearly 1 in 5 adults were lost to follow-up between 1998 and 2007. Innovative strategies focusing on those most likely to drop out of regular care should be developed to maintain regular service engagement and to ensure optimal care.

4.3 Research findings from my published papers

The first published paper included in this chapter is called "*A new method to assign country of HIV infection among heterosexuals born abroad and diagnosed with HIV in the UK"* and was published in the journal *AIDS* in 2012 (24). In this chapter it is referred to as paper 4.1. In the paper, the importance of knowing where HIV was acquired was highlighted. Recognising limitations in the existing method for assigning likely country of HIV acquisition based on clinic HIV reports, in paper 4.1 I introduced a new method of assignment among heterosexual adults born abroad and diagnosed with HIV in E,W&NI between 2004 and 2010. The overwhelming majority of the study population were of black African ethnicity. The new method utilised routinely available clinical and demographic data to establish whether an HIV-diagnosed heterosexual adult who was born abroad acquired HIV before or after their arrival in the UK. A year of HIV infection was calculated for each adult in the study population by applying ethnicity and age specific rates of CD4 cell decline between their CD4 cell count at diagnosis and estimated CD4 cell count at infection. Adults were classified as having probably acquired HIV while living in the UK if their estimated year of infection was later than their reported year of arrival in UK.

According to the new method, over the study period one third of heterosexual adults born abroad acquired HIV whilst living in the UK. This proportion increased from just below one quarter in 2004 to nearly a half in 2010. This estimate of one third of foreign-born adults acquiring HIV whilst living in the UK was three times higher than the national estimate based on clinic reports. A recommendation was made in the paper for the new method to be applied in other countries where there are a high number of HIV diagnoses among migrant populations.

The second published paper included in this chapter is called "*Loss to follow-up among adults attending HIV-services in England, Wales and Northern Ireland"* and was published in the journal *Sexually Transmitted Diseases* in 2011 (37). In this chapter I refer to it as paper 4.2. In paper 4.2 I explored annual patterns of attendance at HIV services in E,W&NI at the national level for the first time. I also investigated factors, other than death, associated with HIV-diagnosed adults no longer accessing HIV care or accessing care intermittently.

Nine out of ten adults attending HIV services in any one year between 1998 and 2006 were shown to also attend services the following year. However, on average nearly 5% of adults attending HIV services in any one year were reported as lost to follow-up from care. An additional 4% of adults were reported as subsequently attending services intermittently, while fewer than 2% were reported as having died. Cumulatively, between 1998 to 2006, one in five adults attending HIV-related services in E,W&NI was lost to follow-up. Nonetheless, the vast majority of adults diagnosed with HIV in the UK continued to engage with services during the study period.

I suggested in the paper that outward migration from the UK may partially explain loss to follow-up. This suggestion was based on analyses showing adults of black African ethnicity, those who acquired HIV outside the UK, those not in receipt of antiretroviral therapy, and those recently diagnosed with HIV in the UK, as the groups most likely to be lost to follow-up. Although these associations provided some evidence of emigration contributing to loss to follow-up, it was not possible to judge the extent to which this was the case in the published paper.

Both papers relied on a definition of migration which has been adopted by PHE. In this chapter, I will explore different definitions of migration both in the general population and in relation to HIV. I go on to highlight the importance of applying clear and meaningful definitions when ascertaining the impact of inward and outward migration on heterosexually-acquired HIV in E,W&NI.

4.4 Literature search

Using the methods I described in Chapter 2 (section 2.8), I conducted computerised and manual literature searches in relation to the topics raised in the two published papers in this chapter. The topics were as follows: (i) heterosexually-acquired HIV and migration (ii) challenges of HIV surveillance; (iii) CD4 decline; (iv) HIV, migrants and migration; (v) HIV and migration in Europe; (vi) HIV and migration in the USA. Appendix iii lists details of the searches conducted for this chapter. The identified papers provided the foundation for the rest of this chapter.

4.5 Different ways of defining migrants in the general population

To understand the different ways migrants may be characterised in relation to HIV, it is useful to first consider national and international definitions of migrants and migration. The European Union's European Foundation for the Improvement of Living and Working Conditions broadly defines migrants as persons moving across borders to live and work (143). The United Nations Educational, Scientific and Cultural Organisation (UNESCO) describes migration as the "*crossing of the boundary of a political or administrative unit for a certain minimum period of time*" or the "*territorial relocation of people between nation-states*" (142). The United Nations also characterises migrants according to the length of time they migrate. Long-Term International Migration (LTIM) is defined as "*A person who moves to a country other than that of his or her usual residence for a period of at least a year… so that the country of destination effectively becomes his or her new country of usual residence*." (144).

The European Migration Network, coordinated by the European Commission, provides a list of different types of migrants and reasons for migration (145). A similar list is provided by UNESCO where migrants are categorised according to their motives or legal status. Table 4.1 presents the European Migration Network and UNESCO categories.

Table 4.1: Types of migrants and reasons for migration

European Migration Network types of migration and migrants
Migration - Economic; Exploitative; Family; Forced; Illegal; Irregular; Labour; Legal; Managed; Permanent; Spontaneous; Temporary
Migrants - Environmentally-driven; Forced; Highly qualified; Illegally resident / staying; Irregular; Labour; Long-term; Second generation; Short-term; Transit; Worker
UNESCO types of migrants
Temporary labour / guest worker migrants; Highly skilled and business migrants; Irregular / undocumented / illegal migrants; Refugees / asylum seekers / people forced to move due to external factors; Family reunion / family reunification migrants; Return migrants

Source: European Migration Network, 2014 (145) and UNESCO, 2013 (142)

No single definition of migrants or migration is applied within the UK. The ONS International Passenger Survey (IPS) and Labour Force Survey (LFS) are two of the main sources of information on migration in the UK (146-148). Both apply different definitions of migrants and different methods for quantifying migration.

The IPS, in combination with data from the Home Office and Irish Central Statistics Office, reports on long-term international migration, with the definition of LTIM being the same as that of the United Nations (146, 147). The survey captures information on passengers travelling into or out of the UK via major routes and includes questions on reason for migration and country of birth. The LFS measures the number of people resident in the UK who were born abroad or have non-British nationality (146, 147). Approximately 53,000 private households are sampled quarterly and the sample is weighted to ONS population estimates so that it is representative of the general population.

The University of Oxford's Migration Observatory suggests that the term migrant is often unclear in public debate and is often conflated with ethnicity, religion and immigration status (149). This lack of clarity is not helped by national and international bodies applying different, and often subjective, definitions of migrants and migration. Several of the definitions described above could be labelled as subjective as they rely on self-definition. For example, estimates of LTIM via the IPS are based on how long a respondent intends to stay in the UK rather than on their actual length of stay.

4.6 Different ways of defining migrants at risk of HIV

A sound epidemiological variable has been described as one that differentiates populations in some underlying characteristic relevant to health (150). In relation to HIV, a definition should highlight the risk among migrants whilst ensuring xenophobia and stigmatisation are not promoted. This final point is of particularly importance given the propensity of the UK media to present migrants in a poor light. Headline such as "*Where Britain's New Hetero AIDS Cases Began*" (151), "*Asylum seekers with killer diseases exploit legal loophole to avoid deportation*" (152), "*Aids infected asylum-seekers overwhelm-UK hospitals*" (153), and "*The secret threat to British lives*" (154) provide evidence for the need to think carefully how best to define migrants in relation to HIV research.

The literature search conducted for this chapter identified several definitions of migrants which may provide a foundation for public health action in relation to heterosexually acquired HIV and, if applied sensitively, avoid negative stereotyping. These include country of birth, ethnicity, nationality, second-generation migrant, and long-term international migrant. Each of these are considered below.

4.6.1 Country of birth

Historical, economic and socio-political ties have facilitated the movement of people to the UK from a wide range of countries. A large number of people arrive in the UK from the Indian sub-continent, where there are concentrated HIV epidemics, sub-Saharan Africa, where many countries have generalised HIV epidemics (HIV prevalence ≥1% in the general population), and other European Union countries, within which HIV prevalence varies greatly (155, 156). Therefore, when presented along with national HIV prevalence estimates, country of birth can provide a crude assessment of risk. Even then, data presented by country of birth can mask variations in HIV risk across sub-populations within countries.

4.6.2 Ethnicity

Ethnicity based on skin colour has been described as subjective, imprecise, and unreliable (150). Collecting information on ethnicity has been labelled complex due to the subjective, multifaceted and changing nature of ethnic identification, which is often self-defined, and due to changing social and political attitudes (157). Recognising the complexities of collecting information on ethnicity in the UK, the ONS provides guidance on how to request, harmonise and present such data (157).

In 1991 a question on ethnic group was introduced to the UK census. It has been suggested that it was introduced, in part, to measure success in tackling social inequalities among the UK population according to ethnicity highlighted by sample surveys in the 1980's (158). It had originally been planned that a question on ethnicity would be introduced in the 1981 census (158, 159). Its introduction was postponed following an unsuccessful trial in 1979 (159). Ethnicity has now been requested in the past three UK censuses (1991, 2001 and 2011), and on all three occasions both the instructions and the categorisation of ethnicity have differed slightly (160). Assignment of ethnic group in the census is based on self-classification and reflects the group an individual see themselves belonging to (161). It has been highlighted that the census question on ethnic group does not necessarily reflect an individual's place of birth (161).

In relation to health research, concern has been raised over the potential for ethnicity data to be misused or misinterpreted (162), or result in stereotyping and exploitation

(163). There is also concern that ethnicity-based research provides ammunition to claims that ethnic minorities are a burden on society (85), and that it transforms ethnic minorities into statistical categories which reinforce stereotypes (164). There is also concern that research into ethnicity and health often applies a comparative approach where the white population is used as a standard against which diseases that are more common in ethnic minority groups are compared (165). It has been argued that this approach may mask preventable diseases among ethnic minority groups because they are less common than among the white population (165).

In support of the use of ethnicity data, it has been argued that to reduce health inequalities and target HIV prevention activities in the UK it important that ethnicity, alongside country of birth, be collected through HIV surveillance (162, 166). By acknowledging ethnic disparities, it has been suggested communities would be empowered to act against HIV (163).

Ethnicity was included in the HIV surveillance system in E,W&NI in 1992. The following broad categorisation of ethnicity was applied: white; black African; black Caribbean; black other; Indian sub-continent; other/mixed; not known. In 2014, the categorisation of ethnicity in HIV surveillance was widened to meet NHS Information Standards Board data standards (167). Ethnicity is now categorised as follows: White (British; Irish; any other white background); Mixed (white and black Caribbean; white and black African; white and Asian; any other mixed background); Asian or Asian British (Indian; Pakistani; Bangladeshi; Any other Asian background); Black or Black British (Caribbean; African; any other black background); Other Ethnic Groups (Chinese; any other ethnic group; not stated). Discussions are on-going with regards how best to present data according to these categories.

When considering how best to present data on ethnicity it should be noted that in the past it has been suggested that there should be a unified approach to HIV prevention among African communities in the UK to increase the potential for raising funds (168). Recently in France, it was similarly suggested nationality be more broadly categorised so that HIV prevention programmes consider sub-Saharan Africans as a single racial minority (169). Not all are in agreement with this homogenous approach. In 2003, HIV researchers in the UK were accused of obscuring heterogeneity within ethnicity groups by applying broad categorisations such as black African (85). The category of black

African will comprise people born in the UK, born in low or high HIV prevalence areas of Africa, or born elsewhere.

4.6.3 Nationality

Nationality is where a person holds citizenship of a national state. There are six types of British Nationality, and it is possible for a person to renounce their British nationality (170). It is also possible for a British citizen to be a national of one or more other countries (171).

In the LFS, a migrant is defined as someone who reports having been born abroad, or being of non-British nationality (146). There is a preference to present LFS outputs by a person's country of birth, as it tends not to change over time. A person's nationality may change over time. For example, a person may arrive in the UK as a foreign national, but subsequently become a UK national.

In France, where nationality is routinely collected through HIV surveillance, it has been acknowledged that a major limitation of this variable in studying the impact of migration on HIV is that foreign-born persons obtaining French citizenship will be assigned as French (172). The use of self-reported nationality in research has also been criticised as it may be based on a person's social or cultural affinity (146), or a combination of their place of birth, culture, and personal histories (173).

4.6.4 Second generation migrant

Second-generation migrants are persons born within a country to parents of whom one or both arrived in the country as a migrant. In terms of HIV risk, sexual mixing between different ethnic groups (known as dissortative sexual mixing) in the Netherlands has been shown to be higher among second-generation "*migrants*" than first-generation migrants (174). This finding led the authors of the study to conclude that disassortative sexual mixing would increase as second-generation "*migrants*" reach adulthood and first-generation migrants give birth to more second-generation "*migrants*" (174). In the Netherlands this could increase the risk of HIV transmission within the country.

In the UK migrants born in sub-Saharan Africa and / or of black African ethnicity are at an elevated risk (as compared to the general population) of being diagnosed with HIV. In combination with additional demographic and epidemiological information, such as

parent's country of birth and ethnicity, generational information may help identify groups at risk of acquiring or living with HIV in the UK.

4.6.5 Long-term international migrant

Long-term international migrants are persons who arrive and effectively make the UK their country of usual residence. The categorisation of long-term international migrant relies on self-reporting or applying an arbitrary cut-off point based on number of years resident in the UK. I would argue that a simple categorisation as to whether a person is a long-term migrant or not provides little insight into the heterogeneity of HIV risk across migrant groups. However, it is likely that a migrant's risk of acquiring HIV in the UK increases with their length of residence, therefore the number of years of residence in the UK may be valuable information.

4.6.6 Combination of methods

Applied alone, none of the variables described in sections 4.6.1 to 4.6.6 clearly differentiate populations at risk of HIV within the UK. Figures relating to persons arriving in the UK from Bangladesh and the Republic of South Africa illustrate the need for combining variables to characterise migrants at risk of HIV.

A similar number of people born in Bangladesh (230,000) and South Africa (211,000) were resident in the UK in 2011 (155). However, during the decade 2003 to 2012, 46 adults born in Bangladesh were diagnosed with HIV in E,W&NI compared to 2,126 adults born in South Africa (1). National HIV prevalence estimates explain this difference. In Bangladesh estimated HIV prevalence among adults aged 15 to 49 years is <0.1% (175), whereas in South Africa it is 17.9% (176). Figures relating to South Africa also highlight the need to consider ethnicity when characterising migrants. Among women attending antenatal care clinics in South Africa, HIV prevalence ranges from 1.1% among white women to 31.4% among black women (177). During the decade 2003 to 2012, 284 white South Africans and 1,599 black South Africans were diagnosed with HIV in the UK (1).

Alongside ethnicity and route of transmission, a recommendation was made in 2004 for HIV surveillance systems in Europe to include country of origin to describe HIV among migrants (178). In E,W&NI, country of birth and ethnicity are routinely collected through national HIV surveillance, as is route and likely country of HIV infection (see

table 2.1). Data completion of both ethnicity and country of birth exceeds 80% among heterosexuals diagnosed with HIV in E,W&NI (36).

Heterogeneity in risk of living with or acquiring HIV can be highlighted when broad ethnicity categories, such as black African, are presented in combination with country or world region of birth. For example, by combining these two variables it has been possible to show that a greater number of black Africans born in Eastern Africa are diagnosed with HIV in E,W&NI than those born in other regions of Africa (36). Elsewhere, the practicality of combining country of birth with ethnicity has been highlighted. Driven by reports of elevated prevalence among people of black ethnicity in the USA, researchers highlighted the need to also consider country of birth by identifying higher rates of HIV among "*foreign-born blacks*" than "*native-born blacks*" (179, 180).

4.7 Migrants at risk of HIV in Europe

Migrants make up a significant and increasing proportion of people diagnosed with HIV in Europe (73, 181-187). Three quarters of European Union / European Free Trade Association countries consider migrants to be an important sub-population in their response to HIV (73). Despite this, no common definition of a migrant, or consistent approach to collecting information about migration, is applied across Europe. It has been suggested that most data relating to HIV among migrants is drawn from small studies, unrepresentative samples or questions added to other data collection exercises (188).

To maximise the public health benefit of surveillance activities across Europe, in 2011 it was recommended that comparable surveillance data be made available to improve the characterisation of migrant and ethnic minorities at risk of HIV in Europe (189). The European Centre for Disease Prevention and Control has designed a set of indicators to monitor and evaluate the HIV response among migrants from countries with generalised HIV epidemics (72, 73). For countries to adopt these indicators a combination of information on country of birth and national HIV prevalence estimates is required.

Of 24 European Union / European Free Trade Association countries responding to a 2012 questionnaire about surveillance systems for monitoring the sexual transmission of HIV, all but Latvia and Romania collected some data to describe the HIV epidemic

among migrant populations at the national level (73). Nineteen of the 24 countries collected the country of birth of newly diagnosed people (73). Sixteen countries collected nationality, three of which did not record country of birth (73).

Although most European Union / European Free Trade Association countries collect information on HIV among migrants, there is variation in their approach. Take France and the Netherlands, for example. In France, nationality and HIV subtype are used to explore the impact of migration on HIV (172, 190, 191). In the Netherlands, combinations of country of birth, HIV prevalence estimates, ethnicity, and generation of migrant are used to characterise migration and HIV (174, 192-194).

Although similar information is collected in the Netherlands as in E,W&NI, the application of this information differs. In the Netherlands country of birth has been used to assess the impact on HIV transmission of people specifically arriving from Surinam and the Netherlands Antilles (174, 192). It has also been used to distinguish differences between first and second generation migrants (174). In E,W&NI, where information on generation is not routinely available, country of birth is usually presented in aggregate form to identify people born in world regions where the prevalence of HIV is high, primarily sub-Saharan Africa (24, 37).

Until there is a standardised approach to characterising HIV among migrants in Europe it will remain difficult to compare the impact of migration on HIV, and the response to this, between European countries. Following their 2011 recommendation for comparable surveillance data to be collected based on country of birth, the ECDC in 2013 reiterated the need for countries to collect and submit standardised data to enable cross border linkages to facilitate a more complete picture of HIV among migrants (195).

4.8 Heterosexual transmission of HIV among migrants living in E,W&NI or elsewhere in Europe

In 2011, an estimated 12% (7,509,000/63,200,000) of the UK resident population was born outside of the UK (155). Of the sixty most common countries of birth (155), adult HIV prevalence, according to UNAIDS country profiles, exceeded 1% in twelve (196). Approximately 1.7% of the UK resident population (1,100,000 people) were born in one of these twelve countries, nine of which are in sub-Saharan Africa (155). The twelve

countries are as follows: Democratic Republic of Congo; Ghana; Jamaica; Kenya; Nigeria; Russia; South Africa; Tanzania; Thailand; Uganda; Zambia; Zimbabwe.

It has been proposed that as disparities in control programmes expand between developed and developing nations, the impact of migration on the epidemiology of HIV in low prevalence countries will increase (197). The impact of migration, particularly migration from high HIV prevalence countries, is often discussed in terms of imported disease or burden. As early as 1991 there were reports of heterosexual HIV infections in London being "*imported*" (198). In 1995 the impact of "*imported*" HIV infections to the UK and of ethnic group "*attributable*" infection was discussed (199). As recently as 2003, the UK Cabinet Office conducted a governmental inquiry into "*imported*" infections, examining the issue of testing people for HIV prior to or at the point of entry into the UK (200).

However, when considering the impact of migration from high prevalence areas on HIV transmission among migrants within E,W&NI we must not simply assume all infections are "*imported*". We need to gauge whether the conditions which facilitate HIV transmission in high prevalence countries remain present after migration and, among those diagnosed, gain robust estimates of where HIV was acquired.

4.8.1 HIV transmission

In paper 4.1, I estimated that nearly half of heterosexuals born abroad and diagnosed with HIV in 2010 acquired their infection while living in the UK. Conditions which facilitate transmission of HIV within populations include a high prevalence of infection (201), sexual risk behaviour (85, 86), assortative sexual mixing (169), and travel to home countries (202, 203). I will address the conditions for HIV transmission while living in the UK in turn.

Many countries in sub-Saharan Africa have generalised HIV epidemics (156), and there is a body of evidence showing HIV prevalence among black Africans in the UK to be greatly elevated compared to that among the general population (3, 48, 204). In a group among whom HIV prevalence is elevated, sexual risk behaviour may include having unprotected sexual intercourse (particularly with persons of unknown HIV status), and having multiple sexual partners. In a study of sexual behaviour among black African heterosexuals living with HIV in London, one in seven reported unprotected intercourse

in the previous three months with one in twenty reported unprotected intercourse with a partner of unknown or negative HIV status (205). Among participants of a cross-sectional community-based survey of Africans in England, the overwhelming majority of whom were born abroad, 22% reported having ever had a previous STI diagnosis (a proxy for sexual risk behaviour) (48). Nearly three quarters of Africans living in England reported having had one or more sexual partners in the previous year (41, 204). Further evidence is presented in section 4.8.2 for HIV transmission occurring among black Africans in E,W&NI.

Among migrant groups there is evidence of assortative sexual mixing where persons have sexual contact with people who share their ethnicity or country of origin (174, 193, 194, 206, 207). It is likely that sexual mixing among migrants groups increases the potential of transmission within these groups. For example, intra-African segregation of sexual networks has probably contributed to HIV transmission amongst sub-Saharan African migrants in France through sexual contact between people from African countries of low and high HIV prevalence (169). In paper 4.1, I highlighted how among black African heterosexuals born abroad and diagnosed with HIV in the UK the percentage acquiring their infection whilst living in the UK increased over time. However, it was not possible to assess how many of those acquiring HIV whilst living in the UK did so through sex with another person of black African ethnicity born abroad. Patterns of sexual mixing are discussed in greater detail in section 4.9.

The conditions which facilitate HIV transmission in countries of origin may also persist after migration because of international travel. A cross-sectional survey of sub-Saharan African communities resident in inner London found 43% of men and 46% of women had visited their home countries within the previous five years (202). Among the men visiting their home country, over a third reported having had new sexual partnerships (202). A similar percentage (40%) of Surinamese and Antillean migrants in the Netherlands reported having visited their homeland during a five year period (192). Of those visiting their homeland, 47% of men and 11% of women had a local sexual partner (192). A subsequent study of migrants to the Netherlands found 60% of participants to have travelled to their homeland in the previous five years (203). Among these participants, approximately one in ten were identified as a potential bridge population for HIV transmission as they reported having unprotected sex with partners in both countries (203).

4.8.2 Likely country of HIV infection

As far back as 1992, it was reported that the heterosexual transmission of HIV in the UK was increasing due to infections being acquired both abroad and in the UK (14). Of heterosexuals diagnosed with HIV in the UK between 1985 and 1996, an estimated six in ten probably acquired HIV in Africa (208). In 1997 black African men and women were singled out as being at particularly risk of "*AIDS*" in the UK (166).

The extent to which HIV was being acquired heterosexually within the UK was unclear. This lack of clarity was mainly due to doctors assigning people diagnosed with HIV who reported unprotected sex both in Britain and an African country as having acquired HIV in Africa (209). This potential bias in assignment led to suggestions that the heterosexual transmission of HIV among African communities in the UK was being underestimated (21), and that national estimates of black Africans acquiring HIV within the UK were too low (23).

As discussed in section 4.3, to reduce potential bias in assigning likely country of HIV infection I introduced in paper 4.1 a new method of assignment based on routinely available data. In paper 4.1, it was estimated that a third of heterosexual adults born abroad and diagnosed with HIV in E,W&NI between 2004 and 2010 acquired their infection whilst living in the UK. Among those of black African ethnicity, the figure was 31%. In another study among persons born or raised in Africa attending one of fifteen London centres for HIV care between April 2004 and February 2006, it was estimated that between a quarter to a third of all HIV-positive Africans currently resident in the UK acquired their infection in the UK (23).

The results presented both in the 2009 Burns paper and paper 4.1 highlight the need to enhance targeted prevention efforts to reduce the transmission of HIV among black African communities living in the UK (23, 24). However, the results also highlight how a substantial number of Africans continue to arrive in the UK having already acquired HIV abroad. There have been calls for developed countries to invest not only domestically in infectious disease control programmes but also in developing countries from which migrants originate (210). Such an approach, in relation to tuberculosis, was shown to be cost effective in a USA based model (211).

Elsewhere in Europe only a small number of countries have considered likely country of HIV infection among migrants. Of 24 European countries responding to a survey on the surveillance of HIV and HIV transmission among migrants from countries with generalised HIV epidemics, only the UK, Norway, Denmark, and the Netherlands provided information on country of infection (73). Of these four countries, only the UK and Norway provided specific estimates on country of infection. United Kingdom estimates were those published in paper 4.1, whilst Norway reported 14% (22/152) of migrants diagnosed with HIV in 2011 as having acquired HIV via sexual transmission whilst resident in Norway (73).

Denmark reported a small and stable proportion of migrants newly diagnosed with HIV as having probably acquired their infection in Denmark from another migrant (this was not quantified) and the Netherlands referred to published literature (73). In 2010, an estimated 40% of new HIV infections among African migrants to the Netherlands were acquired outside the Netherlands (193), thereby suggesting up to 60% were acquired within the Netherlands. This figure is comparable with my estimate for E,W&NI of 43% of infections among black African heterosexuals born abroad being acquired in the UK in 2010.

Research into country of HIV infection has also been conducted in Switzerland and Italy. Among persons of Asian or African nationality diagnosed with non-B HIV in Switzerland, an estimated one in five acquired their infection within Switzerland (212). Applying an HIV avidity test to estimate time of infection among HIV-positive "*illegal*" migrants and then comparing this to time of migration, the authors of a study in Italy reported six of 27 migrants to have acquired HIV in Italy and four to have acquired their infection prior to arrival (213). Country of infection could not be determined for seventeen of the 27 participants (213).

Evidence of migrants having sexual relationships both in the UK and whilst travelling from the UK (see section 4.8.1) highlights some of the complexities in assessing, among those diagnosed, country of HIV infection. In recognition of this, in paper 4.1 people were assigned as having acquired HIV either before or after their arrival in the UK. The group assigned as having acquired HIV after arriving in the UK consists of people infected in the UK as well as those infected whilst travelling away from the UK (but

after first moving here). Both of these groups lend themselves to targeted HIV prevention activities within the UK.

In summary, there is strong evidence of heterosexual transmission of HIV occurring within E,W&NI among black African migrants who live here. Data from other European countries also suggest that there is within-country transmission of HIV among migrants living there.

4.9 Heterosexual transmission of HIV in the general population in E,W&NI or elsewhere in Europe

In the general population, patterns of sexual mixing are an important determinant of HIV transmission (214). In section 4.8.1, I suggested assortative sexual mixing among migrants might increase the potential for transmission within these groups. Conversely, assortative sexual mixing might decrease the potential for HIV transmission between migrant and non-migrant populations.

In the Netherlands, approximately four in ten sexually active migrants reported having had sexual contact with someone from another ethnic group, including "*indigenous*" Dutch (174). A low level of sexual mixing with the "*Dutch*" population has been put forward to partly explain why migrants, among whom HIV prevalence is elevated as compared to the general population, have had little impact on heterosexually-acquired HIV nationally (193, 194). In Israel the risk of HIV transmission between labour migrants and Israelis has been described as being limited as sexual contact between these two groups is rare (207).

In addition to assortative sexual mixing other factors may reduce the potential for HIV transmission between migrant and non-migrant populations. In Denmark, primary infection rather than late presentation has been identified as fuelling HIV transmission among young MSM (215). If primary infection is a key determinant of transmission, then the potential impact of migration on HIV transmission among the general population, as well as among migrant groups, will be reduced. This is because many HIV-positive migrants will arrive after the period of highest infectivity. The potential impact of migration on HIV transmission in the general population is also likely to be limited by the relatively small size of the migrant population (194, 216).

Despite evidence that the heterosexual transmission of HIV will, most probably, remain concentrated among migrant groups, the heterosexual acquisition of HIV is often seen as being analogous to the spread of infection in the general population. This misconception may have arisen as a result of early national mass media campaigns, such as those in the UK (217) and Australia (218), suggesting everyone was potentially at equal risk of acquiring HIV. It may also be due to the situation in industrialised countries with concentrated epidemics, such as the UK, being confused with that in parts of sub-Saharan African where the heterosexual transmission of HIV has resulted in generalised epidemics.

National and international bodies have been accused of exaggerating the potential for the widespread heterosexual transmission of HIV in industrialised countries to garner political and funding support. The Joint United Nations Programme on HIV/AIDS has been accused of overstating the potential for HIV transmission to highlight the need for generalised HIV prevention programmes (219). The United States Public Health Service has been similarly accused to secure increased research funds (220).

It is important that the potential for HIV infection to spread in the general population is not overstated. This is particularly true in the context of HIV and migration. It has been suggested that fears relating to the spread of infectious diseases, such as HIV, have been conflated with those relating to migrants (221). Both in the UK (221) and the USA (222), it has been argued there is a strong association in the public mind between the spread of infectious diseases, such as tuberculosis and HIV, and foreigners and migration.

This conflation between spread of disease and migration is a cause for concern. In 2003, in an article entitled "*The secret threat to British lives*", it was reported that doctors feared African immigration might ignite a heterosexual epidemic in Britain (154). In 2003 and 2004, several UK bodies, including the Conservative party, called for compulsory screening of migrants for HIV (221, 223). One commentator expressed a fear that such calls for immigration control could tarnish the UKs reputation for its rational, coherent, and effective public health policy response to HIV (223).

In response to calls for greater action, including screening, the UK All-Party Parliamentary Group on HIV and AIDS established an inquiry in 2003 into the impact of the nationality and immigration system on people living with HIV (200, 223). Four

hearings were held where evidence was taken from HIV specialist clinicians, general practitioners, solicitors, community-based and national AIDS organisations, and migrants living with HIV (223). The inquiry found no supportive evidence for screening being an effective public health response. It was proposed that the screening of migrants could further stigmatise HIV and result in people actively avoiding testing (200, 223). It was recommended the Government oppose mandatory testing for HIV upon entry and instead promote HIV testing among migrants based on informed consent (200, 223).

In summary, there is evidence that the heterosexual transmission of HIV in E,W&NI will, for the most part, remain concentrated among black African migrants who live here. Equally, it appears that heterosexually-acquired HIV will also remain concentrated among migrants in other European countries.

4.10 Retention in care and outward migration from the UK

When assessing the role of migration in shaping the HIV epidemic among heterosexual adults in E,W&NI outward migration needs to also be considered. In paper 4.2, retention in HIV care was investigated. In the paper, nine out of ten adults attending HIV services in a given year between 1998 and 2006 were shown to attend for care the following year. Cumulatively, almost one in five adults seen for HIV care between 1998 and 2006 were reported as being lost to follow-up by the end of 2007. Nonetheless, the overwhelming majority continued to attend for care during the eight year study period.

In paper 4.2, the following groups were most likely to be lost from HIV care: of black African or "*other*" ethnicity; female; aged 15 to 34; not on antiretroviral therapy at last report; recently diagnosed with HIV; acquired HIV in Africa or elsewhere in Europe; acquired HIV heterosexually. In the paper I suggested that the association between loss to follow-up and black African ethnicity, acquiring HIV abroad, and having been recently diagnosed was indicative of migrants leaving the UK soon after receiving an HIV diagnosis. Although country of birth was not analysed in paper 4.2, there is evidence for the overwhelming majority of black Africans diagnosed with HIV being born abroad (36), and the majority of diagnosed foreign-born people having acquired HIV abroad (24).

Although there is no direct evidence for migrants leaving the UK following an HIV diagnosis, there is evidence for migrants, in general, leaving the UK. In 2012, almost

half of all migrants to the UK intended to stay for one or two years only (224). An estimated 209,000 former immigrants left the UK in 2012 (225). Former immigrants are those entering and leaving the UK as long-term international immigrants, and the figure of 209,000 was obtained from LTIM estimates in the IPS (see section 4.5) (225).

Estimates produced by the IPS should be interpreted with caution. In 2012, large discrepancies between migration estimates based on the IPS and the 2011 Census for England and Wales were identified. The Census based mid-year population estimate was almost 500,000 higher than the estimate based on combined 2001 Census and IPS data (226). The reason identified for the underestimation was that IPS interviews were concentrated at principal airports, such as Heathrow and Gatwick, at a time when an increasing number of migrants were travelling to regional airports (226). One commentator suggested this methodological issue highlighted limitations in using survey data to estimate net migration and emphasised the need for better national migration data (224). To address the inadequate sampling design and coverage of the IPS, more regional UK airports are now included in the survey and an increased number of migration interviews are conducted at key regional airports, such as Luton and Stansted (226).

Other studies have identified loss to follow-up from HIV care. Among HIV-positive individuals attending ten clinical centres in the UK who had one or more CD4 counts reported prior to April 2004, 44% were potentially lost to follow-up at least once (defined by the absence of a CD4 cell count for a year or more) (227). Of those lost to follow-up at least once, 40% were permanently lost to follow-up (227). This suggests approximately 18% of the study population were permanently lost to follow-up. The estimate of 18% of the study population being permanently lost to follow-up in the study by Hill was similar to my estimate of 19% in paper 4.2.

Potential loss to follow-up in the study by Hill was associated with being non-white, having acquired HIV heterosexually or by ‘‘*other*’’ risk, and having had a greater number of previous episodes of loss to follow-up (227). Interestingly, being male was also found to be associated with potential loss to follow-up (227). In paper 4.2, permanent loss of follow-up was associated with being female. This difference may be due to the different definitions of loss to follow-up applied. In paper 4.2, loss to follow-up was permanent (i.e. a person previously seen for HIV care was not seen again)

whereas, in the study by Hill persons were potentially lost to follow-up at least once if they didn't have their CD4 cell count recorded for a year or more. The difference in results by sex may, therefore, indicate that males are more likely than females to return to care following a period of loss to follow-up.

In paper 4.2, it was reported that annual estimates of retention in care would be made available in routine national surveillance outputs. A subsequent analysis of quality of HIV care during the first twelve months from HIV diagnosis, based on national surveillance data, investigated retention in care. Among 5,833 persons diagnosed with HIV in the UK in 2010, who were not reported as having died, 85% were seen for HIV care in 2011 (98). In paper 4.2, a higher percentage (90%) of adults attending services in a given year were shown to attend again the following year. Whereas the original study considered retention in care among all people seen for HIV care, the study by Delpech considered only persons newly diagnosed with HIV. In paper 4.2, a significantly lower rate of retention in care was found among those recently diagnosed. Two reasons for this were proposed. Some people, following an HIV diagnosis, may withdraw from HIV care until they are symptomatic, and some may leave the UK (see above in this section).

In the study by Delpech, little variation was reported across groups of newly diagnosed adults in the percentage retained in care (98). This is in contrast to the study described in paper 4.2. It may be that the association between a recent diagnosis of HIV and loss to follow-up from care masks differences between sub-groups of newly diagnosed adults.

Using the methods described in paper 4.2, a clinic-based audit was conducted among people seen for HIV care in 2010 but not 2011 (228). It was estimated that 2,132 were seen for care in 2010 but not 2011, and were not reported as having died. Of these, 964 (45%) probably remained in the UK, 590 (28%) had probably left the UK and for the remaining 578 (27%) their status was unknown (228). Of those who remained in the UK, it was reported that just over half (508/964; 53%) may have been wrongly assigned and were in care in 2011 and that a further 237 (25%) returned to care in 2012 (228). These findings lend support to the suggestion in paper 4.2 that permanent loss to follow-up from HIV care was, in part, explained by outward migration from the UK. Another potential reason for not accessing care services while remaining in country is fear of stigma and discrimination(119, 229).

Retention in HIV care has also been explored in the USA, and has been shown to be much lower than in the UK. Of the estimated 1,148,200 persons living with HIV in 2009, an estimated 82% had been diagnosed, 66% had been linked into care, and 37% were retained in care (230). Among people of black ethnicity diagnosed with HIV in 2010 in the USA, an estimated 75% were linked to care and 48% were retained in care (132). It was suggested that reasons for a low rate of retention among people of black ethnicity include poverty, lack of health insurance, and stigma (132). Among all adults aged 19 to 64 years seen for HIV care in the USA between January and April 2009, six in ten had a low income, and almost two in ten had no health insurance (231).

Another potential reason for loss to follow-up from HIV care in the USA was outward migration. The potential for HIV-diagnosed people leaving the USA has raised concern over continuity of care. Evidence of HIV-positive Mexicans returning to Mexico led to calls for a bi-national perspective to HIV training activities (232). If, as suggested in paper 4.2, outward migration partially explains loss to follow-up from HIV care in the UK, then continuity of care between countries is also of concern. The inclusion of a recommendation for research on bi-national approaches to continuity of HIV care in paper 4.2 would have been merited. No such recommendation was made.

It was recommended in paper 4.2 that innovative strategies be developed to maintain regular service engagement among groups at increased risk of dropping out of regular care. In response to paper 4.2, clinicians at two London Hospitals reported on an audit of a newly implemented policy to identify patients lost to follow-up and to return them back into care (233). Patients who had not attended either clinic for a period of one year or more were identified and contacted by phone or post. Among those successfully contacted, a third returned to care within a median period of 15.5 days (233).

4.11 Impact of the published research and recommendations

In papers 4.1 and 4.2, the impact of migration on heterosexually-acquired HIV in the UK was addressed. Paper 4.1 highlighted the need for HIV prevention activities targeting migrant communities in E,W&NI, particularly those from sub-Saharan Africa; paper 4.2 highlighted the importance of developing strategies to maintain regular engagement with HIV services in E,W&NI.

When designing and implementing HIV prevention strategies it is important to understand which population groups are at risk of acquiring HIV in the UK through heterosexual contact. In paper 4.1, the number of people born abroad reported as having acquired HIV heterosexually whilst living in the UK was significantly higher than previously estimated. Confident that the revised estimates presented in paper 4.1 were robust, a recommendation was made for this new method of assigning likely country of HIV acquisition to be applied in other countries where the number of HIV diagnoses among migrant populations was high. For this to be viable, country of birth, CD4 cell count at diagnosis, and year of arrival in host country would be required among HIV-diagnosed persons born abroad.

Of 24 European Union / European Free Trade Association countries responding to a 2012 questionnaire about HIV surveillance systems, nineteen reported collecting country of birth, twelve recorded date of arrival into their country, and seventeen collected CD4 count at diagnosis (73). Responding to the recommendation for the new method to be adopted by other countries, the ECDC identified Belgium, Denmark, France, Greece, Lithuania, Luxembourg, Malta, Romania and Slovakia as countries where it could potentially be applied to assign likely country of HIV acquisition (234).

At an ECDC workshop on improving the monitoring of HIV among migrant populations in Europe held in Madrid October 2013, Sweden, Belgium, Portugal and Italy volunteered to use the new method (234). In January 2014, I co-organised a workshop in London where representatives of these four countries, ECDC, and PHE met to discuss the project. During the two day workshop the new method was applied to national datasets from Sweden, Italy and Belgium. The application of the method to non-UK datasets was shown to be feasible. At the annual meeting of the network for Sexually Transmitted Infections and HIV held in Dubrovnik, Croatia in May, 2014, the ECDC reaffirmed its commitment for the new method to be rolled out to all European countries where migrants are disproportionately affected by HIV (234).

Further work is required to assess the level of disaggregation to which estimates of likely country of infection remain robust. To date estimates have only been presented by broad categorisations of sex, age, region of birth or ethnicity, and not by combinations of these variables. Additional analyses are also warranted to investigate whether published estimates of risk behaviour during foreign travel (192, 202, 203) may be

utilised to adjust estimates of likely country of infection. To better understand HIV transmission dynamics driving heterosexually-acquired HIV in the UK, research on assortative sexual mixing among migrant groups is merited, as is research on the potential association between increased dissortative sexual mixing and second generation migrants.

In paper 4.2, it was recommended that annual estimates of loss to follow-up among HIV-diagnosed adults be made available, and that loss to follow-up be included as a quality of care indicator. To conduct the analyses presented in paper 4.2, we created a cohort of adults attending HIV services. Being able to observe patterns of care and treatment among a cohort of HIV-diagnosed adults facilitated the design and implementation of a national set of quality of care indicators (98). Retention in care (the flipside to loss to follow-up) is now routinely reported on as a quality of care indicator (98).

It was also recommended in paper 4.2 that innovative strategies be developed to maintain regular service engagement among persons at increased risk of loss to follow-up. For a sizeable proportion of the study population in a recent clinic based audit of people seen for HIV care in 2010 but not 2011, reason for loss to follow could not be determined (228, 235). Not knowing the reasons for people leaving HIV care makes it difficult to develop strategies to maintain regular service engagement. Following the publication of paper 4.2, a London study reported partial success in maintaining service engagement by directly contacting people lost to follow-up (see section 4.10) (233). To reduce HIV-related morbidity and mortality, further research is warranted to identify more effective methods for retaining people in HIV care.

Paper 4.2 also highlighted the need for research into continuity of care among HIV-diagnosed persons leaving the UK. It is likely that a sizeable proportion of people lost to care are returning to their country of origin. Research should, therefore, be conducted into bi-national approaches to ensure efficient and effective pathways of care among HIV-diagnosed people leaving the UK.

In this chapter I have presented numerous definitions of migrants and migration. It is essential that migrants are defined in a way that clearly highlights their varying risks for HIV. A workable definition of migrants at risk of HIV also needs to avoid reinforcing negative stereotypes that may promote stigma and discrimination.

In papers 4.1 and 4.2, I presented evidence for the utility of categorising migrants according to their ethnicity and country of birth. These two variables can be utilised through research and surveillance to highlight heterogeneity in risk of acquiring or living with HIV among migrants. Heterogeneity in risk is more readily highlighted by these two variables when combined with HIV prevalence estimates according to country of birth and / or ethnicity (see section 4.6.7). In future, information on ethnicity and country of birth should be combined with that on assortative sexual mixing to better understand existing and emerging patterns of risk among migrants.

5. HIV and Tuberculosis co-infection

Summary

In this chapter, I explore HIV-tuberculosis co-infection among heterosexuals. The published paper included in this chapter is called "*Decreasing incidence of tuberculosis among HIV diagnosed heterosexuals in England and Wales*" (39). In the paper I highlighted how one in ten heterosexual adults living with diagnosed HIV in England and Wales between 2002 and 2010 were diagnosed with active tuberculosis. I also reported that the annual incidence rate of active tuberculosis in the HIV-positive study population declined between 2002 and 2010. Despite this decline the incidence of tuberculosis among HIV-diagnosed heterosexuals remained substantially higher than in the general UK population.

In this chapter, I investigate HIV-tuberculosis co-infection in the UK and other European countries. I also explore HIV-tuberculosis service provision in these countries.

5.1 Introduction

The British HIV Association guidelines for the treatment of TB/HIV co-infection state that persons living with HIV and latent tuberculosis are much more likely than their HIV negative counterparts to progress to active tuberculosis (236). Among people living with HIV, tuberculosis is the leading cause of illness and death globally (38, 237). In 2012, HIV-associated tuberculosis was estimated to have killed 320,000 people worldwide (38, 237). The majority of these deaths occurred in sub-Saharan Africa (38, 237).

In 2012, there were 6,364 HIV diagnoses and 8,751 reported cases of active tuberculosis in the UK (3, 46). Diagnoses of both infections were elevated among ethnic minority groups and persons born abroad, including those of black African ethnicity born in sub-Saharan Africa (3, 36, 46). In Chapters 3 and 4, I reported how the majority of heterosexuals diagnosed with HIV in E,W&NI were born in sub-Saharan Africa. As a consequence, HIV-tuberculosis co-infection is of particular importance for this population group.

This chapter includes a paper which I published in a peer-reviewed journal. In the paper I presented annual incidence rates of tuberculosis between 2002 and 2010 among heterosexual adults living with diagnosed HIV in England and Wales. By examining the relationship between the date of HIV diagnosis and the date of tuberculosis diagnosis, I highlighted missed opportunities for early HIV testing in tuberculosis settings and vice versa.

In this chapter, after summarising the key findings from the paper, I go on to explore HIV-tuberculosis co-infection and service provision among heterosexual adults living in the UK and elsewhere in Europe. Unless I state otherwise, tuberculosis refers to active rather than latent infection.

5.2 The published paper: Rice et al., AIDS 2013

Decreasing incidence of tuberculosis among heterosexuals living with diagnosed HIV in England and Wales

http://www.ncbi.nlm.nih.gov/pubmed/23276802

Objectives: To calculate annual tuberculosis incidence rates, and investigate risk factors for tuberculosis, among heterosexual adults living with diagnosed HIV in England and Wales.

Design: Analyses of comprehensive national records of persons seen for HIV care between 2002 and 2010 linked to the national tuberculosis database (1999–2010) for England and Wales.

Methods: Annual incidence rates of tuberculosis among heterosexual adults living with diagnosed HIV were calculated on the basis of the number of heterosexual adults seen for HIV care in a given year and the number, in that same year, with a first episode of tuberculosis at the time of, or subsequent to, their HIV diagnosis.

Results: Between 2002 and 2010, almost one in 10 (4266/45 322) heterosexual adults living with HIV were diagnosed with tuberculosis, of whom the majority (92%) were diagnosed at the time of, or after, their HIV diagnosis; 84% (3307) were black African. The annual tuberculosis incidence rate decreased from 30 per 1000 in 2002 to 8.8 per 1000 in 2010 ($P < 0.01$). The annual tuberculosis incidence rate among those not on antiretroviral therapy (ART) was significantly higher than among those using ART (2010: 36 versus 3 per 1000; $P < 0.01$).

Conclusions: The annual tuberculosis incidence rate among heterosexual adults living with diagnosed HIV in England and Wales has declined significantly over the past decade. However, the 2010 rate remains significantly higher than in the general population. Our findings support routine HIV testing in tuberculosis clinics, screening for latent tuberculosis in HIV diagnosed persons, and the prompt initiation of ART where appropriate.

5.3 Research findings from my published paper

My published paper in this chapter is called "*Decreasing incidence of tuberculosis among HIV diagnosed heterosexuals in England and Wales*" and was published in the journal *AIDS* in 2013 (39). In this chapter, I refer to it as paper 5.1.

In paper 5.1, I described how one in ten heterosexual adults living with diagnosed HIV in England and Wales between 2002 and 2010 were diagnosed with tuberculosis. I reported that the annual incidence rate of tuberculosis among HIV-diagnosed heterosexuals declined from 30 per 1,000 in 2002 to nine per 1,000 in 2010. The incidence rate of tuberculosis in 2010 was elevated among the following groups of HIV-diagnosed heterosexuals: aged 35 year and above at HIV diagnosis; male; born abroad; infected abroad; not on antiretroviral therapy; with a CD4 cell count <200 cells/ml at HIV diagnosis.

I highlighted in paper 5.1 how the decline in the incidence of tuberculosis over time coincided with a decline in the overall number of heterosexuals in the UK acquiring HIV in sub-Saharan Africa and an increase in the uptake of antiretroviral therapy among persons diagnosed late. I also highlighted how, despite the decline in incidence over time, the rate in 2010 of nine tuberculosis cases per 1,000 HIV-diagnosed heterosexuals greatly exceeds the rate of 0.1 per 1,000 in the general UK population.

I investigated in paper 5.1 the relationship between the date of HIV diagnosis and the date of tuberculosis diagnosis. Among those diagnosed with tuberculosis, I reported the majority to have been diagnosed simultaneously with HIV. However, I also reported that a substantial number of heterosexuals were diagnosed with tuberculosis more than six months after HIV, and a small number were diagnosed six or more months prior to HIV diagnosis. Diagnosis of tuberculosis more than six months after an HIV diagnosis represents a missed opportunity for the earlier diagnosis of tuberculosis. However, it's possible that tuberculosis diagnosed more than six months after HIV diagnosis may not have been present at the time of the HIV diagnosis. In which case, this represents a missed opportunity for the prevention of tuberculosis which the patient acquired after being diagnosed with HIV infection. Conversely, the diagnosis of tuberculosis prior to an HIV diagnosis represents a missed opportunity for the early diagnosis of HIV (which almost certainly was present at the time of the tuberculosis diagnosis).

In this chapter I explore HIV-tuberculosis co-infection in the UK and elsewhere in Europe. Considering the evidence I presented in paper 5.1 of missed opportunities for earlier testing, and therefore earlier treatment, I also examine HIV-tuberculosis service provision in the UK and elsewhere in Europe.

5.4 Literature search

Using the methods I describe in Chapter 2 (section 2.8), I conducted a computerised and manual literature search in relation to two topics raised in the published paper in this chapter. These were: (i) the incidence of active tuberculosis among HIV-diagnosed heterosexuals in the UK and elsewhere in Europe; (ii) HIV-tuberculosis service provision in the UK and elsewhere in Europe. Appendix iii lists details of the searches conducted for this chapter. The identified papers provide the foundation for the rest of this chapter.

5.5 HIV-tuberculosis co-infection in the UK and elsewhere in Europe

The degree to which HIV-tuberculosis co-infection is seen as a public health priority differs between European countries dependent on burden of disease (238). Nonetheless, the World Health Organisation recommends the surveillance of tuberculosis among persons living with HIV, and vice versa, be carried out in all countries (239).

Unfortunately, many European countries lack access to reliable data for HIV-tuberculosis co-infection and remain unaware of the current epidemiology of HIV-tuberculosis co-infection (238, 240). In many European countries major gaps in HIV and tuberculosis surveillance result in the prevalence of co-infection being reported as a rough estimate (241, 242).

5.5.1 Incidence of tuberculosis among HIV-diagnosed persons

In section 5.3, I reported rates and trends in tuberculosis incidence among HIV-diagnosed heterosexuals in England and Wales. Similar rates and trends among HIV-diagnosed persons have been reported elsewhere in Europe. In Western Europe as a whole, the incidence of tuberculosis among HIV-diagnosed persons declined between 1994 and 2003 before stabilising between 2004 and 2010 (243). In Denmark, the incidence of tuberculosis among HIV-diagnosed persons decreased from 37 per 1,000 person-years in 1995/1996 to 6.5 per 1,000 person years between 2000 and 2007 (244).

Between 1987 and 2006, the incidence of tuberculosis among HIV-diagnosed persons in Spain decreased from 200 per 1,000 person-years to fifty per 1,000 person-years (245). This decline was observed to continue up to 2010 (246).

Despite a decline over time, the incidence of tuberculosis among HIV-diagnosed persons in Spain greatly exceeds that in the UK and Denmark. It has been suggested that rates of tuberculosis among HIV-diagnosed persons are elevated in countries where the prevalence of tuberculosis in the general population is high (243). After Portugal, Spain has been reported to have the second highest overall tuberculosis incidence rate in Western Europe (247). It is not clear from the literature why the prevalence of tuberculosis is high in Spain. In Spain's neighbour Portugal, elevated prevalence of tuberculosis has been linked with historic failure in integrating tuberculosis prevention programmes into the primary healthcare system, slow economic recovery during the 1970's and 1980s, and migration into overcrowded city areas (248).

In France, the incidence of tuberculosis among HIV-diagnosed persons between 1997 and 2008 was four per 1,000 patient-years (249). In contrast to the UK, Denmark and Spain, the incidence of tuberculosis among HIV-diagnosed persons in France has increased in recent years (249).

The increase observed in France has partially been put down to an *increased* proportion of the HIV-infected population being born in sub-Saharan Africa where there is a high prevalence of tuberculosis (249). Conversely, I suggest in paper 5.1 that the decline in tuberculosis incidence among HIV-diagnosed heterosexuals in England and Wales was partially explained by a *fall* in the number of heterosexuals in the UK acquiring HIV in sub-Saharan Africa. It is possible that the decline in tuberculosis incidence observed among HIV-diagnosed persons in Denmark and Spain are also partly related to fewer migrants acquiring HIV in countries where the prevalence of HIV and tuberculosis is high. In both countries approximately four in ten HIV diagnoses are among migrants (181).

In addition to highlighting the impact of migration on the declining incidence of tuberculosis among HIV-diagnosed heterosexuals I also emphasise in paper 5.1 an association between falling incidence and increased uptake of antiretroviral therapy among HIV-diagnosed persons. In the UK, the incidence of tuberculosis among all HIV-diagnosed persons has been shown to decline in response to the commencement of

antiretroviral therapy (250). A similar association has been observed in Spain (251). In Denmark a decline in tuberculosis incidence after HIV diagnosis has been attributed, in part, to antiretroviral therapy related immunological restitution (244).

There is evidence that the impact of antiretroviral therapy in reducing the incidence of tuberculosis among HIV-infected populations is limited. In a UK study, the incidence of tuberculosis remained substantial among HIV-diagnosed persons of non-white ethnicity even after 24 months of treatment (250). The authors of the study suggested their finding was explained by a higher risk of previous tuberculosis exposure and lower CD4 cell count among black African migrants both at study entry and after the start of antiretroviral treatment (250). Among twelve cohorts from Europe and North America of HIV-diagnosed persons commencing antiretroviral therapy, a considerable risk of tuberculosis was reported, even among those with a good response to treatment (252). In a subsequent study of these twelve cohorts, a reduction of 44% in tuberculosis incidence among all HIV-diagnosed persons commencing antiretroviral therapy was observed (253). However, when focusing on HIV-diagnosed persons aged 50 years or above, or with a CD4 cell counts <50 cells/ml, no reduction was observed (253).

A recent study, based on the same data I presented in paper 5.1, found tuberculosis incidence among HIV-diagnosed black Africans (the majority of whom acquired HIV heterosexually) in receipt of antiretroviral therapy for five years or longer to be similar to that among HIV-negative black Africans (254). However, among white HIV-diagnosed persons in receipt of long-term treatment, tuberculosis incidence remained elevated as compared to the HIV-negative white population (254). The authors of the study suggested additional social risk factors for tuberculosis, difficult to measure on a population-level, may explain this finding (254).

It has been argued that due to limitations in antiretroviral therapy reducing the incidence of tuberculosis among HIV-infected populations additional interventions are required (252). In contrast to this viewpoint, it has been suggested efforts be made to improve the impact of antiretroviral therapy through the promotion of earlier HIV diagnosis allowing treatment to be commenced when clinically indicated rather than at advanced immunodeficiency (253). It has also been proposed that tuberculosis incidence could be further reduced simply by effectively implementing existing recommendations to prevent tuberculosis in early HIV infection (255).

5.5.2 Characteristics of persons co-infected with HIV and tuberculosis

In paper 5.1, I reported the annual incidence of tuberculosis to be elevated among HIV-diagnosed heterosexuals aged 35 year and above at HIV diagnosis, men, persons born and / or infected abroad, and those not on antiretroviral therapy or with a CD4 cell count <200 cells/ml at HIV diagnosis. Although I did not find ethnicity to be associated with an elevated annual incidence of tuberculosis I did report in paper 5.1 that co-infected heterosexuals were more likely to be of black African or Indian, Pakistani and Bangladeshi ethnicity than those without tuberculosis.

It has been proposed that the ethnic distribution of HIV-tuberculosis co-infected persons reflects the wider HIV-infected population in the UK rather than the tuberculosis infected population (256). This makes sense, as many co-infected persons will have acquired tuberculosis as a result of their HIV infection but not vice versa. As such, the characteristics of co-infected persons will be determined by risk factors for HIV infection and not tuberculosis.

In England and Wales between 1993 and 1998 black Africans were shown to constitute a substantially larger proportion of the co-infected population than persons born in the Indian sub-continent (256). Among tuberculosis patients found to be co-infected with HIV in the UK between 1999 and 2003, seven in ten were black African, one in ten were white, and one in fifty were Indian, Pakistani or Bangladeshi (257).

Similar associations to those I reported in paper 5.1 in relation to elevated tuberculosis incidence have been observed elsewhere in Europe. In Switzerland, persons diagnosed with HIV up to 1994 from countries with a high prevalence of tuberculosis had a significantly greater risk of co-infection than those from low prevalence countries (258). African and Asian origin, low CD4 cell count at HIV diagnosis, and a lack of antiretroviral therapy have been identified as risk factors for tuberculosis co-infection among HIV-diagnosed persons in Denmark (244). In France, a higher incidence of tuberculosis has been observed among HIV-diagnosed persons born abroad, not in receipt of antiretroviral therapy, and with a low CD4 cell count (249). Between 1997 and 2008, the incidence rate of tuberculosis among HIV-diagnosed migrants in France was ten per 1,000 whereas among non-migrants the figure was two per 1,000 (249). In Spain, tuberculosis co-infection among HIV-diagnosed persons has been associated with low education level, being "*sub-Saharan African*", not being in receipt of

antiretroviral therapy, and having a CD4 cell count <200 cells/ml (259). The incidence of tuberculosis among HIV-diagnosed persons in Spain was elevated among migrants in all years between 1987 and 2006 (245). In 2006, almost half of all new cases of HIV-tuberculosis co-infection were among migrants to Spain, and migrants were significantly more likely than "*Spaniards*" (83% versus 17%) to be diagnosed with HIV and tuberculosis in the same year (245).

The association with African or Asian origin and co-infection in Denmark has been put down to persons from high tuberculosis burden countries being at greater risk of infection due to reactivation of latent tuberculosis (244). It is likely that reactivation of latent tuberculosis partly explains the associations between HIV-tuberculosis co-infection and non-white ethnicity, being born abroad, and / or being a migrant seen elsewhere in Europe.

In paper 5.1, my study population consisted of only persons who had acquired HIV heterosexually. I therefore did not include probable route of HIV infection in my analysis. Probable route of HIV infection has been analysed in studies conducted in Denmark and Spain. In both countries acquiring HIV heterosexually or through injecting drug use were shown to be risk factors for tuberculosis (244, 245).

In relation to HIV co-infection among tuberculosis patients, males, persons born abroad, injecting drug users, young adults (aged 25 to 30 years), urban residents, the homeless and prisoners represent high-risk groups across Europe (260). Of this list, the first three are also risk factors for tuberculosis among HIV-diagnosed persons (see above). Information on urban residency, homelessness and prison stay are not routinely considered in HIV risk analysis or collected through HIV surveillance.

The finding that tuberculosis patients aged 25 to 30 years are at increased risk of HIV is difficult to interpret. In paper 5.1, I reported that HIV-diagnosed heterosexual in England and Wales aged 35 years or above at HIV diagnosis to be at increased risk of tuberculosis. The contrasting findings may reflect differences between the two study populations. The disparity in age would also be expected if, as compared with tuberculosis diagnoses in HIV settings, a greater proportion of people diagnosed with HIV in tuberculosis setting were identified through routine screening rather than waiting for presentation of disease. I discuss testing policies in sections 5.6.1 and 5.6.2.

Late HIV diagnosis may partly explain the association between older age and elevated annual incidence of tuberculosis. In Chapter 3, section 3.6.1, I report late HIV diagnosis among heterosexuals to be associated with older age at diagnosis. I also report late HIV diagnosis to be associated with male sex. Late HIV diagnosis may, therefore, also partly explain the association I report in paper 5.1 between men and elevated annual incidence of tuberculosis.

5.6 HIV-tuberculosis service provision in the UK and elsewhere in Europe

How should HIV-tuberculosis co-infection be managed? To reduce the burden of HIV and tuberculosis in populations affected by both diseases, the World Health Organisation recommends the implementation of collaborative co-infection activities based on effective national HIV and tuberculosis control strategies (38, 237). In the UK, close cooperation in the clinical management and accurate notification of HIV and tuberculosis cases has been described as being essential for providing appropriate care to persons infected with both diseases (257). Close cooperation would be guaranteed, it has been argued, if HIV-tuberculosis co-infected patients in the UK were managed, where possible, in dedicated co-infection clinics (261). Despite support from the Chief Medical Officer for joint HIV-tuberculosis patient services, a national audit of HIV and tuberculosis services in 2007/2008 found the dominant mode of care for co-infected patients was liaison between HIV and tuberculosis clinicians with each managing their own aspect of care (262).

Several obstacles to implementing collaborative co-infection activities have been identified. These include parallel HIV and tuberculosis control systems and a lack of a national coordination body or national policy on co-infection (242).

In 2005, only four in ten European countries reported having a national body responsible for coordinating HIV-tuberculosis activities and only one in three reported having a national plan for collaborative activities (242). Although no single body co-ordinates HIV-tuberculosis activities in the UK, there are guidelines for collaborative working practice. In 1998, the UK Department of Health published guidance on the prevention and control of transmission of HIV-related tuberculosis (263). In 2007, the Department of Health suggested tuberculosis clinicians share the management of tuberculosis patients found to be co-infected with HIV with HIV specialists and, similarly, HIV clinicians only treat HIV/AIDS patients who develop tuberculosis in

consultation with tuberculosis clinicians (47). In addition to Department of Health guidance, the British HIV Association and National Institute for Health and Clinical publish updated guidelines for the testing and treatment of HIV-tuberculosis co-infection (236, 264).

Stigma and a lack of financial support also act as obstacles to implementing collaborative co-infection activities. It has been argued that the social effect of combining two highly stigmatising diseases adversely affects health-seeking behaviour thereby reducing the effectiveness of co-infection activities (265). Despite persons diagnosed with HIV in Eastern Europe being at a substantially greater risk of developing tuberculosis compared to HIV-diagnosed persons in Western Europe, it has been suggested Eastern European countries struggle to attract much needed international research and financial support for managing HIV-tuberculosis co-infections (265). This is because when compared to many African countries those in Eastern Europe are still seen as low priority (265).

Notwithstanding obstacles, in the UK and elsewhere in Europe efforts are being made to reduce the burden of tuberculosis among persons living with HIV and vice versa. A common approach to achieving this is the promotion of tuberculosis testing in HIV settings and HIV testing in tuberculosis settings.

5.6.1 Testing for tuberculosis among HIV-diagnosed persons

In paper 5.1, I reported a substantial number of heterosexuals being diagnosed with tuberculosis more than six months subsequent to their HIV diagnosis. It is highly likely that a number of these persons could have been prevented from progressing to active tuberculosis had they been tested and treated for latent tuberculosis at the time of their HIV diagnosis.

Preventing progression from latent to active tuberculosis through prescribing chemoprophylaxis (a therapeutic measure for the prevention of tuberculosis or to avoid development of disease in tuberculosis infected persons) has been shown to be achievable among the following groups of HIV-diagnosed people in the UK: from sub-Saharan Africa and on antiretroviral therapy for less than two years; from middle tuberculosis incidence countries on antiretroviral therapy less than two years and with a CD4 cell count <500 cells/ml; from low tuberculosis incidence countries on

antiretroviral therapy for less than six months and with a CD4 cell count <350 cells/ml (236). It is among these three groups of HIV-infected persons that the British HIV Association recommends screening for latent and active tuberculosis (236). The National Institute for Health and Clinical Excellence combines these three groups in its broader recommendation for tuberculosis screening among all HIV-infected persons with a CD4 cell count <500 cells/ml (264). The institute also recommends treatment of latent tuberculosis be considered for all persons living with HIV (264).

In a London-based study, testing HIV patients for tuberculosis was shown to identify more cases of latent and active tuberculosis than typically found during contact tracing (266). The same study also showed tuberculosis preventive treatment among those diagnosed to be acceptable, with 85% of patients completing their tuberculosis chemotherapy regimen (266).

In the UK and elsewhere in Europe effective interventions, tests and treatments for tuberculosis among persons living with HIV are available (236, 242, 252, 264). Despite this, the incidence of tuberculosis remains elevated among HIV-diagnosed populations and a high number of tuberculosis associated deaths still occur among persons living with HIV (250, 252, 254). It has been argued that the underlying reason for this paradox has nothing to do with the effectiveness of diagnostic tests or preventive therapies but rather a lack of adherence by clinicians to existing guidelines (267).

5.6.2 Testing for HIV among tuberculosis patients

In addition to highlighting missed opportunities for earlier testing for tuberculosis, I also presented evidence in paper 5.1 of missed chances to diagnose HIV more promptly. In paper 5.1, I report a small number of HIV-diagnosed heterosexuals to be diagnosed with tuberculosis six or more months prior to HIV. As HIV often remains undiagnosed for several years it is probable that some of these persons were living with HIV when diagnosed with tuberculosis.

Previous studies have presented evidence of potential missed opportunities for earlier HIV testing in tuberculosis setting. Among tuberculosis patients in Greater London between 2003 and 2004, almost half were not offered an HIV test (117). In the West Midlands, less than half of tuberculosis patients seen in 2008/2009 were tested for HIV (118). The authors of a study of tuberculosis among Africans living in London

suggested symptom misinterpretation and HIV-related stigma may result in reducing HIV test uptake in tuberculosis settings (116).

To promote HIV testing, the British HIV Association in 2008 recommended universal HIV testing in healthcare services for persons diagnosed with tuberculosis (138). Subsequent to this, the National Institute for Health and Care Excellence recommended all tuberculosis patients in the UK receive a risk assessment for HIV (264). It is possible that these recommendations are having some impact. In 2013, among persons diagnosed with tuberculosis in the UK and for whom information was available, nine in ten were offered and received HIV testing (268).

As in the UK, many other European countries recommend HIV testing in tuberculosis settings. Amongst European countries surveyed in 2005, four in ten had a national surveillance system to monitor HIV among tuberculosis patients and nine in ten had a national policy offering HIV testing and counselling to tuberculosis patients (242). Of 25 European countries participating in a 2010 survey, 22 reported having a national recommendation for testing tuberculosis patients for HIV infection (241). Despite such recommendations, missed opportunities persist. Among the 22 European countries with a national recommendation, HIV testing among tuberculosis patients ranged from 5% to 90% (241).

The benefit of testing tuberculosis patients for HIV has been questioned. In 2003, it was suggested universal HIV testing among tuberculosis patients in chest clinics within the UK was unlikely to significantly reduce the number of people living with undiagnosed HIV (269). Among HIV-diagnosed persons starting treatment for active tuberculosis in the UK between October 2007 and April 2008, four in ten had their HIV infection diagnosed as part of their investigation for tuberculosis or as a direct result of their tuberculosis diagnosis (262). In 2011, 326 people diagnosed with tuberculosis in the UK were found to be co-infected with HIV (270). If we assume four in ten of these 326 people had their HIV infection diagnosed in 2011 as a result of investigations for tuberculosis this would result in 130 people living with undiagnosed HIV having been found. In 2011, an estimated 22,600 people were living in the UK with undiagnosed HIV (271).

Even if the potential yield from HIV testing among tuberculosis patients is small, the promotion of testing is essential as it is likely that those presenting with undiagnosed

HIV in tuberculosis settings will be in need of antiretroviral therapy (i.e. they are presenting with an AIDS defining illness). Between 2010 and 2012, tuberculosis was the second most common AIDS defining illness among all HIV-diagnosed people, after *Pneumocystis jirovecii* pneumonia (3).

5.7 Impact of published research and recommendations

In paper 5.1, I explored the incidence of tuberculosis among heterosexuals living with diagnosed HIV in England and Wales. In the paper I highlighted how, despite a decline in tuberculosis incidence between 2002 and 2010, the rate among HIV-diagnosed heterosexuals in 2010 still greatly exceeded the rate in the general UK population. I also provided evidence in paper 5.1 of missed opportunities for earlier testing of tuberculosis and HIV.

To conduct the analysis for paper 5.1, I linked national HIV surveillance data with national tuberculosis surveillance data and sought guidance from both HIV and tuberculosis surveillance and clinical specialists. The bringing together of these specialists for the purpose of discussing my analysis was the beginning of the UK Tuberculosis and HIV Research Epidemiology and Development group (UK-THRED). The original membership of the group is reflected in the list of authors on paper 5.1. The group continues to meet on a six monthly basis.

Discussions during UK-THRED meetings have guided three subsequent analyses of the wider dataset I created (i.e. includes persons infected with HIV through all routes). In May, 2015, Dr Rishi Gupta had a paper entitled "*Does antiretroviral therapy reduce HIV-associated tuberculosis incidence to background rates? A national observational cohort study from England, Wales, and Northern Ireland*" published in the *Lancet HIV* (254). In March, 2015, Dr Rishi Gupta also had a paper entitled "*CD4 cell count responses to anti-retroviral therapy are not impaired in HIV-infected individuals with tuberculosis co-infection*" accepted for publication in *AIDS*. Also in March, 2015 Dr Dominik Zenner had a paper entitled "*Impact of tuberculosis on the survival of people living with HIV infection in England, Wales and Northern Ireland, 2000-2008*" published in *Thorax* (272).

Based on the results presented in paper 5.1, I recommended the universal offer of an HIV test to all persons diagnosed with tuberculosis be extended to all relevant

healthcare settings to promote optimal care for patients with tuberculosis and ensure antiretroviral therapy is initiated appropriately. I highlighted the importance of initiating antiretroviral therapy on time to reduce the incidence of active tuberculosis among HIV-diagnosed people and concluded that integrated tuberculosis and HIV services were key to ensuring the recommendation for screening and possibly treating HIV-infected patients for latent tuberculosis was followed. The most recent national guidelines for the treatment of TB/HIV co-infection were published in 2011 prior to the publication of paper 5.1 in 2013 (39, 236). The recommendations of paper 5.1 have not, to date, been adopted.

From the literature search I conducted for this chapter it is clear that a lack of adherence to existing guidelines is a major underlying reason for why the incidence of tuberculosis remains elevated in HIV-diagnosed populations. To improve the impact of antiretroviral therapy on reducing tuberculosis incidence, and to promote earlier diagnosis of HIV, it is essential that existing UK Department of Health, British HIV Association, and National Institute for Health and Clinical recommendations are effectively implemented and adhered to. In addition, it is essential that close cooperation is fostered in the clinical management and accurate notification of HIV and tuberculosis cases. To monitor and evaluate the impact of existing recommendations and interventions, accessible, reliable and comprehensive surveillance data on HIV-tuberculosis co-infection are required.

6. HIV testing

Summary

In this chapter, I explore HIV testing among black Africans living in E,W&NI. The paper accompanying this chapter is called "*HIV testing among black Africans living in England*" (40).

In the paper I presented results from the Mayisha II study, a community-based cross-sectional survey of HIV prevalence, sexual attitudes and lifestyles among black African adults attending commercial and social venues in London, Luton, and the West Midlands in 2004 (41, 48). In Mayisha II less than half (44%) the participants had ever tested for HIV. The percentage was similar for those who were HIV-negative (44%) and those living with undiagnosed HIV (45%) (40).

In this chapter I investigate HIV testing among black Africans living in E,W&NI. I describe the uptake of HIV testing and rates of undiagnosed HIV among black Africans. I also consider the benefits of reducing the number of black African adults living with undiagnosed HIV. I then examine barriers to HIV testing and discuss current strategies for promoting HIV testing in this population.

Based on the published paper and my review of the literature I recommend that HIV testing be promoted among black African women and men in a range of healthcare and community settings and that the 2008 and 2011 national guidelines on HIV testing be adhered to. I also recommend further research into the frequency of HIV testing among black Africans.

6.1 Introduction

Heterosexual men and women living with HIV in E,W&NI, the majority of whom are black African, have elevated rates of late diagnosis and undiagnosed HIV infection (268). In Chapter 3, I reported that the percentage of heterosexuals diagnosed late in E,W&NI changed little between 2002 and 2011. It is important to reduce the number of people living with undiagnosed HIV in order to maximise the benefits of earlier detection (by improving a person's health and life expectancy through treatment), and to minimise the risk of onward transmission (through antiretroviral treatment and

behavioural change). Increasing HIV testing rates among heterosexuals, particularly among black Africans in E,W&NI, is central to achieving this.

In this chapter, I present a paper, published in a peer-reviewed journal, in which I examine the uptake of HIV testing among black Africans living in England prior to the introduction of national testing guidelines in 2008. After summarising the key findings from the paper, I investigate the uptake of HIV testing, undiagnosed HIV and the benefits of reducing the number of black Africans living with undiagnosed HIV in E,W&NI. I also consider current strategies to promote HIV testing in this country.

6.2 The published paper: Rice et al., Epidemiology & Infection 2012

HIV testing in black Africans living in England

http://www.ncbi.nlm.nih.gov/pubmed/23040613

Summary: We examined the uptake of HIV testing in black Africans living in England before the introduction of national testing guidelines. Analyses were conducted using data from an anonymous self-completed questionnaire linked to oral fluid samples to establish HIV status in black Africans attending community venues in England in 2004. Of 946 participants, 44 % had ever been tested for HIV and 29 % had been tested in the previous 24 months. Of those with undiagnosed HIV, 45 % had previously had a negative HIV test. Almost a third of people tested in the UK had been at general practice. Uptake of HIV testing was not associated with perceived risk of HIV. These findings highlight the need for the implementation of national HIV testing guidelines in the UK, including the promotion of testing in general practice. Regular testing in black Africans living in the UK should be promoted regardless of their HIV test history.

6.3 Research findings from my published paper

My published paper in this chapter is called "*HIV testing among black Africans living in England*" and was published in the journal *Epidemiology and Infection* in 2012 (40). In this chapter, I refer to it as paper 6.1.

In paper 6.1, I presented results from the Mayisha II survey. Mayisha II was a community-based cross-sectional survey of HIV-prevalence, sexual attitudes and lifestyles among black Africans aged 16 years and over attending community-identified commercial and social venues in London, Luton and the West Midlands in 2004 (see Chapter 2 (section 2.2.2)) (41, 48). The overwhelming majority of the black African participants were born in Africa (94%) and were heterosexual (92%) (41).

In the paper, I reported that among the 1,006 black African Mayisha participants for whom a valid HIV laboratory test result was available 865 (86%) were HIV negative, 48 (5%) were living with diagnosed HIV infection, and 93 (9%) were living with undiagnosed HIV infection. Less than half (44%) of the black African study participants had ever tested for HIV. The proportion of participants who had ever tested was similar among those who were HIV negative (44%) and those living with undiagnosed HIV (45%). Among participants living with undiagnosed HIV infection who *had* previously tested negative for HIV, the overwhelming majority had had an HIV test in the previous 24 months in the UK.

In this chapter, I explore the uptake of HIV testing among black Africans in E,W&NI, rates of undiagnosed HIV and the benefits of reducing the number of black Africans living with undiagnosed HIV through improved uptake of testing. I also consider barriers to HIV testing and discuss current strategies to promote HIV testing in this country.

6.4 Literature search

I conducted a computerised literature search in relation to two topics raised by the published paper in this chapter. These were: (i) HIV testing among black Africans in E,W&NI; (ii) undiagnosed HIV among black Africans in E,W&NI. I also conducted a related computerised literature search on barriers to, and triggers for, HIV testing among black Africans living in E,W&NI. The searches also included the term "*heterosexuals*" in general. Appendix iii lists details of the searches conducted for this chapter.

6.5 Uptake of HIV testing among Black Africans in E,W&NI

In paper 6.1, I reported that 44% of Mayisha II black African participants in 2004 had ever tested for HIV (after excluding participants living with diagnosed HIV infection). The uptake of testing was similar among HIV-negative participants (44%) and those living with undiagnosed HIV (45%). Among women, 47% reported having ever tested for HIV whereas, among men, the figure was lower at 41%, although this difference was not statistically significant (40).

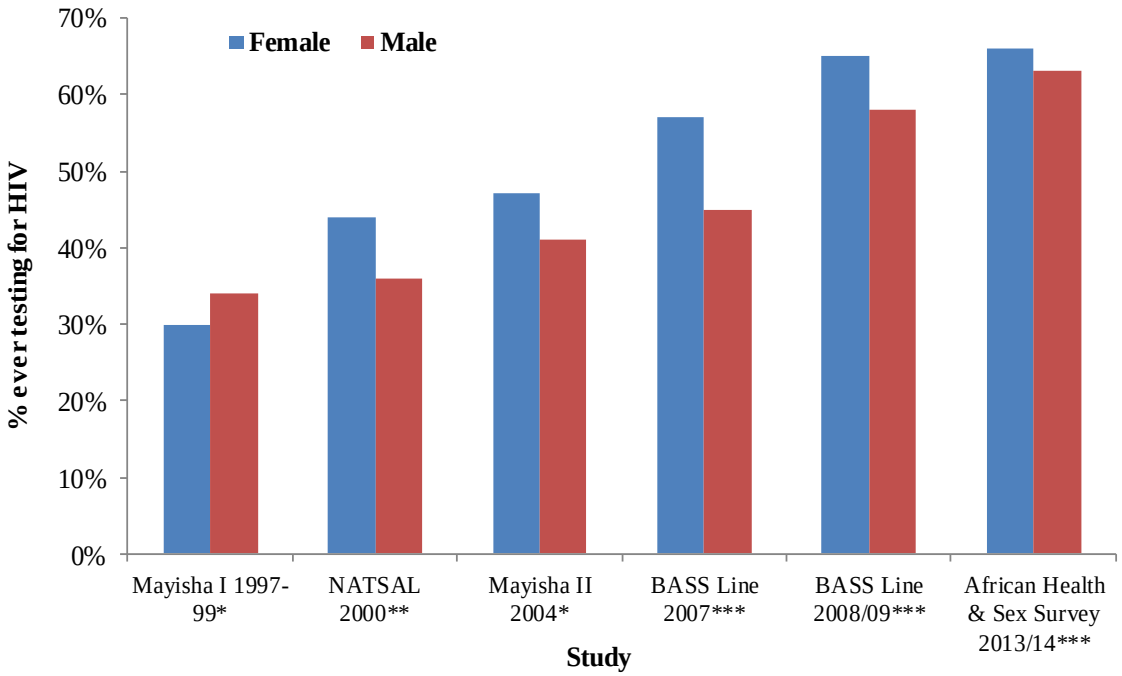
The rates of testing I reported in paper 6.1 were higher than those reported in the Mayisha I study conducted six years earlier. Between 1997 and 1999, 30% of female migrants and 34% of male migrants from five sub-Saharan African communities resident in London reported having ever tested for HIV (273).

Between the two Mayisha studies, the increase in testing was greater among women (17% increase) than men (7% increase). The introduction in 1999 of the routine offer and recommendation of an HIV test to all antenatal clinic attendees probably explains why a greater increase in the uptake of testing was observed among women than men. A similar pattern was seen in France where sub-Saharan African women living in Paris were more likely to have ever tested for HIV than sub-Saharan African men (172). This was also explained by the acceptance of free screening tests systematically offered in France to all women during their first prenatal visit.

In the second National Survey of Sexual Attitudes and Lifestyles (Natsal) conducted in Britain between 1999 and 2001, among black African residents aged 16 to 44 years, 44% of women and 36% of men reported ever having had an HIV test (274). These percentages are similar to those reported in Mayisha II in 2004.

Since 2004, rates of HIV testing among black Africans have continued to increase. Repeated studies of black Africans living in England have shown that the percentage of participants ever testing for HIV has increased from 52% in 2007 to 60% in 2008/2009 and up to 65% by 2013/2014 (204, 275, 276). Figure 6.1 presents rates of HIV testing among black Africans in England or Great Britain.

Figure 6.1: Rates of HIV testing among black Africans living in England or Great Britain



*Conducted in England by Health Protection Agency (Fenton *et al*, 2002; Health Protection Agency, 2005)
**Conducted in Britain by University College London, the London School of Hygiene & Tropical Medicine and NatCen Social Research (Burns *et al*, 2005)
***Conducted in England by Sigma Research (Sigma Research, 2008; Sigma Research, 2009; Bourne *et al*, 2014)

Reasons for the increase in the rate of HIV testing between 2007 and 2008/2009 are not clear as it is unlikely that the introduction in 2008 of national HIV testing guidelines targeting people from countries with a high prevalence of HIV would have had an immediate effect. However, the introduction of the 2008 guidelines, and subsequent testing guidelines in 2011 targeting black Africans, may partially explain the increase between 2008/2009 and 2013/2014 (I discuss the 2008 and 2011 guidelines in section 6.7).

The National Surveys of Sexual Attitudes and Lifestyles (stratified probability sample surveys conducted in 1990 to 1991, 1999 to 2001, and 2010 to 2012) have shown rates of HIV testing among British male and female respondents (the majority of whom were heterosexual) to have also increased over the past twenty years. The percentage of males reporting having had an HIV test in any setting in the previous five years increased from 7% in 1990-1991 to 9% in 1999-2001 and to 17% in 2010-2012 (277). Among females, there was an initial slight decline in the percentage reporting having had an HIV test in

any setting in the previous five years (1990-1991: 10.5%; 1999-2001: 9%) followed by a substantial increase (2010-2012: 28%) (277).

In the 2010-2012 Natsal survey among the British population, rates of HIV testing were highest among women and black Africans (277). It is likely that the success of the universal offer of an HIV test to women attending antenatal care explains the higher rate of testing among British women as compared to men. It is also likely that the success of national HIV testing strategies in promoting the routine offer of an HIV test to people born in high prevalence countries and / or black Africans (see section 6.7) explains the higher rate of testing among black Africans. Among black Africans living in England two of the most common reasons for having had an HIV test were antenatal screening (for women) or that it was part of routine health screening (276).

Despite increases over time, the uptake of HIV testing in England among black Africans remained lower than among MSM in the Natsal survey. Between 2010 and 2012, 52% of men who had had sex with a man in the past five years reported having had an HIV test (also in the past five years) compared with 44% of Black Africans (277).

6.6 Undiagnosed HIV among black Africans in E,W&NI

6.6.1 Rates of undiagnosed HIV

In paper 6.1, I reported that among the 1,006 black African Mayisha participants for whom a valid HIV laboratory test result was available, 9% were living with undiagnosed HIV infection. This means that among the 14% of Mayisha participants living with HIV, two thirds (66%; 93/141) were undiagnosed. It is likely that this proportion is an overestimate of the true population proportion because it is thought that Mayisha II participants previously diagnosed with HIV were less likely to provide a test sample than those who had previously tested negative. As a consequence people with diagnosed HIV were underrepresented in the laboratory sample (41). Nonetheless, in the country as a whole, rates of undiagnosed HIV are elevated among black African men and women. In 2012, an estimated 30% (6,300/21,200) of heterosexual men and 24% (7,700/31,800) of heterosexual women living with HIV in the UK remained undiagnosed (3). The majority of these people were black African. Among MSM living with HIV in the UK in 2012, the figure was 18% (7,300/41,000) (3).

6.6.2 Importance of reducing undiagnosed HIV

In the UK, the overwhelming majority of persons diagnosed with HIV are linked into care within three months, and more than nine out of ten in need of treatment receive antiretroviral therapy (36, 98). Access to this high-quality care is dependent on a person living with HIV being diagnosed. The identification and linkage in to care of people living with HIV has been described as the entry point for a lifelong continuum of care and treatment (278). It has also been described as "*The Holy Grail*" in improving the cascade of care among people living with HIV (279).

Reducing the number of black Africans living with undiagnosed HIV in E,W&NI would not only bring more people into treatment and care but would also reduce the risk of HIV transmission. It has been argued that, in low-prevalence heterosexual populations in high income countries, HIV transmission could be reduced by tackling undiagnosed HIV alone (280).

In the USA, it is estimated that half of all new HIV infections are attributable to the one in five people living with HIV who are undiagnosed (17). As improvements are made in retaining HIV-diagnosed persons in care and providing them with antiretroviral therapy earlier in the course of disease it is estimated that the proportion of new HIV infections attributable to those living with undiagnosed HIV will increase (17). It has been estimated that for every 100 persons newly diagnosed with HIV in the USA eight new HIV infections would be averted (17). Transmission would be averted through a combination of behaviour change and a reduction in infectivity through treatment.

If all people living with undiagnosed HIV in the USA were diagnosed, behavioural change would lead to an estimated 57% decline in unprotected anal and vaginal intercourse among this group (281). This decline in unprotected sex could result in the annual number of new HIV infections acquired through sexual contact in the USA falling by a third (281).

New sexually acquired HIV infections could also be averted by treating people who were previously undiagnosed. Persons diagnosed with HIV who are in receipt of treatment can attain undetectable viral loads (<50 copies/ml) (19). Those who attain undetectable viral loads have a negligible risk of transmitting their infection to others through unprotected sex (19). In light of this evidence, international HIV treatment

guidelines were revised to recommend antiretroviral therapy among all persons with a CD4 cell count <500 cells/ml (282). Treatment was previously recommended among persons with a CD4 cell count <350 cells/ml.

The benefits of reducing the number of people living with undiagnosed HIV through HIV testing may outweigh the benefits of expanding treatment among persons already diagnosed with HIV. Expanding treatment to all diagnosed persons with a CD4 cell count <500 cells/ml in the UK, as opposed to only those with a count <350 cells/ml, would decrease the percentage of all persons living with HIV with detectable viral loads (>50 copies/ml) from an estimated 42% to 38% (130). In contrast, halving the size of the undiagnosed population would decrease this percentage from an estimated 42% to 28% (130). In 2013, a coalition of HIV experts in the UK called for the percentage of people living with HIV who were undiagnosed to be halved by 2015 (283).

Between 2005 (the first year national estimates of undiagnosed HIV were available) and 2013 the estimated percentage of heterosexuals living with HIV in the UK who were undiagnosed only declined from 31% (10,500/33,600) to 27% (14,100/53,000) (3, 284). The majority of these people were black African. It should be noted that the 2005 estimate considered heterosexuals aged between 15 and 59 years whereas the 2013 estimate considered heterosexuals of all ages. Despite this caveat, it remains clear that more needs to be done in improving the uptake of HIV testing among black Africans in E,W&NI if the percentage of people living with undiagnosed HIV is to be halved.

6.7 HIV testing strategies among black Africans in E,W&NI

Currently in the UK a combination of targeted and population-based strategies are employed to promote HIV testing among black Africans and to reduce the prevalence of undiagnosed HIV. The shared goal of many current strategies is to normalise HIV testing. Normalised HIV testing is where HIV is treated like any other infectious disease and where all doctors are confident and competent at HIV testing and diagnosis (101). A review into the effectiveness of interventions to increase the uptake of HIV testing among black Africans living in England found that the uptake of HIV testing increased among migrant and black and minority ethnic groups in England when the provision of testing was normalised (285).

Across Europe attempts have been made to normalise HIV testing among heterosexuals at risk of HIV. A 2010 review of HIV testing policies and practices in migrant and ethnic minority populations across Europe found that HIV testing strategies were broadly categorised into general population approaches, targeted approaches, and a combination of the two (for example, offering routine testing in healthcare settings to the most affected communities) (286).

For HIV testing strategies to be successful in promoting testing among migrant and ethnic minority populations at risk of HIV it is important that HIV-related stigma and discrimination is addressed. A study of all HIV-positive patients attending a London hospital in 1999 and 2000 found the level of concern about a range of practical, social, and emotional issues relating to HIV testing to be high among black Africans as compared to other groups (113). African HIV community informants in the UK have also identified stigma and issues relating to confidentiality as major barriers to accessing HIV testing and other HIV services (119). A study of black Africans living in England in 2008/2009 found that only half of the participants who had never tested for HIV were willing to do so (204). To reduce barriers to testing, public health guidance was published in 2011 highlighting the need for staff offering HIV tests to black Africans to emphasise that testing is confidential and to be aware of, and sensitive to, the cultural issues facing black Africans (139).

Central to the approach of normalising HIV testing is the routine offer of an HIV test by healthcare providers. The routine offer of an HIV test may be targeted at specific groups at risk of HIV infection or based on attendance at a specific healthcare service. It may also be based on disease presentation or HIV population prevalence.

6.7.1 Targeted HIV testing

In an attempt to increase HIV testing among at-risk heterosexuals, national HIV testing guidelines in 2008 introduced testing criteria based on country of origin. In addition to recommending the routine offer of an HIV test to all sexual partners of a known positive person, the guidelines recommend routine testing of all people from a high HIV prevalence country (the majority of whom are from sub-Saharan Africa), and all people reporting sexual contact abroad or in the UK with individuals from high prevalence countries (138). In 2011, public health guidance was released with the specific intention of increasing HIV testing among black Africans in the UK. The guidance recommends

testing in a range of healthcare and community settings frequented by black Africans, recruiting members of local black African communities to act as champions, and making available promotional material tailored to the needs of black Africans (139).

Both the 2008 and 2011 guidelines consider cost effectiveness. The 2008 guidelines suggest that by reducing late HIV diagnoses costs to healthcare services will be reduced (138). The guidelines also refer to modelling conducted in the USA which showed routine screening for HIV infection to be cost effective where the prevalence of HIV exceeds 0.05 percent (138). The 2011 guidelines conclude that testing and treating people before they become symptomatic is likely to be cost effective as it is likely to lead to fewer infections over time through treatment as prevention (139).

Targeted testing may also be based on indicator diseases. In 2008, it was recommended that healthcare professionals in the UK, and elsewhere in Europe, recommend an HIV test to all patients presenting with diseases recognised to be associated with HIV (for example, tuberculosis) (102, 287). In particular, it was recommended that general practitioners, dentists, dermatologists, gynaecologists, sexual health clinicians and emergency physicians should be aware of the range of diseases where the prevalence of HIV is high as they were likely to be the providers who first encountered HIV-infected patients presenting with comorbid conditions (287).

However, the effectiveness of targeted testing strategies has been questioned. In 2009, it was suggested that testing strategies in the UK based on risk were not reducing high rates of undiagnosed HIV and late diagnosis (288). One reason for why targeted testing may not have had the intended impact on undiagnosed HIV is stigma. Targeted, risk-based strategies based on ethnicity have been seen as being judgemental and as a potential cause of stigma (120). To reduce stigma, and further promote testing among at-risk groups, a broader approach to testing has been called for (120, 288).

6.7.2 Population-based HIV testing

National HIV testing guidelines recommend an HIV test be offered to everyone attending contraceptive, sexual health, termination-of-pregnancy and antenatal services, drug-dependency programmes, and services for tuberculosis, lymphoma and hepatitis B and C. In addition, it is recommended that all people with symptoms consistent with primary HIV infection or presenting with a clinical indicator condition should be

offered an HIV test (100, 138). Additionally, in areas of E,W&NI where the prevalence of diagnosed HIV exceeds 2 in 1,000 (based on SOPHID data and referred to as high prevalence areas) an HIV test is recommended for all people admitted for secondary general medical care or registering with a general practice (100, 138).

Antenatal clinics

In the UK, antenatal clinics have routinely offered and recommended an HIV test to all patients since 1999 (18). In 2012, 675,800 pregnant women in England, representing 98% of all pregnant women, were screened for HIV (3). The success of opt-out testing in antenatal clinics has resulted in a substantial decline in both the number of women remaining undiagnosed post-delivery and mother-to-child transmissions (289).

The effectiveness of the antenatal screening programme probably explains why rates of undiagnosed infection are higher among heterosexual men than heterosexual women (see section 6.6.1). The authors of a study of HIV service utilisation among Africans in Britain concluded that, unlike women who may access antenatal services, African men lacked a front door to HIV services (119). Antenatal screening may, however, provide a back door to HIV services for men. A London-based study of HIV-positive African born heterosexual men found that many of the participants had only tested after discovering their female partners were HIV positive (290).

Reaching men through women was identified as one of the few HIV testing strategies implemented in European countries to encourage migrant and ethnic minority heterosexual men to test (286). Men could be reached via women through partner testing or couple testing during antenatal care (286). In 2012, the British HIV Association recommended that people living with HIV be offered support from staff competent in partner or contact notification to enable personal contacts at risk of HIV to access testing (100).

Sexual health clinics

In 2001, the National Strategy for Sexual Health and HIV recommended that all sexual health clinic attendees in the UK be offered an HIV test (291). By 2008, the majority of sexual health clinics had adopted a universal opt-out approach to testing (138). Universal opt-out testing is where all attendees are routinely offered and recommended to have an HIV test and the individual has the option to refuse.

The introduction of opt-out testing in a sexual health clinic in Amsterdam in January 2007 had a substantial effect on HIV test uptake. Among at-risk heterosexuals of all ages, HIV test uptake increased from 64% in 2006 to 94% by the end of 2007 (292). Evidence for the need for opt-out testing in The Netherlands was presented in a 2003 study which found that among migrants to the Netherlands who had previously tested for HIV, only one third had actively requested their test (293).

It has been suggested in the UK that an opt-out approach to testing in sexual health clinics and other healthcare facilities could detect many previously undiagnosed infections and help reduce the stigma associated with testing (120). However, it has also been suggested that the potential for opt-out HIV testing in healthcare facilities, such as sexual health services, to further promote testing and reduce rates of undiagnosed HIV may be limited due to stigma and a lack of information preventing people at risk from accessing these services (115). While this may be true for some sexual health services it appears that the introduction of routine HIV testing in antenatal clinics has been highly successful in this country (see section above).

Primary care, and acute and general medical admissions

In high prevalence areas of E,W&NI where diagnosed HIV prevalence exceeds two in 1,000 population aged 15 to 59 years it is recommended that HIV testing be considered for all people registering in general practice and for all general medical admissions (138). A diagnosed prevalence of 2 in 1,000 or more is a proxy for an undiagnosed prevalence of 1 in 1,000 or more, the threshold at which routine testing in the UK is assumed to be cost effective (138). This cost effective threshold is based on data from the USA.

In the USA, routine HIV screening of all persons aged 13 to 64 years in health-care settings with a prevalence of undiagnosed HIV infection of at least 1 in 1,000 was introduced in 2006 (294). In the USA, hospital emergency departments have been described as the cornerstone of the HIV screening approach in identifying persons living with undiagnosed infection (295). In E,W&NI, I would argue primary care should be the cornerstone of strategies aiming to reduce undiagnosed HIV among heterosexuals.

In the past, primary care has often been a setting for missed opportunities for early HIV diagnosis. Among Africans attending HIV treatment centres in London between April 2004 and February 2006, three quarters had seen their general practitioner in the year prior to their HIV diagnosis (101). It is highly likely that a sizeable proportion of these black African attendees were living with undiagnosed HIV when they saw their general practitioner 12 months before HIV diagnosis. It is estimated that half of the people living with undiagnosed HIV in the UK have been living with their infection for between three and five years (130).

Prior to the 2008 recommendation to normalise HIV testing in primary care in high prevalence areas, African HIV community informants in the UK reported a lack of trust in general practitioners due to HIV-related ignorance and breaches of confidentiality (119). Research conducted since 2008 appears to show a change in attitude towards opt-out testing in primary care. A pilot study conducted in Lewisham in 2010 found opt-out testing of all patients aged 18 to 59 years newly registering at primary care services to be highly acceptable, to reduce the administrative burden of testing, and to help normalise testing (296). The authors of a 2011 study conducted in Brighton reported that nearly all study participants felt that registering with a general practice was a suitable opportunity for opt-out testing and more acceptable than testing on hospital admission (289). Thirty percent of respondents to a 2013/2014 online survey of black Africans living in England identified a general practitioner's surgery as the location where they would like to take an HIV test in the future, making it the most preferred setting (276).

The routine offer of an HIV test in both acute medical admissions and general medical services (such as where blood tests are routinely conducted for medical admissions) has also been shown to be acceptable to patients, feasible to establish, and effective in detecting previously undiagnosed infection (296). It is therefore disappointing that a 2012 study of sexual health commissioners in forty high prevalence areas found that only half had commissioned HIV testing in the community and/or in general practice and only one third had commissioned HIV testing in hospital departments (297). Only one in ten areas had commissioned HIV testing in all three settings, and in areas where HIV testing in general practice was taking place it was typically in less than one in five of practices (297). If the number of black Africans living with undiagnosed HIV is to be

reduced, let alone halved, it is essential that existing testing strategies are widely implemented. The support of sexual health commissioners is critical in achieving this.

6.7.3 Self-sampling and testing

Stigma, discrimination, and a lack of privacy may partially explain why people living with undiagnosed HIV do not access facility-based testing (114). Self-sampling and testing may partially address these concerns.

Self-sampling is where a person takes a blood finger prick or saliva sample and forwards it to a laboratory for testing, from which a test result is subsequently received. Self-sampling HIV test kits are already available in the UK.

Self-testing is where a person takes and tests a sample themselves and obtains a result immediately. In 2014, the UK law was amended to allow the sale of HIV self-test kits in England, Scotland and Wales (298). In April, 2015 the first legally approved HIV self-test kit went on sale in England, Scotland and Wales.

Although self-testing for HIV has been shown to be acceptable among groups of heterosexuals at risk of HIV there are some concerns about this approach (299). It has been suggested that linkage into HIV services of people testing HIV positive with self-testing kits will be a major challenge (299). Also, most currently available HIV self-test kits are third generation. As compared to fourth generation tests used in healthcare settings, third generation tests have a longer window period (time between becoming infected with HIV and the infection being detectable). This may result in a person who has recently acquired HIV testing positive with a fourth generation test but negative with a third generation test. Due to a lack of literature, it is difficult to predict the extent to which self-sampling and testing will help reduce the number of heterosexuals living with undiagnosed HIV.

6.7.4 Repeat testing

In paper 6.1, I estimated that almost half of the 93 black African study participants living with undiagnosed HIV infection in the Mayisha study had previously tested negative for HIV, the overwhelming majority of whom had tested negative in the UK in the previous 24 months. This finding provides evidence of HIV transmission among black Africans living in England and the need not to see testing as a one-off event. In

paper 6.1, I recommended that regular HIV testing in black Africans be promoted. In my recommendation, however, I did not define what I meant by "*regular testing*".

In 2006 in the USA, it was recommended that all persons at high risk for HIV infection be tested for HIV at least annually (294). Following the introduction of repeat testing, the authors of a study in the USA reported median initial CD4 cell count to be higher among patients diagnosed through repeat testing than among those identified through first time testing (300). The study authors concluded that both the diagnosis of prevalent HIV among those who have never tested and repeat testing of target populations for incident infection were important (300).

In 2011, the National Institute for Health and Clinical Excellence recommended repeat testing be encouraged among black Africans living in England who had previously tested negative for HIV but who remained at risk of infection (139). As with the recommendation I made in paper 6.1, no time period was included in this recommendation. It is only in relation to repeat testing among MSM that a time period has been recommended. It is recommended that sexually active MSM in the UK have an HIV test at least annually, and more frequently if clinical symptoms are suggestive of seroconversion or if there is on-going high risk exposure (138, 301). However, to date, no recommendation has been made as to how often black Africans in E,W&NI should test for HIV.

6.8 Recommendations

In paper 6.1, I examined the uptake of HIV testing in black Africans living in England before the introduction of national testing guidelines in 2008. In the paper, I reported that less than half the black African study participants in 2004 had ever tested for HIV. In the paper, I recommended that HIV testing should not be seen as a one-off event but rather regular testing in black Africans should be promoted. I also recommended further research into the frequency of HIV testing.

In the literature search I conducted for this chapter I found evidence of a disproportionate number of new HIV infections being attributable to persons living with undiagnosed HIV and of rates of HIV testing among black Africans in E.W&NI being lower than among MSM. It appears that the routine offer of an HIV test through targeted and population-based strategies in traditional and non-traditional settings may

have increased the uptake of HIV testing among black Africans in E,W&NI. Nonetheless, there remains much room for improvement.

I recommend that regular HIV testing be promoted among black African women and men in a range of healthcare and community settings in this country, but particularly in primary care. I also emphasise the need for research into the frequency of HIV testing. Any future recommendation on testing frequency should include African community input and take into account HIV-related stigma among black Africans. I also recommend that the 2008 and 2011 national guidelines on the offering of an HIV test be adhered to. To promote adherence to national testing guidelines in high prevalence areas in E,W&NI, it is essential that the support of sexual health commissioners is secured.

7. Conclusion

Summary

In this concluding chapter, I revisit my research question and the approach that I have taken to answer it. Focusing on my research findings and methodological innovations, I summarise the six peer-reviewed published papers and the accompanying texts that are in Chapters 3, 4, 5 and 6. I then assess the public health importance and impact of my research and discuss the strengths and limitations of using national HIV surveillance data to examine how the epidemiology of heterosexually-acquired HIV in E,W&NI has evolved. Finally, I make recommendations based on my published papers and accompanying texts. My key recommendation is that regular HIV testing be promoted among black African women and men in E,W&NI in a range of healthcare settings, particularly in primary care.

7.1 Rationale for the PhD

In 2002, I joined the HIV and sexual transmitted infections department of the Public Health Laboratory Service as an HIV scientist. In my first few years as an HIV scientist a rapid increase in HIV diagnoses among heterosexuals in E,W&NI was observed (1). Despite this rapid increase little had been, or was being, published on the epidemiology of heterosexually-acquired HIV in E,W&NI at the time. Having developed an interest in this area, and recognising a gap in the research literature, I submitted an application for a part-time research degree to City University London in 2008 to examine the epidemiology of heterosexually-acquired HIV in E,W&NI in greater detail.

7.2 Research question and objectives

The overarching research question of my thesis is "*How is the epidemiology of heterosexually-acquired HIV infection evolving, particularly among black Africans, in England, Wales and Northern Ireland?"*. To answer this question, I analysed national HIV surveillance data and undertook literature searches. My specific objectives were to:

1. analyse epidemiological data and undertake literature searches to highlight who is at risk of heterosexually-acquired HIV in E,W&NI;

2. consider challenges in accurately ascertaining epidemiological trends in heterosexually-acquired HIV, and design new methods to improve precision;

3. explore the quality of HIV care provided to HIV-diagnosed heterosexuals in E,W&NI by examining key indicators of care available from routine HIV surveillance data;

4. examine the impact of migration on the heterosexual transmission of HIV in E,W&NI and consider whether a "*home-grown*" epidemic has developed among both heterosexuals born abroad and those born in the UK;

5. conduct research into HIV tuberculosis co-infection among heterosexuals in E,W&NI and consider the role of testing for HIV in tuberculosis clinics and vice-versa;

6. investigate HIV testing trends among heterosexuals in E,W&NI and why high rates of undiagnosed HIV and late presentation persist in this group.

7.3 How I answered the research question

To answer the research question I conducted a quantitative analysis of national surveillance datasets. Most of my analysis was based on data from the three national HIV surveillance systems which constitute the HIV and AIDS Reporting System. The three systems are the New HIV Diagnoses database, the Survey of Prevalent HIV Infections Diagnosed, and the CD4 Surveillance Scheme (42). I also analysed data from the national Enhanced Tuberculosis Surveillance system and the Mayisha II community-based survey of sexual attitudes and lifestyles among black African communities in England, as well as information from national death registrations and the Index of Multiple Deprivation (41, 46, 48-51, 53, 54).

I analysed the three HARS datasets independently and in combination. I analysed Enhanced Tuberculosis Surveillance data in combination with merged HARS data. I analysed death registrations as part of the New HIV Diagnoses database and the Index of Multiple Deprivation rankings as part of the SOPHID dataset. I analysed the Mayisha II dataset, which I cleaned and validated for the purpose of my thesis, independently of the other data sources.

I published the results of my analyses in six peer-reviewed papers between 2007 and 2014. I also presented the results of my analyses at conferences, workshops, and advisory group meetings (see Appendix iv). Guided by topics raised in the six published papers, I undertook computerised literature searches to explore these topics in greater detail. I applied key terms to search article titles and abstracts for papers published in the English language, which I then reviewed. I also conducted a manual internet key word search using Google Scholar to identify relevant grey literature. I have presented the findings from the six papers, together with the results of my literature searches, in four empirical chapters in this thesis (Chapters 3 to 6).

7.4 New research findings

7.4.1 Impact of migration

In my thesis I estimated that one third of heterosexual adults born abroad and diagnosed with HIV in E,W&NI between 2004 and 2010 had acquired HIV whilst living in the UK, increasing from one quarter in 2004 to almost a half in 2010. The overwhelming majority of the study population were black African. My overall estimate of one third was three times higher than that ascertained via clinic reports, based on an assessment of a person's sexual history.

Focusing on 2010 (the latest year for which results were presented), I estimated that 543 heterosexuals born abroad (mostly in sub-Saharan Africa) and diagnosed with HIV in E,W&NI that year had acquired their HIV infection whilst living in the UK. The equivalent number according to clinic-based assignment was 224. My analysis clearly highlights that the heterosexual transmission of HIV within E,W&NI among persons born abroad is greater than previously thought. My analysis also highlights the need for targeted HIV prevention among black-African communities in E,W&NI.

7.4.2 Loss to follow-up from HIV care

In exploring annual patterns of attendance at HIV services in E,W&NI I reported, on average, one in twenty adults attending HIV services in any one year were subsequently lost to follow-up from care. Cumulatively, over a nine year period, I reported one in five adults seen for HIV care being lost to follow-up. The groups most likely to be lost to follow-up from care were black Africans (the overwhelming majority of whom acquired HIV heterosexually), those who acquired HIV outside of the UK, those not receiving

antiretroviral therapy, and those recently diagnosed with HIV in E,W&NI. Based on my analysis and literature review, I suggested that outward migration from the UK may explain why these groups were more likely to be lost to follow-up from HIV care.

7.4.3 Improved quality of HIV care

For the period 2002 to 2011, I found an increase in the proportion of newly diagnosed heterosexuals in E,W&NI promptly integrated into HIV care (having a CD4 cell count within 28 days of HIV diagnosis) and receiving antiretroviral therapy within one year of diagnosis. The majority of these patients were of black African ethnicity. During the same period, I reported a reduction in the proportion of HIV-diagnosed heterosexuals (a) diagnosed beyond the point when treatment should have started (CD4 cell count <350 cells/ml), (b) diagnosed with an AIDS defining illness, or (c) having died of any cause within one year of HIV diagnosis. Despite a slight decrease over time, the proportion of heterosexuals diagnosed late with HIV remained unacceptably high. This was particularly true among black African heterosexuals.

7.4.4 Decreased incidence of tuberculosis

I reported a decline in the annual incidence rate of tuberculosis among HIV-diagnosed heterosexuals (the majority were of black African ethnicity) in England and Wales. The incidence of tuberculosis declined from 30 per 1,000 HIV-diagnosed heterosexuals in 2002 to nine per 1,000 in 2010.

The decline I reported in tuberculosis incidence coincided with a decline in the overall number of HIV-diagnosed heterosexuals in E,W&NI, including black Africans, acquiring HIV in sub-Saharan Africa (the prevalence of HIV and tuberculosis is high in many sub-Saharan Africa countries) and an increase in the uptake of antiretroviral therapy among persons diagnosed late (antiretroviral therapy can reduce a person's susceptibility to HIV-related infections). Nonetheless, despite the decline over time, I reported the incidence of tuberculosis among HIV-diagnosed heterosexuals to remain substantially higher than in the general UK population.

7.4.5 HIV testing among black Africans

Among black Africans in England participating in a 2004 community-based study (the overwhelming majority of participants were born abroad), 44% had ever tested for HIV.

Nine percent of the study population were living with undiagnosed HIV infection. Among those living with undiagnosed HIV, almost half had previously tested negative for HIV, the majority of whom had had an HIV test in the UK in the preceding 24 months. This finding highlighted that new infections had been acquired while the participants were already living in England.

7.4.6 Summary of my research findings

In response to the question "*How is the epidemiology of heterosexually-acquired HIV infection evolving, particularly among black Africans, in England, Wales and Northern Ireland?"* my key findings are that, over the last ten years:

(i) an increasing proportion of black African heterosexual men and women, born abroad but diagnosed with HIV in the UK, acquired their HIV infection whilst living in the UK;

(ii) outward migration from the UK may explain why some black African heterosexual men and women were lost to follow-up from HIV care;

(iii) the proportion of black African heterosexual men and women diagnosed late with HIV in E,W&NI has not changed substantially;

(iv) the uptake of HIV testing among black African heterosexual men and women in E,W&NI has increased but remains low compared with that among MSM.

7.5 Methodological innovations

7.5.1 Objectively assigning likely country of HIV infection

Heterosexuals born abroad and diagnosed with HIV in E,W&NI may have acquired their infection before or after their arrival in the UK. To accurately consider the impact of migration on the heterosexual transmission of HIV in E,W&NI, I developed and applied, with my colleagues Dr Valerie Delpech and Dr Zheng Yin, a new method to assign likely country of infection based on objective, routinely collected surveillance data. The method assigns likely country of infection according to whether the estimated year of infection (ascertained by modelling rates of CD4 cell count decline) for a heterosexual born abroad is before or after their year of arrival in the UK.

Prior to the application of this method, assignment of likely country of HIV infection among persons born abroad was based on a clinic-based assessment of a patient's sexual history. This method probably overestimated the number of heterosexuals acquiring HIV before arriving in the UK. This was due to clinic staff underestimating the risk of HIV transmission in the UK as compared to abroad (particularly in countries with a high prevalence of HIV), the underreporting of high-risk sexual behaviours in the UK due to social desirability bias or associated stigma, complex sexual and migration histories, and the difficulty of taking a complete sexual history in a clinical setting.

7.5.2 Creating a cohort of adults seen for HIV care

I created, with my colleague Dr Valerie Delpech, a cohort of adults attending NHS services for HIV-related care in E,W&NI. This was achieved by linking records across annual cross-sectional SOPHIDs on full identifiers (a four character coding of an adults surname, sex, date of birth, and postcode of residence) and by applying a deterministic matching algorithm which takes into consideration a variety of possible matches based on part identifiers.

Prior to this methodological change, only aggregate, population-level trends in care could be monitored over time. These population-level trends were monitored by simply combining data from each annual survey in a single dataset (these data were referred to as stacked data). Data from each annual SOPHID remained independent of data collected in other years, therefore prohibiting the monitoring of trends across time at the individual level. By creating a cohort of people diagnosed with HIV we could monitor at the individual level patterns of HIV service attendance over time as well as developing quality of HIV care indicators.

7.5.3 Linking national HIV and tuberculosis surveillance datasets

To conduct research on the incidence of tuberculosis among HIV-diagnosed heterosexuals in E,W&NI, HIV surveillance data were linked with Enhanced Tuberculosis Surveillance data. To link these data I, along with colleagues from the HIV and tuberculosis surveillance teams at Public Health England, developed and applied a method of probabilistic matching. This method considers the frequency and uniqueness of data and expresses, as a percentage, the probability of two or more records belonging to the same person.

7.6 Public health impact of my research

My work is of public health importance since I have published new research findings that have improved our understanding of heterosexually-acquired HIV in E,W&NI. In particular, I have enhanced our understanding of the impact of migration on heterosexually-acquired HIV in this country. Before I did the research for my PhD relatively little was known about the epidemiology of heterosexually acquired HIV in this country. I have also developed new methods which have improved the accuracy and validity of national HIV surveillance outputs.

7.6.1 Accurately measuring the impact of migration on heterosexual HIV transmission

Ascertaining whether HIV has been acquired before or after arrival in the UK is of critical public health importance. Accurate information on the number of people acquiring HIV whilst living in the UK helps public health professionals design and implement HIV prevention activities to scale. Colleagues and I designed and applied a new model to assign likely country of infection among persons born abroad and diagnosed with HIV in E,W&NI based on objective, routinely collected surveillance data.

The new model is now routinely used in national HIV surveillance to objectively assign likely country of infection among all persons diagnosed with HIV in E,W&NI who are born abroad. It replaces a previous method which relied on sexual histories and clinic-based risk assessment which underestimated the number of foreign-born people acquiring HIV after their arrival in the UK.

Confident that the estimates derived from the new model were robust, I recommended that the new method be adopted in other countries where the number of HIV diagnoses among migrants is high. The European Centre for Disease Prevention and Control supported my recommendation (234). The revised European HIV/AIDS dataset, hosted by ECDC, has been designed to improve the capturing of information to allow for probable country of HIV infection to be ascertained for persons born abroad and diagnosed with HIV using the model.

Following a workshop organised by Dr Valerie Delpech and myself from Public Health England and Teymur Noori of the ECDC, the model is being piloted in Sweden,

Belgium and Italy. In November 2014, I presented preliminary results based on Belgium's national HIV surveillance data to the Belgian Research on AIDS and HIV Consortium in Brussels. In February, 2015, preliminary results based on Swedish and Italian national HIV surveillance data were shared with the respective countries.

7.6.2 Monitoring patterns of HIV service attendance and quality of HIV care

The creation of a cohort of adults seen for HIV care allowed for patterns of care and treatment to be observed over time among HIV-diagnosed adults. The ability to analyse trends over time at the individual level facilitated the design and implementation of a national set of quality of care indicators.

Currently, seven indicators of the uptake of HIV testing and quality of HIV care are routinely monitored in E,W&NI. Two of these indicators are directly related to my analysis on loss to follow-up from HIV care. These two indicators monitor retention in care (the flipside of loss to follow-up). One of the indicators monitors retention in care among new patients (seen for care after 12 and 24 months of diagnosis) and the other retention in care among all patients (seen for care in the current and previous year).

The two indicators on retention in care have been incorporated into British HIV Association quality standards to promote equity of access to care in the UK and to ensure people living with HIV can access the care they need (100). They form part of BHIVA Standard Two which monitors access to, and retention in HIV treatment and care. In 2013, the British HIV Association, in association with the Health Protection Agency (predecessor of PHE), adopted the methods I used to measure loss to follow-up to conduct a clinic-based audit of people seen for HIV care in the UK in 2010 but not in 2011 (228, 235).

7.6.3 Facilitating further research on HIV-tuberculosis co-infection

In conducting my analysis of the incidence of tuberculosis among HIV-diagnosed heterosexual adults living in England and Wales I sought guidance from HIV and tuberculosis surveillance and clinical specialists. The bringing together of these specialists was the beginning of the UK Tuberculosis and HIV Research Epidemiology and Development group. This group, which continues to meet on a six monthly basis, has guided subsequent analysis of the combined HIV and tuberculosis dataset I helped create. In addition to the paper I published on the incidence of tuberculosis (included in

this thesis), three other papers have subsequently been published, or accepted for publication, in peer-reviewed journals. I am a co-author on all three papers.

7.7 Strengths and limitations of my analysis

I described in section 7.4 how the majority of my analysis was based on data from the three national surveillance systems which constitute HARS. There are both strengths and limitations in using established, already-collected surveillance data to answer my research question. In my discussion of the strengths and limitations of my analysis I refer to HARS as a combined system (i.e. I will not refer specifically to the three separate systems within HARS).

7.7.1 Strengths

An evaluation of all HIV and Sexually Transmitted Infections national surveillance systems in E,W&NI was conducted in 2007 and 2008 by internal and external stakeholders. It was concluded that HARS data were both comprehensive and valid (62).

Only laboratory-confirmed cases of HIV are reported to HARS. To reduce the potential for underreporting, all diagnosing laboratories, diagnosing healthcare facilities, and facilities offering HIV care and treatment are encouraged to report. Each year, reporting sites that either have not reported, or have reported fewer patients than might be expected based on previous reports, are identified, contacted and encouraged to report.

The reporting of HIV-diagnosed adults seen for care to SOPHID is linked to the local commissioning of HIV services. Underreporting could result in the underfunding of services in subsequent years. It is likely that this acts as an incentive to report all adults seen for HIV care in this country.

The reporting of a first AIDS diagnosis at the time of an HIV diagnosis is likely to be comprehensive as first HIV and AIDS diagnoses can be reported to HARS jointly. The reporting of deaths among HIV-infected persons is also likely to be comprehensive as notifications reported directly by clinics to HARS are supplemented by death notifications from the Office of National Statistic (50).

All HARS data are checked for duplicate records and missing or inaccurate information. Through routine data linkage within and between the three HARS constituents,

duplicate records are identified and removed from final amalgamated datasets. Data linkage and routinely run validation checks, within and between the three systems, identify missing and inaccurate information. Where possible, missing and inaccurate information in one system is populated or corrected by equivalent available and validated information in another. Where information is still missing or inaccurate, follow-up is undertaken by telephone and / or email with clinicians, health advisors, or data managers. Data completion exceeds 90% for most variables.

In addition to completeness and validity, an advantage of using HARS data for my analysis was that they were readily available. It would not have been feasible for me to assemble from scratch a comparable dataset for my thesis. Also, analysing data I am familiar with (I have worked with HARS data since 2002) enabled me to recognise and understand the strengths and limitations of the data. It also meant that I was able to introduce methodological change to improve the validity of my analyses. These changes included linking annual cross-sectional surveys to create a cohort of adults seen for HIV care and developing a new method to assign likely country of infection among persons born abroad.

7.7.2 Limitations

To promote reporting and encourage clinician co-operation the number of variables in the HARS dataset is kept to a minimum as well as being standardised and fixed. The HARS data I used in my analysis were therefore limited and inflexible.

It is likely that, in my analysis, I overestimated the number of HIV-diagnosed heterosexuals in E,W&NI. My definition of heterosexually-acquired HIV is based on probable route of HIV infection as reported by clinics. There is a potential for misclassification here. Due to social stigma, some men who have acquired HIV through sex with other men may report having acquired HIV heterosexually (66, 67). In particular, this may be the case for some black African men (69).

Data from HARS relate only to HIV-diagnosed heterosexuals. In the UK, an estimated one in four heterosexuals living with HIV remain undiagnosed (3). Therefore, results relating to HIV-diagnosed heterosexuals underestimate the true number of heterosexuals living with HIV.

It is probable that my estimates of heterosexuals acquiring HIV after their arrival in the UK included some people who had acquired their infection whilst travelling abroad from the UK. Travel abroad after arrival in the UK may also have introduced error in my analysis on HIV testing among black Africans living in England. In my analysis of Mayisha II data, I classified black Africans born abroad who had ever been tested for HIV as having been tested in the UK if their year of arrival was before the year of their last test. It is possible that I misclassified some people as having tested in the UK when they actually tested while travelling abroad. I believe this misclassification will be limited as, unlike in many other countries, in the UK voluntary and confidential HIV testing is available free of charge in open access clinics.

It is possible that error crept into some of my results due to the challenges of linking data within and between datasets. For example, if a person is reported over time to SOPHID under a different surname or date of birth linkage between these records may not occur. As a consequence, it is possible that my estimates of loss to follow-up from HIV care in E,W&NI were inflated. To reduce the potential for overestimation, I increased the likelihood of matching records in my analysis on loss to follow-up by using a matching algorithm that included variations in surname and date of birth. Limitations in data linkage between the national HIV and tuberculosis datasets may also have resulted in the incidence of tuberculosis among HIV-diagnosed heterosexuals in England and Wales being underestimated. To increase the likelihood of linking records relating to the same adult in both datasets probabilistic matching was applied. All possible matches were subsequently reviewed by me or another member of the research team.

In summary, HARS data are complete, valid and readily available. The most important limitation of my analysis is the potential for misclassification due to some men who have acquired HIV through sex with other men reporting having acquired HIV heterosexually. However, it is likely that such misclassification is limited (as explained in Chapter 2 (section 2.4.2)).

7.8 Recommendations

7.8.1 Review and roll-out the new method of assigning likely country of HIV infection

To widen the application of the method I introduced in my thesis to assign likely country of HIV infection, I recommended additional analyses to assess the level of disaggregation at which the outputs of the model remain robust. For example, providing outputs at the sub-national level or according to sex, age, region of birth and ethnicity.

To improve our understanding of the outputs from the new model I also recommended further research to investigate the extent to which heterosexuals born abroad acquire HIV whilst travelling away from the UK. Following the piloting of the new method in Sweden, Belgium and Italy, I also recommended that it be adopted in other countries where the number of HIV diagnoses among migrant populations is high. To enable roll-out, national HIV surveillance systems should routinely collect information on CD4 cell count at diagnosis and year of arrival among persons born abroad.

7.8.2 Consider the impact of inward and outward migration

To improve precision, I recommended that predictive models of heterosexually-acquired HIV incorporate estimates of migration patterns based on the International Passenger Survey and the Labour Force Survey (146-148). I also recommended that national estimates of loss to follow-up from HIV care and objective estimates of likely country of HIV infection continue to be incorporated into routine surveillance outputs. I base my recommendations on the evidence that I presented on HIV transmission among migrants in E,W&NI, on persons being lost to follow-up from HIV care, and on potential outward migration of previously diagnosed persons

7.8.3 Increased uptake of HIV testing

In my analysis and literature review I presented evidence of heterosexual transmission of HIV among migrants in E,W&NI and of a disproportionate number of HIV infections being attributable to persons living with undiagnosed HIV. I highlighted late diagnosis among heterosexuals, particularly among black Africans, and that AIDS diagnoses and deaths were strongly associated with late diagnosis.

To reduce HIV transmission and late diagnosis, it is essential that the number of black Africans living with undiagnosed HIV in E,W&NI is greatly reduced. To achieve this I recommended that regular HIV testing be promoted among black African women and men in a range of healthcare and community settings, particularly in primary care. However, further research on the frequency of testing is warranted (please see section 3.8).

I also recommended that national guidelines on the offering of an HIV test to all persons in specific settings be adhered to. These guidelines recommend that an HIV test be offered to everyone attending contraceptive, sexual health, termination-of-pregnancy and antenatal services, drug-dependency programmes, services for tuberculosis, lymphoma and hepatitis B and C. In addition, all people with symptoms consistent with primary HIV infection or presenting with a clinical indicator condition should be offered an HIV test (100, 138). They also recommend that in areas where the prevalence of diagnosed HIV exceeds 2 in 1,000, an HIV test should be offered to all people admitted for secondary general medical care or registering with a general practice (100, 138). Gaining the support of sexual health commissioners is critical for ensuring that these HIV testing strategies are widely implemented. As discussed in section 3.8, it is important that HIV testing be viewed as part of a wider HIV prevention strategy that includes the provision of condoms and lubricant as well as health promotion and outreach work.

7.8.4 Maintain regular service engagement with HIV-diagnosed heterosexuals

Based on the evidence I presented on loss to follow-up from HIV care I recommended that national and NHS trust-specific strategies be developed to maintain regular service engagement among black Africans, those who acquired HIV abroad, those not in receipt of antiretroviral therapy, and those recently diagnosed with HIV. I also recommended research on bi-national approaches to ensure efficient and effective pathways of care among HIV-diagnosed people leaving the UK on a permanent or semi-permanent basis. Evidence of heterosexual transmission of HIV within E,W&NI also highlights the need for maintaining regular service engagement with HIV-diagnosed heterosexuals to optimise treatment and reduce the risk of on-going transmission (19).

7.8.5 Reduce the incidence of tuberculosis among HIV-diagnosed heterosexuals

Despite reporting a decline over time in the annual incidence rate of tuberculosis among HIV-diagnosed heterosexuals in England and Wales, I highlighted that incidence among this group remains substantially higher than in the general UK population. In my analysis I presented evidence of missed opportunities to diagnose HIV earlier in tuberculosis settings and to diagnose latent tuberculosis in HIV settings. I also highlighted the importance of initiating antiretroviral therapy on time to reduce the incidence of active tuberculosis among HIV-diagnosed people.

It is essential that the recommendation for an HIV test to be offered to everyone attending services for tuberculosis should be followed (100, 138). British HIV Association, Department of Health, and National Institute for Health and Clinical Excellence guidelines on screening and possibly treating HIV-infected patients for latent tuberculosis infection should also be adhered to fully (47, 236, 264). I recommended close cooperation between tuberculosis and HIV services in the clinical management and accurate notification of HIV and tuberculosis cases. Finally, I recommended that the HIV and tuberculosis surveillance teams at Public Health England review, modify (if necessary), and repeat data linkage between the HIV and tuberculosis datasets to ensure reliable and comprehensive surveillance data on HIV-tuberculosis co-infection are available to monitor and evaluate the impact of interventions.

7.8.6 Improve data quality

The strengths and limitations of national HIV surveillance data need to be considered when utilising these data to describe the evolving epidemiology of heterosexually-acquired HIV. To reduce or account for potential bias in the reporting of probable route of HIV infection, I recommend that research be conducted to assess the extent to which social stigma results in men who have acquired HIV through sex with other men being classified as having acquired HIV heterosexually. To improve accuracy in time trend analysis, I recommend an on-going review of methods used to link records within and between the national HIV surveillance systems.

7.8.7 Categorise migrants according to ethnicity and country of birth

I presented evidence for the utility of categorising migrants according to their ethnicity and country of birth to highlight heterogeneity in risk of acquiring or living with HIV. I therefore recommended migrants be categorised in HIV research according to their ethnicity and country of birth. To ensure heterogeneity in risk is more readily highlighted by these two variables I recommended that they be combined in HIV research with HIV prevalence estimates according to country of birth and / or ethnicity.

7.8.8 Key recommendation

Throughout my thesis I have presented evidence of the epidemiology of heterosexually-acquired HIV infection in E,W&NI being shaped by black African migrants. I also presented evidence of high rates of undiagnosed HIV and late diagnosis, as well as HIV transmission occurring within this population in E,W&NI. To minimize the risk of HIV transmission and to maximise the benefits of earlier detection my key recommendation is to promote regular HIV testing among black African women and men in a range of healthcare and community settings, but particularly in primary care in E,W&NI.

Bibliography

1. Public Health England. National HIV Surveillance Data Tables. London: Public Health England; 2014 [cited 2014 10/01/2014]. Available from: https://www.gov.uk/government/statistics/hiv-data-tables.

2. Hope VD, Harris RJ, De Angelis D, Croxford S, Marongiu A, Parry JV, et al. Two decades of successes and failures in controlling the transmission of HIV through injecting drug use in England and Wales, 1990 to 2011. Euro Surveill. 2014;19(14).

3. Aghaizu A, Brown AE, Nardone A, Gill ON, Delpech VC, Contributors. HIV in the United Kingdom 2013 report: data to end 2012 London: Public Health England; 2013 [cited 2015 17/03/2015]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/326601/HIV_annual_report_2013.pdf.

4. Gunson HH, Rawlinson VI. HIV antibody screening of blood donations in the United Kingdom. Vox Sang. 1988;54(1):34-8.

5. Skegg DC. Heterosexually acquired HIV infection. BMJ. 1989;298(6671):401-2.

6. Allen JR. Heterosexual transmission of human immunodeficiency virus (HIV) in the United States. Bull N Y Acad Med. 1988;64(6):464-79.

7. Brunet JB, Bouvet E, Leibowitch J, Chaperon J, Mayaud C, Gluckman JC, et al. Acquired immunodeficiency syndrome in France. Lancet. 1983;1(8326 Pt 1):700-1.

8. Clumeck N, Sonnet J, Taelman H, Mascart-Lemone F, De Bruyere M, Vandeperre P, et al. Acquired Immunodeficiency Syndrome in African Patients. New England Journal of Medicine. 1984;310(8):492-7.

9. Piot P, Quinn TC, Taelman H, Feinsod FM, Minlangu KB, Wobin O, et al. Acquired immunodeficiency syndrome in a heterosexual population in Zaire. Lancet. 1984;2(8394):65-9.

10. Melbye M, Njelesani EK, Bayley A, Mukelabai K, Manuwele JK, Bowa FJ, et al. Evidence for heterosexual transmission and clinical manifestations of human

immunodeficiency virus infection and related conditions in Lusaka, Zambia. Lancet. 1986;2(8516):1113-5.

11. Van de Perre P, Clumeck N, Carael M, Nzabihimana E, Robert-Guroff M, De Mol P, et al. Female prostitutes: a risk group for infection with human T-cell lymphotropic virus type III. Lancet. 1985;2(8454):524-7.

12. France AJ, Skidmore CA, Robertson JR, Brettle RP, Roberts JJ, Burns SM, et al. Heterosexual spread of human immunodeficiency virus in Edinburgh. Br Med J (Clin Res Ed). 1988;296(6621):526-9.

13. Loveday C, Pomeroy L, Weller IV, Quirk J, Hawkins A, Williams H, et al. Human immunodeficiency viruses in patients attending a sexually transmitted disease clinic in London, 1982-7. BMJ. 1989;298(6671):419-22.

14. Evans BG, Noone A, Mortimer JY, Gilbart VL, Gill ON, Nicoll A, et al. Heterosexually acquired HIV-1 infection: cases reported in England, Wales and Northern Ireland, 1985 to 1991. Commun Dis Rep CDR Rev. 1992;2(5):R49-55.

15. Gilbart VL, Dougan S, Sinka K, Evans BG. Late diagnosis of HIV infection among individuals with low, unrecognised or unacknowledged risks in England, Wales and Northern Ireland. AIDS Care. 2006;18(2):133-9.

16. Hughes G. An overview of the HIV and AIDS epidemic in the United Kingdom. Commun Dis Rep CDR Rev. 1997;7(9):R121-2.

17. Hall HI, Holtgrave DR, Maulsby C. HIV transmission rates from persons living with HIV who are aware and unaware of their infection. AIDS. 2012;26(7):893-6.

18. Health Protection Agency. HIV in the United Kingdom: 2011 Report 2011 [cited 2011 December 2011]. Available from: http://www.ivecic.com/uploads/7/5/4/1/7541913/hiv_in_the_uk_2011_report.pdf.

19. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011;365(6):493-505.

20. Chadborn TR, Delpech VC, Sabin CA, Sinka K, Evans BG. The late diagnosis and consequent short-term mortality of HIV-infected heterosexuals (England and Wales, 2000-2004). AIDS. 2006;20(18):2371-9.

21. Sinka K, Mortimer J, Evans B, Morgan D. Impact of the HIV epidemic in sub-Saharan Africa on the pattern of HIV in the UK. AIDS. 2003;17(11):1683-90.

22. Dougan S, Gilbart VL, Sinka K, Evans BG. HIV infections acquired through heterosexual intercourse in the United Kingdom: findings from national surveillance. BMJ. 2005;330(7503):1303-4.

23. Burns FM, Arthur G, Johnson AM, Nazroo J, Fenton KA, group Sc. United Kingdom acquisition of HIV infection in African residents in London: more than previously thought. AIDS. 2009;23(2):262-6.

24. Rice BD, Elford J, Yin Z, Delpech VC. A new method to assign country of HIV infection among heterosexuals born abroad and diagnosed with HIV. AIDS. 2012;26(15):1961-6.

25. Bonell C, Hickson F, Beaumont M, Weatherburn P. Sexually transmitted infections as risk factors for HIV infection among MSMs: systematic review. Sex Transm Dis. 2008;35(2):209.

26. Chadborn TR, Baster K, Delpech VC, Sabin CA, Sinka K, Rice BD, et al. No time to wait: how many HIV-infected homosexual men are diagnosed late and consequently die? (England and Wales, 1993-2002). AIDS. 2005;19(5):513-20.

27. Dougan S, Elford J, Chadborn TR, Brown AE, Roy K, Murphy G, et al. Does the recent increase in HIV diagnoses among men who have sex with men in the UK reflect a rise in HIV incidence or increased uptake of HIV testing? Sex Transm Infect. 2007;83(2):120-5; discussion 5.

28. Dougan S, Elford J, Rice B, Brown AE, Sinka K, Evans BG, et al. Epidemiology of HIV among black and minority ethnic men who have sex with men in England and Wales. Sex Transm Infect. 2005;81(4):345-50.

29. Dougan S, Elford J, Sinka K, Fenton KA, Evans BG. Men who have sex with men who are born abroad and diagnosed with HIV in England and Wales: an epidemiological perspective. Int J STD AIDS. 2005;16(9):618-21.

30. Elam G, Macdonald N, Hickson FC, Imrie J, Power R, McGarrigle CA, et al. Risky sexual behaviour in context: qualitative results from an investigation into risk factors for seroconversion among gay men who test for HIV. Sex Transm Infect. 2008;84(6):473-7.

31. Elford J, Bolding G, Davis M, Sherr L, Hart G. Web-based behavioral surveillance among men who have sex with men: a comparison of online and offline samples in London, UK. J Acquir Immune Defic Syndr. 2004;35(4):421-6.

32. Elford J, Hart G. If HIV prevention works, why are rates of high-risk sexual behavior increasing among MSM? AIDS Educ Prev. 2003;15(4):294-308.

33. Hickson F, Reid D, Weatherburn P, Stephens M, Nutland W, Boakye P. HIV, sexual risk, and ethnicity among men in England who have sex with men. Sex Transm Infect. 2004;80(6):443-50.

34. Macdonald N, Elam G, Hickson F, Imrie J, McGarrigle CA, Fenton KA, et al. Factors associated with HIV seroconversion in gay men in England at the start of the 21st century. Sex Transm Infect. 2008;84(1):8-13.

35. Rice BD, Sinka K, Patel B, Chadborn TR, Delpech VC. The changing epidemiology of diagnosed prevalent HIV infections in England: greatest impact on the London environs. Epidemiol Infect. 2007;135(1):151-8.

36. Rice B, Elford J, Yin Z, Croxford S, Brown A, Delpech V. Trends in HIV diagnoses, HIV care, and uptake of antiretroviral therapy among heterosexual adults in England, Wales, and Northern Ireland. Sex Transm Dis. 2014;41(4):257-65.

37. Rice BD, Delpech VC, Chadborn TR, Elford J. Loss to follow-up among adults attending human immunodeficiency virus services in England, Wales, and Northern Ireland. Sex Transm Dis. 2011;38(8):685-90.

38. World Health Organisation. TB/HIV facts 2013. 2013 [cited 2013 16/01/2013]. Available from: http://www.who.int/tb/publications/TBHIVfactsheet_24Oct2013.pdf.

39. Rice B, Elford J, Yin Z, Kruijshaar M, Abubakar I, Lipman M, et al. Decreasing incidence of tuberculosis among heterosexuals living with diagnosed HIV in England and Wales. AIDS. 2013;27(7):1151-7.

40. Rice B, Delpech V, Sadler KE, Yin Z, Elford J. HIV testing in black Africans living in England. Epidemiol Infect. 2013;141(8):1741-8.

41. Mayisha II Collaborative Group. Assessing the feasibility and acceptability of community based prevalence surveys of HIV among black Africans in England. London: Health Protection Agency Centre for Infections.; 2005. Available from: http://www.ahpn.org/research_and_publications.

42. Public Health England. HIV surveillance systems London: Public Health England; 2015 [cited 2015 19/03/2015]. Available from: https://www.gov.uk/government/collections/hiv-surveillance-data-and-management.

43. Public Health England. What we do. London: Public Health England; 2013 [cited 2013 10/04/2013]. Available from: https://www.gov.uk/government/organisations/public-health-england/about.

44. UK NEQAS. About UK NEQAS for Leucocyte Immunophenotyping. 2013 [cited 2013 10/04/2013]. Available from: http://www.ukneqasli.co.uk/about-us/

45. Mortimer JY, Salathiel JA. 'Soundex' codes of surnames provide confidentiality and accuracy in a national HIV database. Commun Dis Rep CDR Rev. 1995;5(12):R183-6.

46. Public Health England. UK TB Surveillance. London: Public Health England; 2013 [cited 2013 10/04/2013]. Available from: https://www.gov.uk/government/collections/tuberculosis-and-other-mycobacterial-diseases-diagnosis-screening-management-and-data.

47. Department of Health. Tuberculosis prevention and treatment: a toolkit for planning, commissioning and delivering high-quality services in England. 2007. Available from: http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_075638.pdf

48. Sadler KE, McGarrigle CA, Elam G, Ssanyu-Sseruma W, Davidson O, Nichols T, et al. Sexual behaviour and HIV infection in black-Africans in England: results from the Mayisha II survey of sexual attitudes and lifestyles. Sex Transm Infect. 2007;83(7):523-9.

49. Sadler KE, McGarrigle CA, Elam G, Ssanyu-Sseruma W, Othieno G, Davidson O, et al. Mayisha II: pilot of a community-based survey of sexual attitudes and lifestyles and anonymous HIV testing within African communities in London. AIDS Care. 2006;18(4):398-403.

50. Office for National Statistics. Death Registrations Summary Tables, England and Wales, 2013. 2013 [cited 2014 19/09/2014]. Available from: http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-317522

51. Office for National Statistics. About ONS. 2013 [cited 2013 10/04/2013]. Available from: http://www.ons.gov.uk/ons/about-ons/index.html

52. Legislation.gov.uk. The Births and Deaths Registration Act, 1836. 2013 [cited 2013 10/04/2013]. Available from: http://www.legislation.gov.uk/ukpga/Eliz2/1-2/37/schedule/FIRST/crossheading/a-the-births-and-deaths-registration-act-1836-6-7-will-4-c-86.

53. HM Government. English Indices of Deprivation 2010. 2010 [cited 2013 10/04/2013]. Available from: http://data.gov.uk/dataset/index-of-multiple-deprivation

54. Department for Communities and Local Government. What we do. 2013 [cited 2013 10/04/2013]. Available from: https://www.gov.uk/government/organisations/department-for-communities-and-local-government.

55. Office for National Statistics. Super Output Areas (SOAs). 2013 [cited 2013 10/04/2013]. Available from: http://www.ons.gov.uk/ons/guide-method/geography/beginner-s-guide/census/super-output-areas--soas-/index.html

56. Department of Health. NHS Trusts and Primary Care Trusts (Sexually Transmitted Diseases) Directions 2000 London: Department of Health; 2000 [cited 2015 19/03/2015]. Available from:

http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsLegislation/DH_4083027.

57. Connecting for Health. National Information Governance Board for Health and Social Care. 2013 [cited 2013 10/04/2013]. Available from: http://www.connectingforhealth.nhs.uk/nigb.

58. Patient Information Advisory Group. PIAG Register - Health Research Authority. 2013 [cited 2013 10/04/2013]. Available from: www.hra.nhs.uk/documents/2013/10/piag-register.xls

59. National Health Service England and Wales. The Health Service (Control of Patient Information) Regulations 2002. 2002 [cited 2013 10/04/2013]. Available from: http://www.legislation.gov.uk/uksi/2002/1438/introduction/made.

60. Gov.UK. The Data Protection Act. 2013 [cited 2013 10/04/2013]. Available from: https://www.gov.uk/data-protection.

61. Department of Health. Publications policy and guidance: Confidentiality London: Department of Health; 2000 [cited 2015 19/03/2015]. Available from: http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/en/publicationsandstatistics/publications/publicationspolicyandguidance/browsable/dh_5133529.

62. Health Protection Agency. External evaluation of national surveillance systems. 2008.

63. Klevens RM, Fleming PL, Neal JJ, Li J. Is there really a heterosexual AIDS epidemic in the United States? Findings from a multisite validation study, 1992-1995. Mode of Transmission Validation Study Group. Am J Epidemiol. 1999;149(1):75-84.

64. Haverkos HW, Chung RC, Norville Perez LC. Is there an epidemic of HIV/AIDS among heterosexuals in the USA? Postgrad Med J. 2003;79(934):444-8.

65. Morlat P, Helmer C, Chene G, Bernard N, Monlun E, Beylot J, et al. Surveillance of heterosexually acquired HIV infection and AIDS. Lancet. 1995;346(8970):308-9.

66. Brody S. Questioning the validity of self-reported heterosexual HIV transmission. Am J Public Health. 1996;86(8):1172.

67. Serraino D, Franceschi S, Dal Maso L, Lepri AC, Tirelli U, Rezza G. The classification of AIDS cases: concordance between two AIDS surveillance systems in Italy. Am J Public Health. 1995;85(8 Pt 1):1112-4.

68. Nwanyanwu OC, Conti LA, Ciesielski CA, Stehr-Green JK, Berkelman RL, Lieb S, et al. Increasing frequency of heterosexually transmitted AIDS in southern Florida: artifact or reality? Am J Public Health. 1993;83(4):571-3.

69. Guasp A. Gay in Britain London: Stonewall; 2013. Available from: http://www.stonewall.org.uk/documents/gay_in_britain.pdf.

70. Guasp A. Gay and Bisexual Men's Health Survey London: Stonewall; 2012 [cited 2015 19/03/2015]. Available from: http://www.stonewall.org.uk/documents/stonewall_gay_mens_health_final_1.pdf.

71. UNAIDS. Monitoring and Evaluation Reference Group Indicator Working Group. 2013 [cited 2013 10/04/2013]. Available from: http://www.unaids.org/en/media/unaids/contentassets/documents/pcb/2012/20121111_PCB31_MERG_FINAL_en_with_new_coverpage.pdf.

72. European Centre for Disease Prevention and Control. Implementing the Dublin Declaration on Partnership to Fight HIV/AIDS in Europe and Central Asia: 2010 Progress Report Stockholm: European Centre for Disease Prevention and Control; 2010 [cited 2015 19/03/2015]. Available from: http://ecdc.europa.eu/en/publications/Publications/1009_SPR_Dublin_declaration_progress_report.pdf.

73. European Centre for Disease Prevention and Control. Migrant health: Sexual transmission of HIV within migrant groups in the EU/EEA and implications for effective interventions Stockholm: European Centre for Disease Prevention and Control; 2013 [cited 2015 19/03/2015]. Available from: http://ecdc.europa.eu/en/publications/Publications/Migrant-health-sexual-transmission.pdf.

74. European Centre for Disease Prevention and Control. Revised HIV/AIDS surveillance in Europe, including collection of data about country of HIV infection. 2013.

75. Quality Action. Joint Action on Improving Quality in HIV Prevention. 2013 [cited 2013 10/04/2013]. Available from: http://www.qualityaction.eu/

76. City University London. Health and Society E-Resource Databses. 2013 [cited 2013 12/12/2013]. Available from: http://encore.city.ac.uk/iii/encore/search/C__Skeyhealthandsociety__Ff:facetfields:communitytag:communitytag:Community%25252BTag::__Orightresult?lang=eng.

77. US National Library of Medicine National Institutes of Health. PubMed Central overview 2015 [cited 2015 02/06/2015]. Available from: http://www.ncbi.nlm.nih.gov/pmc/about/intro/.

78. Google. About Google Scholar 2015 [cited 2015 02/06/2015]. Available from: http://scholar.google.co.uk/intl/en/scholar/about.html.

79. Datu K. Settlement patterns of rich- and poor-country migrants into the London metropolitan region since 2001. 2014 [cited 2014 28/07/2-14]. Available from: http://lselondonmigration.files.wordpress.com/2014/03/datu_settlement-patterns-of-rich-and-poor-country-migrants-into-the-london-metropolitan-region-since-2001.pdf

80. Legislation.gov.uk. Immigration and Asylum Act 1999. 1999 [cited 2014 21/03/2014]. Available from: http://www.legislation.gov.uk/ukpga/1999/33/contents.

81. Easterbrook PJ, Hawkins DA. What is the potential for a heterosexual HIV epidemic in the UK? Int J STD AIDS. 1993;4(4):187-9.

82. Antonio G. The AIDS Cover Up San Francisco: Ignatius Press; 1986.

83. Sionean C, Le BC, Hageman K, Oster AM, Wejnert C, Hess KL, et al. HIV Risk, prevention, and testing behaviors among heterosexuals at increased risk for HIV infection--National HIV Behavioral Surveillance System, 21 U.S. cities, 2010. MMWR Surveill Summ. 2014;63(14):1-39.

84. Stoneburner RL, Chiasson MA, Weisfuse IB, Thomas PA. The epidemic of AIDS and HIV-1 infection among heterosexuals in New York City. AIDS. 1990;4(2):99-106.

85. Kesby M, Fenton K, Boyle P, Power R. An agenda for future research on HIV and sexual behaviour among African migrant communities in the UK. Soc Sci Med. 2003;57(9):1573-92.

86. Nyindo M. Complementary factors contributing to the rapid spread of HIV-I in sub-Saharan Africa: a review. East Afr Med J. 2005;82(1):40-6.

87. Auvert B, Buve A, Ferry B, Carael M, Morison L, Lagarde E, et al. Ecological and individual level analysis of risk factors for HIV infection in four urban populations in sub-Saharan Africa with different levels of HIV infection. AIDS. 2001;15 Suppl 4:S15-30.

88. Bailey RC, Moses S, Parker CB, Agot K, Maclean I, Krieger JN, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. Lancet. 2007;369(9562):643-56.

89. Gray RH, Kigozi G, Serwadda D, Makumbi F, Watya S, Nalugoda F, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. Lancet. 2007;369(9562):657-66.

90. Weiss HA, Quigley MA, Hayes RJ. Male circumcision and risk of HIV infection in sub-Saharan Africa: a systematic review and meta-analysis. AIDS. 2000;14(15):2361-70.

91. Halperin DT, Epstein H. Concurrent sexual partnerships help to explain Africa's high HIV prevalence: implications for prevention. Lancet. 2004;364(9428):4-6.

92. Halperin DT, Epstein H. Why is HIV prevalence so severe in southern Africa? The role of multiple concurrent partnerships and lack of male circumcision. . Southern African Journal of HIV Medicine. 2007;26:19-25.

93. Mah TL, Halperin DT. Concurrent sexual partnerships and the HIV epidemics in Africa: evidence to move forward. AIDS Behav. 2010;14(1):11-6; dicussion 34-7.

94. Abu-Raddad LJ, Magaret AS, Celum C, Wald A, Longini IM, Jr., Self SG, et al. Genital herpes has played a more important role than any other sexually transmitted infection in driving HIV prevalence in Africa. PLoS One. 2008;3(5):e2230.

95. Buve A, Carael M, Hayes RJ, Auvert B, Ferry B, Robinson NJ, et al. The multicentre study on factors determining the differential spread of HIV in four African cities: summary and conclusions. AIDS. 2001;15 Suppl 4:S127-31.

96. NHS Choices. The NHS in England. 2014 [cited 2014 21/03/2014]. Available from: http://www.nhs.uk/NHSEngland/thenhs/about/Pages/authoritiesandtrusts.aspx.

97. Legislation.gov.uk. Health and Social Care Act 2012. 2012 [cited 2014 21/03/2014]. Available from: http://www.legislation.gov.uk/ukpga/2012/7/contents/enacted.

98. Delpech V, Brown AE, Croxford S, Chau C, Polavarapu V, Cooper N, et al. Quality of HIV care in the United Kingdom: key indicators for the first 12 months from HIV diagnosis. HIV Med. 2013;14 Suppl 3:19-24.

99. Gardner EM, McLees MP, Steiner JF, Del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. Clin Infect Dis. 2011;52(6):793-800.

100. British HIV Association. British HIV Association: Standards of Care for People Living with HIV 2013 London: Mediscript Ltd; 2012 [cited 2015 17/03/2015]. Available from: http://www.bhiva.org/documents/Standards-of-care/BHIVAStandardsA4.pdf.

101. Burns FM, Johnson AM, Nazroo J, Ainsworth J, Anderson J, Fakoya A, et al. Missed opportunities for earlier HIV diagnosis within primary and secondary healthcare settings in the UK. AIDS. 2008;22(1):115-22.

102. Fisher M. Late diagnosis of HIV infection: major consequences and missed opportunities. Curr Opin Infect Dis. 2008;21(1):1-3.

103. Hogg RS, Yip B, Chan KJ, Wood E, Craib KJ, O'Shaughnessy MV, et al. Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. Jama. 2001;286(20):2568-77.

104. Smith RD, Delpech VC, Brown AE, Rice BD. HIV transmission and high rates of late diagnoses among adults aged 50 years and over. AIDS. 2010;24(13):2109-15.

105. Egger M, May M, Chene G, Phillips AN, Ledergerber B, Dabis F, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet. 2002;360(9327):119-29.

106. Fleishman JA, Yehia BR, Moore RD, Gebo KA, Network HIVR. The economic burden of late entry into medical care for patients with HIV infection. Med Care. 2010;48(12):1071-9.

107. Public Health England. Addressing Late HIV Diagnosis through Screening and Testing: An Evidence Summary. London: Public Health England; 2014 [cited 2014 11/08/2014]. Available from: http://webarchive.nationalarchives.gov.uk/20140722091854/http:/www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317141126407.

108. Mugavero MJ, Castellano C, Edelman D, Hicks C. Late diagnosis of HIV infection: the role of age and sex. Am J Med. 2007;120(4):370-3.

109. Girardi E, Sabin CA, Monforte AD. Late diagnosis of HIV infection: epidemiological features, consequences and strategies to encourage earlier testing. J Acquir Immune Defic Syndr. 2007;46 Suppl 1:S3-8.

110. Adekeye OA, Heiman HJ, Onyeabor OS, Hyacinth HI. The new invincibles: HIV screening among older adults in the U.S. PLoS One. 2012;7(8):e43618.

111. Bhatia R, Wallace P. Experiences of refugees and asylum seekers in general practice: a qualitative study. BMC Fam Pract. 2007;8:48.

112. Woodhead D. The health and well-being of asylum seekers and refugees London: The Kings Fund; 2000 [cited 2015 19/03/2015]. Available from: http://www.researchasylum.org.uk/health-and-well-being-asylum-seekers-and-refugees.

113. Erwin J. Pathways to HIV testing and care by black African and white patients in London. Sexually Transmitted Infections. 2002;78(1):37-9.

114. Pant Pai N, Sharma J, Shivkumar S, Pillay S, Vadnais C, Joseph L, et al. Supervised and unsupervised self-testing for HIV in high- and low-risk populations: a systematic review. PLoS Med. 2013;10(4):e1001414.

115. Prost A, Griffiths CJ, Anderson J, Wight D, Hart GJ. Feasibility and acceptability of offering rapid HIV tests to patients registering with primary care in London (UK): a pilot study. Sex Transm Infect. 2009;85(5):326-9.

116. Nnoaham KE, Pool R, Bothamley G, Grant AD. Perceptions and experiences of tuberculosis among African patients attending a tuberculosis clinic in London. Int J Tuberc Lung Dis. 2006;10(9):1013-7.

117. Rodger AJ, Story A, Fox Z, Hayward A, London Tuberculosis Nurses N. HIV prevalence and testing practices among tuberculosis cases in London: a missed opportunity for HIV diagnosis? Thorax. 2010;65(1):63-9.

118. Thomas William S, Taylor R, Barrett S, Janmohamed K. Changes in HIV testing rates among patients with tuberculosis in a large multiethnic city in the UK. Int J STD AIDS. 2011;22(12):748-50.

119. Burns FM, Imrie JY, Nazroo J, Johnson AM, Fenton KA. Why the(y) wait? Key informant understandings of factors contributing to late presentation and poor utilization of HIV health and social care services by African migrants in Britain. AIDS Care. 2007;19(1):102-8.

120. Hamill M, Burgoine K, Farrell F, Hemelaar J, Patel G, Welchew DE, et al. Time to move towards opt-out testing for HIV in the UK. BMJ. 2007;334(7608):1352-4.

121. Boyd AE, Murad S, O'Shea S, de Ruiter A, Watson C, Easterbrook PJ. Ethnic differences in stage of presentation of adults newly diagnosed with HIV-1 infection in south London. HIV Med. 2005;6(2):59-65.

122. Delpierre C, Dray-Spira R, Cuzin L, Marchou B, Massip P, Lang T, et al. Correlates of late HIV diagnosis: implications for testing policy. Int J STD AIDS. 2007;18(5):312-7.

123. Metallidis S, Pilalas D, Skoura L, Haidich AB, Tsachouridou O, Papaioannou M, et al. Time trends and correlates of late presentation for HIV care in Northern Greece during the decade 2000 to 2010. J Int AIDS Soc. 2012;15(2):17395.

124. Vives N, Carnicer-Pont D, Garcia de Olalla P, Camps N, Esteve A, Casabona J. Factors associated with late presentation of HIV infection in Catalonia, Spain. Int J STD AIDS. 2012;23(7):475-80.

125. Gazzard BG, Anderson J, Babiker A, Boffito M, Brook G, Brough G, et al. British HIV Association Guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008. HIV Med. 2008;9(8):563-608.

126. Yin Z, Brown A, Hughes G, Nardone A, Gill ON, Delpech V. HIV in the United Kingdom: 2014 Report London: Public Health England; 2014 [cited 2015 17/03/2015]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/401662/2014_PHE_HIV_annual_report_draft_Final_07-01-2015.pdf.

127. Nakagawa F, Lodwick RK, Smith CJ, Smith R, Cambiano V, Lundgren JD, et al. Projected life expectancy of people with HIV according to timing of diagnosis. AIDS. 2012;26(3):335-43.

128. Office for National Statistics. Mortality Rates. 2013 [cited 2013 10/04/2013]. Available from: http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Mortality+Rates#tab-data-tables

129. Simmons RD, Ciancio BC, Kall MM, Rice BD, Delpech VC. Ten-year mortality trends among persons diagnosed with HIV infection in England and Wales in the era of antiretroviral therapy: AIDS remains a silent killer. HIV Med. 2013;14(10):596-604.

130. Brown AE, Nardone A, Delpech VC. WHO 'Treatment as Prevention' guidelines are unlikely to decrease HIV transmission in the UK unless undiagnosed HIV infections are reduced. AIDS. 2014;28(2):281-3.

131. Centers for Disease Control and Prevention. Key Graphics from CDC Analysis Showing Proportion of People Engaged in Each of the Five Main Stages of HIV Care Atlanta: Centers for Disease Control and Prevention, ; 2012 [cited 2015 19/03/2015].

Available from: http://www.cdc.gov/nchhstp/newsroom/2012/Continuum-of-Care-Graphics.html.

132. Whiteside YO, Cohen SM, Bradley H, Skarbinski J, Hall HI, Lansky A, et al. Progress along the continuum of HIV care among blacks with diagnosed HIV- United States, 2010. MMWR Morb Mortal Wkly Rep. 2014;63(5):85-9.

133. Office for Budget Responsibility. Fiscal sustainability report. 2013 [cited 2014 19/09/2014]. Available from: http://cdn.budgetresponsibility.independent.gov.uk/2013-FSR_OBR_web.pdf

134. Centers for Disease Control and Prevention. Factsheet: HIV among older adults. 2013 [cited 2014 16/09/2014]. Available from: http://www.cdc.gov/hiv/pdf/library_factsheet_HIV_%20AmongOlderAmericans.pdf.

135. von Simson R, Kulasegaram R. Sexual health and the older adult: Trends show that doctors must be more vigilant. Student BMJ. 2012;20:e688.

136. Office for National Statistics. Population Ageing in the United Kingdom, its Constituent Countries and the European Union. 2012 [cited 2014 16/09/2014]. Available from: http://www.ons.gov.uk/ons/dcp171776_258607.pdf.

137. Beckman N, Waern M, Gustafson D, Skoog I. Secular trends in self reported sexual activity and satisfaction in Swedish 70 year olds: cross sectional survey of four populations, 1971-2001. Bmj. 2008;337:a279.

138. British HIV Association, British Association for Sexual Health and HIV, British Infection Society. UK National Guidelines for HIV Testing 2008. London: British HIV Association; 2008 [13/02/2013]. Available from: http://www.bhiva.org/HIVTesting2008.aspx.

139. National Institute for Health and Clinical Excellence. Increasing the uptake of HIV testing among black Africans in England Manchester: National Institute for Health and Clinical Excellence; 2011 [cited 2015 17/03/2015]. Available from: https://www.nice.org.uk/guidance/ph33/resources/guidance-increasing-the-uptake-of-hiv-testing-among-black-africans-in-england-pdf.

140. National AIDS Trust. HIV and Black African Communities in the UK JUNE 2014: A POLICY REPORT London: National AIDS Trust; 2014 [cited 2016 13/03/16]. Available from: http://www.nat.org.uk/media/Files/Publications/NAT-African-Communities-Report-June-2014-FINAL.pdf.

141. Gay C, Adimora A, Miller W, Cohen MS. Surveillance of HIV in the United States and England, Scotland, and Northern Ireland: what have we learned and what do we do about it? Sex Transm Dis. 2014;41(4):266-7.

142. UNESCO. Glossary migrant/migration. 2013 [cited 2013 16/01/2013]. Available from: http://www.unesco.org/new/en/social-and-human-sciences/themes/international-migration/glossary/migrant/.

143. Eurofound. Migration. 2014 [cited 2014 30/01/2014]. Available from: http://www.eurofound.europa.eu/areas/industrialrelations/dictionary/definitions/migration.htm

144. United Nations Statistics Division. International migration. 2013 [cited 2013 16/01/2013]. Available from: http://unstats.un.org/unsd/demographic/sconcerns/migration/migrmethods.htm.

145. European Migration Network. Glossary. 2014 [cited 2014 30/01/2014]. Available from: http://emn.intrasoft-intl.com/Glossary/index.do#M.

146. Ker D, Zumpe J, Blake A. Estimating International Migration: An exploration of the definitional differences between the Labour Force Survey, Annual Population Survey, International Passenger Survey and Long-Term International Migration: Office for National Statistics; 2009 [cited 2015 25/03/2015]. Available from: http://www.google.co.uk/url?url=http://www.ons.gov.uk/ons/rel/migration1/population-by-country-of-birth-and-nationality/sources-of-international-migration-data/differences-between-sources-of-international-migration-data.pdf&rct=j&frm=1&q=&esrc=s&sa=U&ei=oMESVZSDMoToaOTpgrgF&ved=0CBQQFjAA&usg=AFQjCNH9tJIe3NglOAcp6zF81B6OBLQkPw.

147. Office for National Statistics. International Passenger Survey (IPS). 2013 [cited 2013 10/04/2013]. Available from: http://www.ons.gov.uk/ons/guide-method/surveys/respondents/household/international-passenger-survey/index.html.

148. Office for National Statistics. Labour Force Survey. 2013 [cited 2013 10/04/2013]. Available from: http://www.ons.gov.uk/ons/guide-method/surveys/list-of-surveys/survey.html?survey=Labour+Force+Survey.

149. Anderson B, Blinder S. Who Counts as a Migrant? Definitions and their Consequences Oxford: The Migration Observatory; 2012 [cited 2015 25/03/2015]. Available from: http://www.migrationobservatory.ox.ac.uk/briefings/who-counts-migrant-definitions-and-their-consequences.

150. Senior PA, Bhopal R. Ethnicity as a variable in epidemiological research. BMJ. 1994;309(6950):327-30.

151. The-Sun. Where Britain's New Hetero AIDS Cases Began. The Sun. 2003.

152. Sunday-Express. Asylum seekers with killer diseases exploit legal loophole to avoid deportation; Got Aids? Welcome to Britain. Sunday Express. 2002.

153. Elliott F, Foggo D, Shaikh T. Aids infected asylum-seekers overwhelm UK hospitals. The Telegraph. 2003.

154. Browne A. The secret threat to British lives. The Spectator. 2003.

155. Office for National Statistics. Population by Country of birth and Nationality July 2010 to June 2011. 2013 [cited 2013 10/04/2013]. Available from: http://www.ons.gov.uk/ons/rel/migration1/migration-statistics-quarterly-report/february-2012/population-by-country-of-birth-and-nationality.xls.

156. UNAIDS. Global report: UNAIDS report on the global AIDS epidemic 2013 Geneva: UNAIDS; 2013 [cited 2015 18/03/2015]. Available from: http://www.unaids.org/sites/default/files/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/UNAIDS_Global_Report_2013_en.pdf.

157. Office for National Statistics. Ethnic group. 2013 [cited 2014 13/01/2014]. Available from: http://www.ons.gov.uk/ons/guide-method/measuring-equality/equality/ethnic-nat-identity-religion/ethnic-group/index.html#1

158. Sillitoe K, White PH. Ethnic group and the British census: the search for a question. J R Stat Soc Ser A Stat Soc. 1992;155(1):141-63.

159. Ni Bhrolchain M. The ethnicity question for the 1991 census: background and issues. Ethnic Racial Stud. 1990;13:542-67.

160. Centre on Dynamics of Ethnicity. Census Briefing. 2014 [cited 2014 31/01/2014]. Available from: http://www.ethnicity.ac.uk/census/eth_categories.html.

161. Elford J, McKeown E, Doerner R, Nelson S, Low N, Anderson J. Sexual health of ethnic minority MSM in Britain (MESH project): design and methods. BMC Public Health. 2010;10:419.

162. De Cock KM, Low N. HIV and AIDS, other sexually transmitted diseases, and tuberculosis in ethnic minorities in United Kingdom: is surveillance serving its purpose? BMJ. 1997;314(7096):1747-51.

163. Fenton K, Johnson AM, Nicoll A. Race, ethnicity, and sexual health. BMJ. 1997;314(7096):1703-4.

164. Sheldon TA, Parker H. Race and ethnicity in health research. J Public Health Med. 1992;14(2):104-10.

165. Bhopal R. Is research into ethnicity and health racist, unsound, or important science? BMJ. 1997;314(7096):1751-6.

166. Nicoll A, Catchpole M, Watson JM. Improving ethnic data within surveillance must be priority. BMJ. 1997;315(7116):1160.

167. National Health Service Information Standards Board. Data Standards: Ethnic category default code. 2004 [cited 2014 29/05/2014]. Available from: http://www.isb.nhs.uk/documents/dscn/dscn2004/212004.pdf.

168. McMunn AM, Mwanje R, Pozniak AL. Issues facing Africans in London with HIV infection. Genitourin Med. 1997;73(3):157-8.

169. Marsicano E, Lydie N, Bajos N. 'Migrants from over there' or 'racial minority here'? Sexual networks and prevention practices among sub-Saharan African migrants in France. Cult Health Sex. 2013;15(7):819-35.

170. Gov.UK. Types of British nationality. 2014 [cited 2014 14/07/2014]. Available from: https://www.gov.uk/types-of-british-nationality/overview.

171. Home Office UK Border Agency. BN18 - information about dual nationality. 2014 [cited 2014 14/07/2014]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/261499/bn18.pdf

172. Lapostolle A, Massari V, Chauvin P. Time since the last HIV test and migration origin in the Paris metropolitan area, France. AIDS Care. 2011;23(9):1117-27.

173. Chinouya M, Davidson O. Assessing health-related knowledge, attitudes and behaviours of HIV-positive Africans accessing services in north central London London: African HIV Policy Network & Camden Primary Care Trust; 2003 [cited 2015 25/03/2015]. Available from: http://ahrf.org.uk/articles/padare.pdf.

174. van Veen MG, Kramer MA, Op de Coul EL, van Leeuwen AP, de Zwart O, van de Laar MJ, et al. Disassortative sexual mixing among migrant populations in The Netherlands: a potential for HIV/STI transmission? AIDS Care. 2009;21(6):683-91.

175. UNAIDS. Bangladesh: HIV and AIDS estimates 2012. 2013 [cited 2013 16/01/2013]. Available from: http://www.unaids.org/en/regionscountries/countries/bangladesh/.

176. UNAIDS. South Africa: HIV and AIDS estimates 2012. 2013 [cited 2013 16/01/2013]. Available from: http://www.unaids.org/en/regionscountries/countries/southafrica/

177. National Department of Health. The National Antenatal Sentinel HIV and Syphilis Prevalence Survey, South Africa, 2011 Pretoria: National Department of Health; 2012 [cited 2015 25/03/2015]. Available from: http://www.health-e.org.za/2012/12/11/2011-national-antenatal-hiv-syphilis-prevalence-survey-released/.

178. Del Amo J, Broring G, Hamers FF, Infuso A, Fenton K. Monitoring HIV/AIDS in Europe's migrant communities and ethnic minorities. AIDS. 2004;18(14):1867-73.

179. Johnson AS, Hu X, Dean HD. Epidemiologic differences between native-born and foreign-born black people diagnosed with HIV infection in 33 U.S. states, 2001-2007. Public Health Rep. 2010;125 Suppl 4:61-9.

180. Kerani RP, Kent JB, Sides T, Dennis G, Ibrahim AR, Cross H, et al. HIV among African-born persons in the United States: a hidden epidemic? J Acquir Immune Defic Syndr. 2008;49(1):102-6.

181. European Centre for Disease Prevention and Control/WHO Regional Office for Europe. HIV/AIDS surveillance in Europe 2012 Stockholm: European Centre for Disease Prevention and Control.; 2013 [19/12/2013]. Available from: http://ecdc.europa.eu/en/publications/Publications/hiv-aids-surveillance-report-2012-20131127.pdf.

182. European Centre for Disease Prevention and Control. Thematic report: Migrants. Monitoring implementation of the Dublin Declaration on Partnership to Fight HIV/AIDS in Europe and Central Asia: 2012 Progress Report. Stockholm: European Centre for Disease Prevention and Control; 2013 [cited 2015 01/04/2015]. Available from: http://ecdc.europa.eu/en/publications/Publications/dublin-declaration-monitoring-report-migrants-september-2013.pdf.

183. Gyarmathy VA, Neaigus A. Marginalized and socially integrated groups of IDUs in Hungary: potential bridges of HIV infection. J Urban Health. 2005;82(3 Suppl 4):iv101-12.

184. Hamers FF, Downs AM. The changing face of the HIV epidemic in western Europe: what are the implications for public health policies? Lancet. 2004;364(9428):83-94.

185. Hawkes SJ, Hart GJ. Travel, migration and HIV. AIDS Care. 1993;5(2):207-14.

186. Rachlis B, Brouwer KC, Mills EJ, Hayes M, Kerr T, Hogg RS. Migration and transmission of blood-borne infections among injection drug users: understanding the epidemiologic bridge. Drug Alcohol Depend. 2007;90(2-3):107-19.

187. White RG. What can we make of an association between human immunodeficiency virus prevalence and population mobility? . Int J Epidemiol. 2003;32(5):753-54.

188. European Centre for Disease Prevention and Control. Migrant health: Background note to the ECDC Report on migration and infectious diseases in the EU Stockholm: European Centre for Disease Prevention and Control; 2009 [cited 2015

01/04/2015]. Available from: http://www.episouth.org/doc/r_documents/0907_TER_Migrant_health_Background_note.pdf.

189. European Centre for Disease Prevention and Control. Improving HIV data comparability in migrant populations and ethnic minorities in EU/EEA/EFTA countries: findings from a literature review and expert panel. Stockholm: European Centre for Disease Prevention and Control,; 2011 [cited 2015 01/04/2015]. Available from: http://ecdc.europa.eu/en/publications/Publications/1108_TER_Improving_HIV_data_comparability_in_migrants.pdf.

190. Chee CC, Mortier E, Dupont C, Bloch M, Simonpoli AM, Rouveix E. Medical and social differences between French and migrant patients consulting for the first time for HIV infection. AIDS Care. 2005;17(4):516-20.

191. Semaille C, Barin F, Cazein F, Pillonel J, Lot F, Brand D, et al. Monitoring the Dynamics of the HIV Epidemic Using Assays for Recent Infection and Serotyping among New HIV Diagnoses: Experience after 2 Years in France. The Journal of Infectious Diseases. 2007;196(3):377-83.

192. Kramer MA, van den Hoek A, Coutinho RA, Prins M. Sexual risk behaviour among Surinamese and Antillean migrants travelling to their countries of origin. Sex Transm Infect. 2005;81(6):508-10.

193. Xiridou M, van Veen M, Coutinho R, Prins M. Can migrants from high-endemic countries cause new HIV outbreaks among heterosexuals in low-endemic countries? AIDS. 2010;24(13):2081-8.

194. Xiridou M, van Veen M, Prins M, Coutinho R. How patterns of migration can influence the heterosexual transmission of HIV in The Netherlands. Sex Transm Infect. 2011;87(4):289-91.

195. European Centre for Disease Prevention and Control. Responses to HIV and migration in western industrialised countries: current challenges, promising practices, future directions Stockholm: European Centre for Disease Prevention and Control; 2013 [cited 2015 01/04/2015]. Available from: http://ecdc.europa.eu/en/publications/Publications/HIV-migration-meeting-report.pdf.

196. UNAIDS. Country progress reports. 2013 [cited 2013 16/01/2013]. Available from: http://www.unaids.org/en/regionscountries/countries/

197. Gushulak BD, MacPherson DW. Globalization of infectious diseases: the impact of migration. Clin Infect Dis. 2004;38(12):1742-8.

198. Mitchell S, Band B, Bradbeer C, Barlow D. Imported heterosexual HIV infection in London. Lancet. 1991;337(8757):1614-5.

199. Swan AV, Nicoll A, McGarrigle C, Noone A, Gill ON. An investigation assessing the fraction of human immunodeficiency virus infection attributable to ethnic group variations in risk. Int J Epidemiol. 1995;24 Suppl 1:S15-20.

200. All-Party Parliamentary Group on AIDS. Migration and HIV: Improving Lives in Britain. London: All-Party Parliamentary Group on AIDS,; 2003 [cited 2015 01/04/2015]. Available from: http://appghivaids.org.uk/sites/default/files/pdf/2003/migrationandhiv.pdf.

201. Prevots DR, Ancelle-Park RA, Neal JJ, Remis RS. The epidemiology of heterosexually-acquired HIV infection and AIDS in western industrialised countries. AIDS Behav. 1994;8((Suppl1)):S109-17.

202. Fenton KA, Chinouya M, Davidson O, Copas A, team Mr. HIV transmission risk among sub-Saharan Africans in London travelling to their countries of origin. AIDS. 2001;15(11):1442-5.

203. Kramer MA, van Veen MG, de Coul EL, Geskus RB, Coutinho RA, van de Laar MJ, et al. Migrants travelling to their country of origin: a bridge population for HIV transmission? Sex Transm Infect. 2008;84(7):554-5.

204. Hickson F, Owuor J, Weatherburn P, Reid D, Hammond G, Jessup K. Bass Line 2008-09: Assessing the sexual HIV prevention needs of African people in England London: Sigma Research; 2009 [cited 2015 17/03/2015]. Available from: http://www.sigmaresearch.org.uk/files/report2009h.pdf.

205. Elford J, Ibrahim F, Bukutu C, Anderson J. Sexual behaviour of people living with HIV in London: implications for HIV transmission. AIDS. 2007;21 Suppl 1:S63-70.

206. Barlow D, Daker-White G, Band B. Assortative sexual mixing in a heterosexual clinic population--a limiting factor in HIV spread? AIDS. 1997;11(8):1039-44.

207. Mor Z, Grotto I, Leventhal A. [Tuberculosis and AIDS in labor migrants in Israel--are we really facing a new challenge?]. Harefuah. 2012;151(3):175-7, 88.

208. McGarrigle C, Gilbart V, Nicoll A. AIDS and HIV infection acquired heterosexually. Commun Dis Rep CDR Rev. 1997;7(9):R125-8.

209. Brown P. Rate of HIV transmission among Africans in UK "underestimated". BMJ. 2000;320(7237):735.

210. Alvarez GG, Gushulak B, Abu Rumman K, Altpeter E, Chemtob D, Douglas P, et al. A comparative examination of tuberculosis immigration medical screening programs from selected countries with high immigration and low tuberculosis incidence rates. BMC Infect Dis. 2011;11:3.

211. Schwartzman K, Oxlade O, Barr RG, Grimard F, Acosta I, Baez J, et al. Domestic returns from investment in the control of tuberculosis in other countries. N Engl J Med. 2005;353(10):1008-20.

212. von Wyl V, Kouyos RD, Yerly S, Boni J, Shah C, Burgisser P, et al. The role of migration and domestic transmission in the spread of HIV-1 non-B subtypes in Switzerland. J Infect Dis. 2011;204(7):1095-103.

213. Pezzoli MC, Hamad IE, Scarcella C, Vassallo F, Speziani F, Cristini G, et al. HIV infection among illegal migrants, Italy, 2004-2007. Emerg Infect Dis. 2009;15(11):1802-4.

214. May RM, Anderson RM. Transmission dynamics of HIV infection. Nature. 1987;326(6109):137-42.

215. Audelin AM, Cowan SA, Obel N, Nielsen C, Jorgensen LB, Gerstoft J. Phylogenetics of the Danish HIV epidemic: the role of very late presenters in sustaining the epidemic. J Acquir Immune Defic Syndr. 2013;62(1):102-8.

216. Aral SO. Patterns of sexual mixing: mechanisms for or limits to the spread of STIs? Sex Transm Infect. 2000;76(6):415-6.

217. Wellcome Trust. Wellcomecollection: AIDS. 2013 [cited 2013 16/01/2013]. Available from: http://www.wellcomecollection.org/explore/sickness--health/topics/epidemics/articles/aids.aspx

218. NACAIDS. Grim Reaper. 1987 [cited 2013 16/01/2013]. Available from: http://www.youtube.com/watch?v=U219eUIZ7Qo.

219. Chin J. The AIDS pandemic; the collision of epidemiology with politically correctness. Milton Keynes: Radcliffe Publishing; 2007.

220. Fumento M. The myth of heterosexual AIDS. New York: Basic Books; 1990.

221. Coker R. Migration, public health and compulsory screening for TB and HIV. London: Institute for Public Policy Research; 2003.

222. Markel H, Stern AM. The foreignness of germs: the persistent association of immigrants and disease in American society. Milbank Q. 2002;80(4):757-88, v.

223. Coker R. Compulsory screening of immigrants for tuberculosis and HIV. BMJ. 2004;328(7435):298-300.

224. Vargas-Silva C. Long-Term International Migration flows to and from the UK Oxford: University of Oxford; 2014 [cited 2015 01/04/2015]. Available from: http://www.migrationobservatory.ox.ac.uk/sites/files/migobs/Briefing%20-%20Geographical%20Distribution%20and%20Characteristics.pdf.

225. Office for National Statistics. Migration Statistics Quarterly Report, August 2013. 2013 [cited 2014 02/06/2014]. Available from: http://www.ons.gov.uk/ons/dcp171778_324444.pdf.

226. Office for National Statistics. Quality of Long-Term International Migration Estimates from 2001 to 2011. 2014 [cited 2014 05/06/2014]. Available from: http://www.ons.gov.uk/ons/rel/migration1/long-term-international-migration/quality-of-long-term-international-migration-estimates-from-2001-to-2011/sty-quality-of-ltim.html

227. Hill T, Bansi L, Sabin C, Phillips A, Dunn D, Anderson J, et al. Data linkage reduces loss to follow-up in an observational HIV cohort study. J Clin Epidemiol. 2010;63(10):1101-9.

228. British HIV Association and Health Protection Agency. Clinical Audit: People with diagnosed HIV infection apparently not in care London: British HIV Association and Health Protection Agency; 2014 [cited 2015 01/04/2015]. Available from: http://bhiva.org/documents/ClinicalAudit/FindingsandReports/NotInCare2013webversion.pptx.

229. Nyblade L, Stangl A, Weiss E, Ashburn K. Combating HIV stigma in health care settings: what works? Journal of the International AIDS Society. 2009;12:15-.

230. Hall HI, Frazier EL, Rhodes P, Holtgrave DR, Furlow-Parmley C, Tang T, et al. Differences in human immunodeficiency virus care and treatment among subpopulations in the United States. JAMA Intern Med. 2013;173(14):1337-44.

231. Kates J. Implications of the Affordable Care Act for people with HIV infection and the Ryan White HIV/AIDS Program: what does the future hold? Top Antivir Med. 2013;21(4):138-42.

232. Donohoe T, Reyes M, Armas L, Mandel N. Continuum of care for HIV patients returning to Mexico. J Assoc Nurses AIDS Care. 2008;19(5):335-7.

233. Doctor J, Ghorani E, Carder M, Walsh J, editors. Lost for good? - an audit of local guidelines to return HIV patients back to care. 18th Annual Conference of the BHIVA: Poster 6; 2012.

234. Rice B. Discussions with the ECDC on the application of a new method to assign likely country of HIV infection in January and May 2014. 2014.

235. Delpech VC, Curtis H, Brown AE, Ong E, Hughes G, Gill ON. Migrant patients' access to HIV care: testing should always be free. BMJ. 2013;347:f7056.

236. Pozniak AL, Coyne KM, Miller RF, Lipman MC, Freedman AR, Ormerod LP, et al. British HIV Association guidelines for the treatment of TB/HIV coinfection 2011. HIV Med. 2011;12(9):517-24.

237. World Health Organisation. HIV-Associated TB Facts 2013. 2013. Available from: http://www.who.int/tb/challenges/hiv/tbhiv_factsheet_2013_web.pdf?ua=1.

238. Pontali E, Pasticci MB, Matteelli A, Baldelli F, Migliori GB. Tuberculosis and HIV co-infection: do we have a surveillance system in Europe? Eur Respir J 2011;38:1258–60.

239. World Health Organisation. The WHO Technical HIV Incidence Assay Working Group objectives. 2012 [March 2012]. Available from: http://www.who.int/diagnostics_laboratory/links/hiv_incidence_assay/en/index1.html.

240. Giehl C, Roy RB, Knellwolf AL. The Situation of HIV/M. tuberculosis Co-Infection in Europe. Open Infect Dis J. 2011;5(Suppl 1-M3):21-35.

241. Kruijshaar ME, Pimpin L, Abubakar I, Rice B, Delpech V, Drumright LN, et al. The burden of TB-HIV in the EU: how much do we know? A survey of surveillance practices and results. Eur Respir J. 2011;38(6):1374-81.

242. Lazarus JV, Olsen M, Ditiu L, Matic S. Tuberculosis-HIV co-infection: policy and epidemiology in 25 countries in the WHO European region. HIV Med. 2008;9(6):406-14.

243. Kruk A, Bannister W, Podlekareva DN, Chentsova NP, Rakhmanova AG, Horban A, et al. Tuberculosis among HIV-positive patients across Europe: changes over time and risk factors. AIDS. 2011;25(12):1505-13.

244. Taarnhoj GA, Engsig FN, Ravn P, Johansen IS, Larsen CS, Roge B, et al. Incidence, risk factors and mortality of tuberculosis in Danish HIV patients 1995-2007. BMC Pulm Med. 2011;11:26.

245. Velasco M, Castilla V, Cervero M, Sanz J, Condes E, Gaspar G, et al. The changing pattern of tuberculosis and HIV co-infection in immigrants and Spaniards in the last 20 years. HIV Med. 2008;9(4):227-33.

246. Alvaro-Meca A, Rodríguez-Gijón L, Díaz A, Gil A, Resino S. Incidence and mortality of tuberculosis disease in Spain between 1997 and 2010: impact of human immunodeficiency virus (HIV) status. J Infect. 2014;68(4):355-62.

247. Valín ER. Current situation of respiratory tuberculosis in Spain. Euro Surveill. 2002;6(15).

248. Antunes ML, Fonseca-Antunes A. The tuberculosis situation in Portugal : a historical perspective to 1994. Euro Surveill. 1996;1(3):19-21.

249. Abgrall S, Del Giudice P, Melica G, Costagliola D, Fhdh-Anrs CO. HIV-associated tuberculosis and immigration in a high-income country: incidence trends and risk factors in recent years. AIDS. 2010;24(5):763-71.

250. Grant AD, Bansi L, Ainsworth J, Anderson J, Delpech V, Easterbrook P, et al. Tuberculosis among people with HIV infection in the United Kingdom: opportunities for prevention? AIDS. 2009;23(18):2507-15.

251. Moreno S, Jarrin I, Iribarren JA, Perez-Elias MJ, Viciana P, Parra-Ruiz J, et al. Incidence and risk factors for tuberculosis in HIV-positive subjects by HAART status. Int J Tuberc Lung Dis. 2008;12(12):1393-400.

252. Girardi E, Sabin CA, d'Arminio Monforte A, Hogg B, Phillips AN, Gill MJ, et al. Incidence of Tuberculosis among HIV-infected patients receiving highly active antiretroviral therapy in Europe and North America. Clin Infect Dis. 2005 41(12):1772-82.

253. del Amo J, Moreno S, Bucher HC, Furrer H, Logan R, Sterne J, et al. Impact of antiretroviral therapy on tuberculosis incidence among HIV-positive patients in high-income countries. Clin Infect Dis. 2012;54(9):1364-72.

254. Gupta RK, Rice B, Brown AE, Thomas HL, Zenner D, Anderson L, et al. Does antiretroviral therapy reduce HIV-associated tuberculosis incidence to background rates? A national observational cohort study from England, Wales, and Northern Ireland. The Lancet HIV. 2015;2(6):e243-e51.

255. Lodi S, del Amo J, d'Arminio Monforte A, Abgrall S, Sabin C, Morrison C, et al. Risk of tuberculosis following HIV seroconversion in high-income countries. Thorax. 2013;68(3):207-13.

256. Rose AM, Sinka K, Watson JM, Mortimer JY, Charlett A. An estimate of the contribution of HIV infection to the recent rise in tuberculosis in England and Wales. Thorax. 2002;57(5):442-5.

257. Ahmed AB, Abubakar I, Delpech V, Lipman M, Boccia D, Forde J, et al. The growing impact of HIV infection on the epidemiology of tuberculosis in England and Wales: 1999 2003. Thorax. 2007;62(8):672-6.

258. Sudre P, Hirschel B, Toscani L, Ledergerber B, Rieder HL. Risk factors for tuberculosis among HIV-infected patients in Switzerland. European Respiratory Journal. 1996;9(2):279-83.

259. Monge S, Diez M, Pulido F, Iribarren JA, Campins AA, Arazo P, et al. Tuberculosis in a cohort of HIV-positive patients: epidemiology, clinical practice and treatment outcomes. Int J Tuberc Lung Dis. 2014;18(6):700-8.

260. Pimpin L, Drumright LN, Kruijshaar ME, Abubakar I, Rice B, Delpech V, et al. Tuberculosis and HIV co-infection in European Union and European Economic Area countries. Eur Respir J. 2011;38(6):1382-92.

261. Gill H, Chakraborty R, Dedicoat M, Barrett S. An HIV and TB co-infection clinic: Patient characteristics, experience and outcomes. 19th Annual Conference of the British HIV Association Manchester2013.

262. Backx M, Curtis H, Freedman A, Johnson M, British HIVA, Sub-Committee BCA. British HIV Association national audit on the management of patients co-infected with tuberculosis and HIV. Clin Med. 2011;11(3):222-6.

263. Department of Health. The Interdepartmental Working Group on Tuberculosis. The Prevention and Control of Tuberculosis in the United Kingdom, 1998. 1998. Available from: www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4006196

264. National Institute for Health and Clinical Excellence. Tuberculosis: Clinical diagnosis and management of tuberculosis, and measures for its prevention and control - NICE clinical guideline 117 Manchester: National Institute for Health and Clinical Excellence; 2011 [cited 2015 23/03/2015]. Available from: https://www.nice.org.uk/guidance/cg117.

265. Sester M, Giehl C, McNerney R, Kampmann B, Walzl G, Cuchi P, et al. Challenges and perspectives for improved management of HIV/Mycobacterium tuberculosis co-infection. Eur Respir J. 2010;36(6):1242-7.

266. Kall MM, Coyne KM, Garrett NJ, Boyd AE, Ashcroft AT, Reeves I, et al. Latent and subclinical tuberculosis in HIV infected patients: a cross-sectional study. BMC Infect Dis. 2012;12:107.

267. Rieder HL. Preventing latent tuberculosis among HIV-infected patients: efficacious and effective, yet inefficient? Clin Infect Dis. 2007;44(1):103-4.

268. Public Health England. Tuberculosis in the UK: 2014 report London: Public Health England; 2014 [cited 2015 23/03/2015]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/360335/TB_Annual_report__4_0_300914.pdf.

269. Melzer M, Warley A, Milburn H, O'Sullivan D, Barker RD, Hutchinson D, et al. Tuberculosis and HIV seroprevalence in Lambeth, Southwark and Lewisham, an area of South London. Respir Med. 2003;97(2):167-72.

270. Public Health England. Tuberculosis in the UK: Annual report on tuberculosis surveillance in the UK, 2013 London: Public Health England; 2013 [cited 2015 24/03/2015]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/325632/TB_in_the_UK.pdf.

271. Health Protection Agency. HIV in the United Kingdom: 2012 Report 2012 [cited 2013 13/02/2013]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/335452/HIV_annual_report_2012.pdf.

272. Zenner D, Abubakar I, Conti S, Gupta RK, Yin Z, Kall M, et al. Impact of TB on the survival of people living with HIV infection in England, Wales and Northern Ireland. Thorax. 2015;70(6):566-73.

273. Fenton KA. HIV testing and high risk sexual behaviour among London's migrant African communities: a participatory research study. Sexually Transmitted Infections. 2002;78(4):241-5.

274. Burns F, Fenton KA, Morison L, Mercer C, Erens B, Field J, et al. Factors associated with HIV testing among black Africans in Britain. Sex Transm Infect. 2005;81(6):494-500.

275. Dodds C, Hickson F, Weatherburn P, Reid D, Hammond G, Jessup K, et al. BASS Line 2007 survey: Assessing the sexual HIV prevention needs of African people in England London: Sigma Research; 2008 [cited 2015 17/03/2015]. Available from: http://www.sigmaresearch.org.uk/files/report2008b.pdf.

276. Bourne A, Reid D, Weatherburn P. African Health & Sex Survey 2013-2014: headline findings London: Sigma Research, London School of Hygiene & Tropical Medicine; 2014 [cited 2015 17/03/2015]. Available from: http://www.sigmaresearch.org.uk/files/report2014c.pdf.

277. Sonnenberg P, Clifton S, Beddows S, Field N, Soldan K, Tanton C, et al. Prevalence, risk factors, and uptake of interventions for sexually transmitted infections in Britain: findings from the National Surveys of Sexual Attitudes and Lifestyles (Natsal). The Lancet. 2013;382(9907):1795-806.

278. Chen M, Rhodes PH, Hall IH, Kilmarx PH, Branson BM, Valleroy LA, et al. Prevalence of undiagnosed HIV infection among persons aged >/=13 years--National HIV Surveillance System, United States, 2005-2008. MMWR Morb Mortal Wkly Rep. 2012;61 Suppl:57-64.

279. Eyawo O, Hogg RS, Montaner JS. The Holy Grail: The search for undiagnosed cases is paramount in improving the cascade of care among people living with HIV. Can J Public Health. 2013;104(5):e418-9.

280. Lehman C, Keen A, Kerr B. Controlling the heterosexual HIV epidemic in low-prevalence domains. 19th Biennial Conference Of The International Society For Sexually Transmitted Diseases Research Quebec: Sexually Transmitted Infectionssti.bmj.com; 2011.

281. Marks G, Crepaz N, Janssen RS. Estimating sexual transmission of HIV from persons aware and unaware that they are infected with the virus in the USA. AIDS. 2006;20(10):1447-50.

282. World Health Organisation. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection 2013 [cited 2015 24/04/2015]. Available from: http://www.who.int/hiv/pub/guidelines/arv2013/en/.

283. Halve It. Early testing saves lives: HIV is a public health priority Third edition London: Halve It; 2013 [cited 2015 17/03/2015]. Available from: http://www.halveit.org.uk/resources/Halve_It_Position_Paper.pdf.

284. The UK Collaborative Group for HIV and STI Surveillance. A Complex Picture. HIV and other Sexually Transmitted Infections

in the United Kingdom: 2006 London: Health Protection Agency; 2006 [cited 2015 24/04/2015]. Available from: http://webarchive.nationalarchives.gov.uk/20140714084352/http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947365435.

285. Fakoya I, Evans A, Burns FM, Baio G, Morris S, Hart GJ. Review of effectiveness and cost effectiveness: Increasing the uptake of HIV testing to reduce undiagnosed infection and prevent transmission among black African communities living in England London: NICE; 2010 [cited 2015 24/04/2015]. Available from: http://www.nice.org.uk/guidance/ph33/documents/increasing-the-uptake-of-hiv-testing-among-black-africans-in-england-review-of-effectiveness-and-cost-effectiveness2

286. European Centre for Disease Prevention and Control. Migrant health: HIV testing and counselling in migrant populations and ethnic minorities in EU/EEA/EFTA Member States Stockholm: European Centre for Disease Prevention and Control; 2011 [cited 2015 17/-3/2015]. Available from: http://www.ecdc.europa.eu/en/publications/Publications/1108_TER_HIV_in_migrants.pdf.

287. Gazzard B, Clumeck N, d'Arminio Monforte A, Lundgren JD. Indicator disease-guided testing for HIV--the next step for Europe? HIV Med. 2008;9 Suppl 2:34-40.

288. Barton S. Introduction: Reaching the HIV infected but undiagnosed individual. International Journal of STD & AIDS. 2009;20(suppl 1):1-.

289. Glew S, Pollard A, Hughes L, Llewellyn C. Public attitudes towards opt-out testing for HIV in primary care: a qualitative study. Br J Gen Pract. 2014;64(619):e60-6.

290. Doyal L, Anderson J, Apenteng P. 'I want to survive, I want to win, I want tomorrow': An exploratory study of African men living with HIV in London London: Homerton University Hospital NHS Foundation Trust; 2005 [cited 2015 17/03/2015]. Available from: http://www.homerton.nhs.uk/media/105818/iwanttosurvive.pdf.

291. Department of Health. The national strategy for sexual health and HIV London: Department of Health; 2001 [cited 2015 18/03/2015]. Available from: http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4058945.pdf .

292. Heijman RL, Stolte IG, Thiesbrummel HF, van Leent E, Coutinho RA, Fennema JS, et al. Opting out increases HIV testing in a large sexually transmitted infections outpatient clinic. Sex Transm Infect. 2009;85(4):249-55.

293. Stolte IG, Gras M, Van Benthem BH, Coutinho RA, van den Hoek JA. HIV testing behaviour among heterosexual migrants in Amsterdam. AIDS Care. 2003;15(4):563-74.

294. Branson BM, Handsfield HH, Lampe MA, Janssen RS, Taylor AW, Lyss SB, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. MMWR Recomm Rep. 2006;55(Rr-14):1-17; quiz CE1-4.

295. Hsieh Y, Beck K, Kelen G, Shahan J, Kraus C, Laeyendecker O, et al. High prevalence of undiagnosed HIV infection in patients who were not offered screening and patients who declined screening: Evaluation of a rapid hiv screening programme in a U.S. Urban Emergency Department. . STI and AIDS World Congress 2013; Vienna: BMJ Publishing Group; 2013.

296. Health Protection Agency. Time to test for HIV: Expanding HIV testing in healthcare and community services in England London: Health Protection Agency; 2012 [cited 2015 17/03/2015]. Available from:

http://www.bhiva.org/documents/Publications/Time_to_test_final_report__Sept_2011.pdf.

297. Hartney T, Kennedy I, Crook P, Nardone A. Expanded HIV testing in high-prevalence areas in England: results of a 2012 audit of sexual health commissioners. HIV Med. 2014;15(4):251-4.

298. NHS Choices. Home HIV testing kits now legal in UK 2014 [cited 2015 14/04/2015]. Available from: http://www.nhs.uk/news/2014/04April/Pages/Home-HIV-testing-kits-now-legal-in-UK.aspx.

299. Krause J, Subklew-Sehume F, Kenyon C, Colebunders R. Acceptability of HIV self-testing: a systematic literature review. BMC Public Health. 2013;13:735.

300. Lyons MS, Lindsell CJ, Ruffner AH, Trott AT, Fichtenbaum CJ. Relationship of self-reported prior testing history to undiagnosed HIV positivity and HIV risk. Curr HIV Res. 2009;7(6):580-8.

301. National Institute for Health and Clinical Excellence. Increasing the uptake of HIV testing among men who have sex with men London: National Institute for Health and Clinical Excellence; 2011 [cited 2015 17/03/2015]. Available from: https://www.nice.org.uk/guidance/ph34/resources/guidance-increasing-the-uptake-of-hiv-testing-among-men-who-have-sex-with-men-pdf.

Appendices

Appendix i: co-author contributions on published papers

Paper 3.1: Rice BD, Sinka K, Patel B, Chadborn T, Delpech V. The changing epidemiology of diagnosed prevalent HIV infections in England: greatest impact on the London environs. Epidemiol & Infect 2007; 135:151-158

Brian D Rice: HIV Epidemiological Scientist. Co-ordinated the 2002 and 2003 SOPHID surveys and first author. Carried out majority of the analyses and writing.

Katy Sinka: Lead Scientist of the HIV and AIDS Reporting Section at CDSC, and second author. Provided input into the data analyses, layout and writing of the paper. Co-ordinated the 2001 SOPHID survey and the 1998 to 2001 London SOPHID surveys.

Bela Patel: SOPHID (London) Scientist. Collected data shown in results and provided guidance as to the structure of the paper.

Timothy Chadborn: SOPHID co-ordinator. Provided input into the writing of the paper.

Valerie Delpech: Lead Consultant for SOPHID and person to whom correspondence should be forwarded. Provided input into the writing of the paper.

Paper 3.2: Rice B, Elford J, Yin Z, Croxford S, Brown A, Delpech V. Trends in HIV diagnoses, HIV care and uptake of antiretroviral therapy among heterosexual adults in England, Wales and Northern Ireland. Sex Transm Dis 2014; 41(4): 257-265

Brian D Rice: HIV Epidemiological Scientist. Conceived the paper, carried out majority of the analyses and writing.

Jonathan Elford: Professor. Contributed to data analysis, interpretation and drafting the paper.

Zheng Yin: Epidemiological HIV scientist. Contributed to data analysis, interpretation and drafting the paper.

Sara Croxford: Epidemiological HIV scientist. Contributed to data analysis, interpretation and drafting the paper.

Alison Brown: Principal HIV Scientist. Contributed to data analysis, interpretation and drafting the paper.

Valerie Delpech: Lead HIV Consultant. Contributed to data analysis, interpretation and drafting the paper.

Paper 4.1: Rice BD, Elford J, Yin Z, Delpech D. A new method to assign country of HIV infection among heterosexuals born abroad and diagnosed with HIV in the UK. AIDS 2012; 26(15): 1961-1966

Brian D Rice: HIV Epidemiological Scientist. Conceived the paper, carried out majority of the analyses and writing.

Jonathan Elford: Professor. Contributed to data analysis, interpretation and drafting the paper.

Zheng Yin: Epidemiological Scientist. Contributed to data analysis, interpretation and drafting the paper.

Valerie Delpech: Lead HIV Consultant. Contributed to data analysis, interpretation and drafting the paper.

Paper 4.2: Rice BD, Delpech VC, Chadborn TR, Elford J. Loss to follow-up among adults attending HIV-services in England, Wales and Northern Ireland. Sex Transm Dis 2011; 38(8):685-690

Brian D Rice: HIV Epidemiological Scientist. Conceived the paper, carried out majority of the analyses and writing.

Valerie Delpech: Lead Consultant for SOPHID and new HIV diagnoses. Contributed to data analysis, interpretation and drafting the paper.

Timothy Chadborn: Epidemiological Scientist leading on SOPHID. Contributed to data analysis, interpretation and drafting the paper.

Jonathan Elford: Professor. Contributed to data analysis, interpretation and drafting the paper.

Paper 5.1: Rice BD, Elford J, Yin Z, Kruijshaar M, Abubakar I, Lipman M, et al. Decreasing incidence of tuberculosis among HIV diagnosed heterosexuals in England and Wales. AIDS 2013; 27(7):1151–1157

Brian D Rice: HIV Epidemiological Scientist. Conceived the paper, carried out majority of the analyses and writing.

Jonathan Elford: Professor. Contributed to data analysis, interpretation and drafting the paper.

Zheng Yin: Epidemiological Scientist SOPHID. Contributed to data analysis, interpretation and drafting the paper.

Michelle Kruijshaar: Principal TB Scientist: Contributed to data analysis, interpretation and drafting the paper.

Ibrahim Abubakar: Lead TB Consultant. Contributed to data analysis, interpretation and drafting the paper.

Marc Lipman: Consultant Physician. Contributed to data interpretation and drafting the paper.

Anton Pozniak: Consultant Physician. Contributed to data interpretation and drafting the paper.

Meaghan Kall:Epidemiological Scientist HIV and AIDS New Diagnoses. Contributed to data analysis and interpretation.

Valerie Delpech: Lead Consultant for SOPHID and HIV and AIDS New Diagnoses. Contributed to data analysis, interpretation and drafting the paper.

Paper 6.1: Rice BD, Delpech V, Sadler KE, Yin Z, Elford J. HIV testing among black Africans living in England. Epidemiol & Infec 2012; 141:1741–1748

Brian D Rice: HIV Epidemiological Scientist. Conceived the paper, carried out majority of the analyses and writing.

Valerie Delpech: Lead HIV Consultant. Contributed to data analysis, interpretation and drafting the paper.

Katharine Sadler: Research Director at NATCEN and lead scientist on Mayisha II. Contributed to data analysis, interpretation and drafting the paper.

Zheng Yin: Epidemiological Scientist SOPHID. Contributed to data analysis, interpretation and drafting the paper.

Jonathan Elford: Professor. Contributed to data analysis, interpretation and drafting the paper.

Appendix iii: Literature search strategy

Resources used

- Ovid MEDLINE and EMBASE by means of City University London's Health and Society E-Resource Databases.
- Ovid EMBASE AutoAlert (SDI) feeds.
- Reference lists of key review articles.
- Conference abstract databases of the International AIDS Society and British HIV Association.
- Google, Google Scholar and PubMed Central.

Literature review

In Chapter 2.8, I describe my methods for conducting computerised and manual literature searches. In summary, I undertook computerised literature searches using Ovid MEDLINE and EMBASE. I applied key terms to search article titles and abstracts for papers published in the English language. Publications with relevant titles were selected for abstract screening. The reference lists of key publications were reviewed and publications of interest were obtained through title and author searches using Google Scholar and PubMed Central. To identify grey literature, I conducted manual Internet key word searches using Google.

Literature search strategy specific to each chapter

Chapter 1: Introduction

Information on the history of the HIV epidemic and of heterosexually-acquired HIV in E,W&NI was obtained from a review of Health Protection Agency / Public Health England publications (1985-2015). The references of key papers were reviewed.

Chapter 2: Methods

A description of each of the datasets I utilise for the purpose of my thesis was obtained from a review of Health Protection Agency / Public Health England publications and web-based documents. I conducted computerised and manual literature searches on the

following key words: data confidentiality; surveillance strengths; surveillance weaknesses.

Chapter 3: Trends in heterosexually-acquired HIV in England, Wales and Northern Ireland

I conducted computerised and manual searches on the following topics: (i) HIV trends and predicting trends; (ii) quality of HIV care; (iii) late HIV diagnosis; (iv) older age at HIV diagnosis. The following key words were applied: HIV; AIDS; predictions; quality of care; surveillance; late diagnosis; HIV older adults; United Kingdom; Europe; USA.

Computerised literature searches

- Heterosexually-acquired HIV - MEDLINE

1. MEDLINE; HIV.ti,ab [Limit to: English Language and Humans and Publication Year 2000-Current]; 107085 results.

2. MEDLINE; heterosexual.ti,ab [Limit to: English Language and Humans and Publication Year 2000-Current]; 4074 results.

3. MEDLINE; 1 AND 2 [Limit to: English Language and Humans and Publication Year 2000-Current]; 1980 results.

4. MEDLINE; europe.ti,ab [Limit to: English Language and Humans and Publication Year 2000-Current]; 25653 results.

5. MEDLINE; 3 AND 4 [Limit to: English Language and Humans and Publication Year 2000-Current]; 76 results.

Following review, 76 papers published on heterosexually-acquired HIV between January 1990 and August 2014 were selected for abstract screening. Of these, 27 were included for extraction and review.

- Epidemiological trends in heterosexually-acquired HIV - Embase

1. HIV.mp. or Human immunodeficiency virus/

2. HIV.mp. or Human immunodeficiency virus/

3. limit 2 to (human and english language and yr="1990 -Current")

4. heterosexual.mp. or heterosexuality/

5. limit 4 to (human and english language and yr="1990 -Current")

6. 3 and 5

7. epidemiology/

8. limit 7 to (human and english language and yr="1990 -Current")

9. 6 and 8

10. trend study/ or trend.mp.

11. limit 10 to (human and yr="1990 -Current")

12. 6 and 11

Following review, 210 papers published on epidemiological trends in heterosexually-acquired HIV between January 1990 and August 2014 were selected for abstract screening. Of these, 79 were included for extraction and review.

- Quality of HIV care – Embase

1. hiv.mp. or Human immunodeficiency virus/

2. limit 1 to (human and english language and yr="2000 -Current")

3. heterosexual.mp. or heterosexuality/

4. limit 3 to (human and english language and yr="2000 -Current")

5. quality.m_titl.

6. limit 5 to (human and english language and yr="2000 -Current")

7. cascade.m_titl.

8. limit 7 to (human and english language and yr="2000 -Current")

9. continuum.m_titl.

10. limit 9 to (human and english language and yr="2000 -Current")

11. 2 and 4 and 6

12. 2 and 4 and 8

13. 2 and 4 and 10

Following review, 30 papers published on quality of HIV care among heterosexuals between January 2000 and August 2014 were selected for abstract screening. Of these, 18 were included for extraction and review.

- Late HIV diagnosis - Embase

1. hiv.mp. or Human immunodeficiency virus/

2. limit 1 to (human and english language and yr="2000 -Current")

3. late diagnosis.mp. or delayed diagnosis/

4. limit 3 to (human and english language and yr="2000 -Current")

5. late diagnosis.m_titl.

6. limit 5 to (human and english language and yr="2000 -Current")

7. 2 and 4

8. 2 and 6

Following review, 50 papers published on late HIV diagnosis between January 2000 and August 2014 were selected for abstract screening. Of these, 39 were included for extraction and review.

- Older adults and HIV- Embase

1. hiv.mp. or Human immunodeficiency virus/

2. limit 1 to (human and english language and yr="2000 -Current")

3. heterosexual.mp. or heterosexuality/

4. limit 3 to (human and english language and yr="2000 -Current")

5. older.m_titl.

6. limit 5 to (human and english language and yr="2000 -Current")

7. elderly.m_titl.

8. limit 7 to (human and english language and yr="2000 -Current")

9. "50".m_titl.

10. limit 9 to (human and english language and yr="2000 -Current")

11. 2 and 4 and 6

12. 2 and 4 and 8

13. 2 and 4 and 10

Following review, 67 papers published on HIV among older adults between January 2000 and August 2014 were selected for abstract screening. Of these, 33 were included for extraction and review.

Chapter 4: Migration

I conducted computerised and manual literature searches in relation to the following topics: (i) Heterosexually-acquired HIV and migration (ii) challenges of HIV surveillance; (iii) CD4 decline; (iv) HIV, migrants and migration; (v) HIV and migration in Europe; (vi) HIV and migration in the USA. The following key words were applied: HIV; AIDS; migration; migrants; surveillance; United Kingdom; Europe; USA; Australia.

Based on the Embase search entitled "*HIV, migrants and migration*" (see below), I set up monthly EBSCOhost Auto Alert Notifications via EPNET.com to my personal Yahoo email account. Alerts were reviewed on receipt for new and relevant papers on HIV, migrants and migration. Relevant papers were selected for abstract screening.

Computerised literature searches

- Heterosexually-acquired HIV and migration - MEDLINE

1. MEDLINE; diagnosis.ti [Limit to: Publication Year 2000-2011 and Humans and English Language]; 52991 results.

3. MEDLINE; hiv.ti [Limit to: Publication Year 2000-2011 and Humans and English Language]; 63952 results.

7. MEDLINE; heterosexual.ti,ab [Limit to: Publication Year 2000-2011 and Humans and English Language]; 3613 results.

8. MEDLINE; 1 AND 3 AND 7 [Limit to: Publication Year 2000-2011 and Humans and English Language]; 22 results.

9. MEDLINE; diagnosis.ti [Limit to: Publication Year 2000-2011 and Humans and English Language]; 52991 results.

10. MEDLINE; hiv.ti [Limit to: Publication Year 2000-2011 and Humans and English Language]; 63952 results.

15. MEDLINE; 9 AND 10 AND 14 [Limit to: Publication Year 2000-2011 and Humans and English Language]; 22 results.

16. MEDLINE; migrant.ti,ab [Limit to: Publication Year 2000-2011 and Humans and English Language]; 1696 results.

17. MEDLINE; 1 AND 3 AND 16 [Limit to: Publication Year 2000-2011 and Humans and English Language]; 1 results.

18. MEDLINE; 3 AND 16 [Limit to: Publication Year 2000-2011 and Humans and English Language]; 182 results.

21. MEDLINE; migrant.ti [Limit to: Publication Year 2000-2011 and Humans and English Language]; 595 results.

22. MEDLINE; 3 AND 21 [Limit to: Publication Year 2000-2011 and Humans and English Language]; 77 results.

Following review, 77 papers published on heterosexually-acquired HIV and migration, between January 2000 and October 2011 were selected for abstract screening. Of these, 42 were included for extraction and review.

- Challenges of HIV surveillance - MEDLINE

1. MEDLINE; surveillance.ti [Limit to: Publication Year 1990-Current and Humans]; 15526 results.

2. MEDLINE; hiv.ti [Limit to: Publication Year 1990-Current and Humans]; 105094 results.

3. MEDLINE; 1 AND 2 [Limit to: Publication Year 1990-Current and Humans]; 625 results.

4. MEDLINE; criteria.ti,ab; 290528 results.

5. MEDLINE; 3 AND 4 [Limit to: Publication Year 1990-Current and Humans]; 12 results.

6. MEDLINE; challenges.ti,ab; 90590 results.

7. MEDLINE; 3 AND 6 [Limit to: Publication Year 1990-Current and Humans]; 15 results.

Following review, 27 papers published on the criteria for, and challenges of, HIV surveillance, between January 2000 and October 2011 were selected for abstract screening. Of these, 12 were included for extraction and review.

- CD4 decline - MEDLINE

1. MEDLINE; CD4.ti [Limit to: Publication Year 1990-Current and Humans]; 12292 results.

2. MEDLINE; progression.ti,ab [Limit to: Publication Year 1990-Current and Humans]; 176155 results.

3. MEDLINE; HIV.ti,ab [Limit to: Publication Year 1990-Current and Humans]; 166116 results.

4. MEDLINE; decline.ti,ab [Limit to: Publication Year 1990-Current and Humans]; 59931 results.

5. MEDLINE; 1 AND 2 AND 3 [Limit to: Publication Year 1990-Current and Humans]; 617 results.

6. MEDLINE; 1 AND 3 AND 4 [Limit to: Publication Year 1990-Current and Humans]; 331 results.

7. MEDLINE; markov.ti,ab; 9368 results.

8. MEDLINE; 6 AND 7 [Limit to: Publication Year 1990-Current and Humans]; 4 results.

9. MEDLINE; seroconversion.ti,ab; 10281 results.

10. MEDLINE; 6 AND 9 [Limit to: Publication Year 1990-Current and Humans]; 41 results.

Following review, 45 papers published on CD4 decline between January 2000 and October 2011 were selected for abstract screening. Of these, 14 were included for extraction and review.

- HIV, migrants and migration - Embase

1. *Human immunodeficiency virus/

2. (HIV or AIDS).ab.

3. 1 or 2

4. *migration/ or *population migration/

5. (migrat* or migrant).ab.

6. 4 or 5

7. 3 and 6

8. limit 7 to (human and yr="2000 -Current")

9. limit 8 to (english and (adult <18 to 64 years> or aged <65+ years>))

10. (migrat* or migrant).ti.

11. 4 or 10

12. 3 and 11

13. limit 12 to (human and yr="2000 -Current")

14. limit 13 to (english and (adult <18 to 64 years> or aged <65+ years>))

Following review, 281 papers published on HIV, migrants and migration between January 2000 and June 2014 were selected for abstract screening. Of these, 95 were included for extraction and review.

- HIV and migration in Europe - Embase

1. HIV.mp. or Human immunodeficiency virus/

2. limit 1 to (human and english language and yr="2000 -Current")

3. migration/

4. limit 3 to (human and english language and yr="2000 -Current")

5. 2 and 4

6. europe.mp. or Europe/ or Eastern Europe/ or Western Europe/ or Southern Europe/

7. limit 6 to (human and english language and yr="2000 -Current")

8. 5 and 7

9. from 8 keep 1-2,4,6-8,10-11,13,15-16,19-20,23-24,34-36,39-40

Following review, 42 papers published on HIV and migration in Europe between January 2000 and June 2014 were selected for abstract screening. Of these, 20 were included for extraction and review.

- HIV and migration in the USA - Embase

1. HIV.mp. or Human immunodeficiency virus/

2. limit 1 to (human and english language and yr="2000 -Current")

3. migration/

4. limit 3 to (human and english language and yr="2000 -Current")

5. 2 and 4

6. United States/

7. 5 and 6

8. from 7 keep 7,9-10,16,18,20-21,37,48-50,74,76,78,98,148

Following review, 173 papers published on HIV and migration in the USA between January 2000 and June 2014 were selected for abstract screening. Of these, 16 were included for extraction and review.

Chapter 5: HIV and Tuberculosis co-infection

I conducted computerised and manual literature searches in relation to the following topics: (i) the incidence of active tuberculosis among HIV-diagnosed heterosexuals in the UK and elsewhere in Europe; (ii) HIV-tuberculosis service provision in the UK and elsewhere in Europe. The following key words were applied: HIV; AIDS; heterosexual; tuberculosis; co-infection; surveillance; integrate; missed; United Kingdom; Europe.

Computerised literature search

- HIV and tuberculosis co-infection -Embase

1. hiv.m_titl.

2. limit 1 to (human and english language and yr="1990 -Current")

3. tuberculosis.m_titl.

4. limit 3 to (human and english language and yr="1990 -Current")

5. 2 and 4

6. europe.mp. or Europe/ or Eastern Europe/ or Western Europe/ or Southern Europe/

7. limit 6 to (human and english language and yr="1990 -Current")

8. 5 and 7

9. united kingdom.mp. or United Kingdom/

10. limit 9 to (human and english language and yr="1990 -Current")

11. 5 and 10

12. spain.mp. or Spain/

13. limit 12 to (human and english language and yr="1990 -Current")

14. 5 and 13

15. germany.mp. or Germany/

16. limit 15 to (human and english language and yr="1990 -Current")

17. 5 and 16

18. france.mp. or France/

19. limit 18 to (human and english language and yr="1990 -Current")

20. 5 and 19

21. heterosexual.mp. or heterosexuality/

22. limit 21 to (human and english language and yr="1990 -Current")

23. 5 and 22

24. from 8 keep 2-3,9-12,15-20,23,25-27,29,31,33-34,38

25. from 11 keep 1,7-9,12-14,17-18,20-21,23,29-30,34,38,40,43,45,47-48,50-51

26. from 23 keep 10,13,17-18

27. integrate.mp.

28. limit 27 to (human and english language and yr="1990 -Current")

29. 5 and 28

30. services.m_titl.

31. limit 30 to (human and english language and yr="1990 -Current")

32. 5 and 31

33. 10 and 32

34. 7 and 32

35. missed.m_titl.

36. limit 35 to (human and english language and yr="1990 -Current")

37. 5 and 36

Following review, 241 papers published on HIV and tuberculosis between January 2000 and October 2014 were selected for abstract screening. Of these, 57 were included for extraction and review.

Chapter 6: HIV testing

I conducted computerised and manual literature searches in relation to the following topics among heterosexuals and black Africans: (i) undiagnosed HIV; (ii) HIV testing; (iii) testing barriers and triggers. The following key words were applied: HIV; AIDS; heterosexual; black African; testing; barriers; stigma; discrimination; United Kingdom; Europe; USA.

Computerised literature searches

- Undiagnosed HIV among heterosexuals and black Africans –Embase

1. hiv.m_titl.

2. limit 1 to (human and english language and yr="2002 -Current")

3. undiagnosed.m_titl.

4. limit 3 to (human and english language and yr="2002 -Current")

5. 2 and 4

6. heterosexual.mp. or heterosexuality/

7. limit 6 to (human and english language and yr="2002 -Current")

8. 5 and 7

9. black.mp. or Black person/

10. limit 9 to (human and english language and yr="2002 -Current")

11. 5 and 10

Following review, 16 papers published on undiagnosed HIV among heterosexuals or black Africans between January 2000 and February 2015 were selected for abstract screening. Of these, 11 were included for extraction and review.

- HIV testing among heterosexuals and black Africans –Embase

1. hiv.m_titl.

2. limit 1 to (human and english language and yr="2002 -Current")

3. heterosexual.mp. or heterosexuality/

4. limit 3 to (human and english language and yr="2002 -Current")

5. black.mp. or Black person/

6. limit 5 to (human and english language and yr="2002 -Current")

7. test.m_titl.

8. limit 7 to (human and english language and yr="2002 -Current")

9. testing.m_titl.

10. limit 9 to (human and english language and yr="2002 -Current")

11. 2 and 4 and 8

12. 1 and 3 and 10

13. 1 and 6 and 10

14. UK.mp. or United Kingdom/

15. limit 14 to (human and english language and yr="2002 -Current")

16. 12 and 15

17. 13 and 15

18. USA.mp. or United States/

19. limit 18 to (human and english language and yr="2002 -Current")

20. 12 and 19

21. 13 and 19

22. Europe.mp. or Europe/ or Western Europe/ or Southern Europe/

23. limit 22 to (human and english language and yr="2002 -Current")

24. 12 and 23

25. 13 and 23

Following review, 171 papers published on undiagnosed HIV among heterosexuals or black Africans between January 2000 and February 2015 were selected for abstract screening. Of these, 65 were included for extraction and review.

- Barriers to HIV testing among heterosexuals and black Africans - Embase

1. hiv.m_titl.

2. limit 1 to (human and english language and yr="2002 -Current")

3. heterosexual.mp. or heterosexuality/

4. limit 3 to (human and english language and yr="2002 -Current")

5. black.mp. or Black person/

6. limit 5 to (human and english language and yr="2002 -Current")

7. testing.m_titl.

8. limit 7 to (human and english language and yr="2002 -Current")

9. barrier.m_titl.

10. limit 9 to (human and english language and yr="2002 -Current")

11. 2 and 4 and 8 and 10

12. 2 and 6 and 8 and 10

13. barriers.mp.

14. limit 13 to (human and english language and yr="2002 - 2015")

15. 2 and 4 and 8 and 14

16. 2 and 4 and 6 and 14

17. stigma.m_titl.

18. limit 17 to (human and english language and yr="2002 - 2015")

19. 2 and 4 and 18

20. 2 and 6 and 18

Following review, 62 papers published on barriers to HV testing among heterosexuals and black Africans between January 2000 and February 2015 were selected for abstract screening. Of these, 32 were included for extraction and review.

Chapter 7: Conclusion

Not applicable.

Appendix iv: Presentations arising from this work

Oral

1. Rice, B.D. HIV testing in African communities. National AIDS Trust expert roundtable on HIV testing in African communities, London, UK, 2011.

2. Rice, B.D. The HIV epidemic in black-African communities in the UK. National AIDS Trust expert roundtable on HIV policy in African communities, London, UK, 2012.

3. Rice, B.D. Migrants from countries with generalised HIV epidemics: UK experience. European workshop of monitoring the Dublin Declaration, Lisbon, Portugal, 2012.

4. Rice, B.D. Information for action – HIV among black Africans and MSM in the UK. International Conference on HIV infection among hidden populations, Lisbon, Portugal, 2013.

5. Rice, B.D. HIV treatment and care indicators. UNAIDS MERG Indicator Working Group annual meeting, Geneva, Switzerland, 2013.

6. Rice, B.D. HIV care and treatment indicators. ECDC Advisory-Group to monitor the Dublin Declaration, Zagreb, Croatia, 2013.

7. Rice, B.D. CD4 cell decline and count at HIV seroconversion: a review of the literature. ECDC workshop on a CD4 based method to assign country of HIV infection, London, UK, 2014.

8. Rice B.D. Estimating probable country of infection among adults born abroad and diagnosed with HIV in the UK. ECDC workshop on a CD4 based method to assign country of HIV infection, London, UK, 2014.

9. Rice B.D. HIV quality of care indicators and probable country of infection. UNAIDS MERG Indicator Working Group, Montreux, Switzerland, 2014.

10. Rice, B.D. Estimating probable place of HIV infection. BREACH symposium, Brussels, Belgium, 2014.

11. Rice, B.D. Key indicator and monitoring related issues – United Kingdom. UNAIDS MERG Indicator Working Group, Geneva, Switzerland, 2015.

Poster

1. Rice, BD., Smith R., Elford J., Delpech V. A new method for assigning country of infection for people born abroad: a population based approach. Health Protection Agency Scientific Conference, Warwick, UK, 2011

2. Rice, B.D., Smith R., Elford J., Delpech V. Population-based estimates of UK-acquired HIV infections among persons born abroad and infected heterosexually. British HIV Association 17th Annual Conference, Bournemouth, UK, abstract p159, 2011.

3. Rice, B., Yin, Z., Elford, J., Kall, M., Abubakar, I., Delpech, V. Trends in the incidence of tuberculosis among heterosexuals living with HIV in England and Wales. XIX International AIDS Conference, Washington DC, USA, abstract WEPE156, 2012.

4. Rice, B., Yin, Z., Elford, J., Delpech, V. Transmission of HIV among black-African communities living in the United Kingdom: the need for improved prevention efforts. XIX International AIDS Conference, Washington DC, USA, abstract TUPE101, 2012.

5. Rice, B.D., Elford, J., Yin, Z., Abubakar, I., Kall, M., Delpech, V. Trends in the incidence of tuberculosis among heterosexuals living with HIV in England and Wales. Doctoral Student Conference, London, UK, 2013.