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

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Citation style for this article:
Aghaizu A, Murphy G, Tosswill J, DeAngelis D, Charlett A, Gill ON, Ward H, Lattimore S, Simmons RD, Delpech V. Recent infection testing algorithm (RITA) applied to new HIV diagnoses in England, Wales and Northern Ireland, 2009 to 2011. Euro Surveill. 2014;19(2):pii=20673. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20673

Article submitted on 25 July 2013 / published on 16 January 2014

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

Introduction

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

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

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

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

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

Methods

Surveillance of recently acquired HIV infections

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

The RITA classifies new diagnoses with an avidity index ‹80% as positive (a likely recent infection) unless other available clinical information, which completes the algorithm, indicates a likely long-standing infection, i.e. a CD4 count ‹200 cells/mm^3 at diagnosis, a report of an AIDS-defining illness within a year of diagnosis or history of antiretroviral treatment. A RITA-positive result is indicative of likely acquisition of infection around six months before diagnosis. In this paper, we refer to RITA-positive diagnoses as ‘recent infections’. The avidity assay results are returned to the clinician via local laboratories; at patient level, clinicians interpret the avidity results alongside other test results and in context of information in case notes.

Laboratory testing

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

Statistical analysis

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

Results

Testing coverage and representativeness

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

Recent infections among new HIV diagnoses

After reclassifying individuals whose samples had an avidity score ‹80% and a CD4 count ‹200 cells/mm^3 (n=61), diagnosis of an AIDS-defining illness (n=5) or antiretroviral treatment before or at the time the sample was taken (for example, pre- or post-exposure prophylaxis) (n=44) as having long-standing infections, the overall proportion of recent infection was 14.7% (1,022/6,966) (Figure 1). The highest proportion of recent infection was among MSM, 22.3% (720/3,223) compared with 7.8% (247/3,164) among heterosexual men and women, 5.6% (6/108) among PWID and 10.4% (49/471) among ‘other’. The proportion was slightly higher among heterosexual women (8.1%, 153/1,892) compared with heterosexual men (7.4%, 94/1,272) and the proportions were similar across the categories for all three years (data not shown).

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

Table 1

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

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

HIV: human immunodeficiency virus.

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

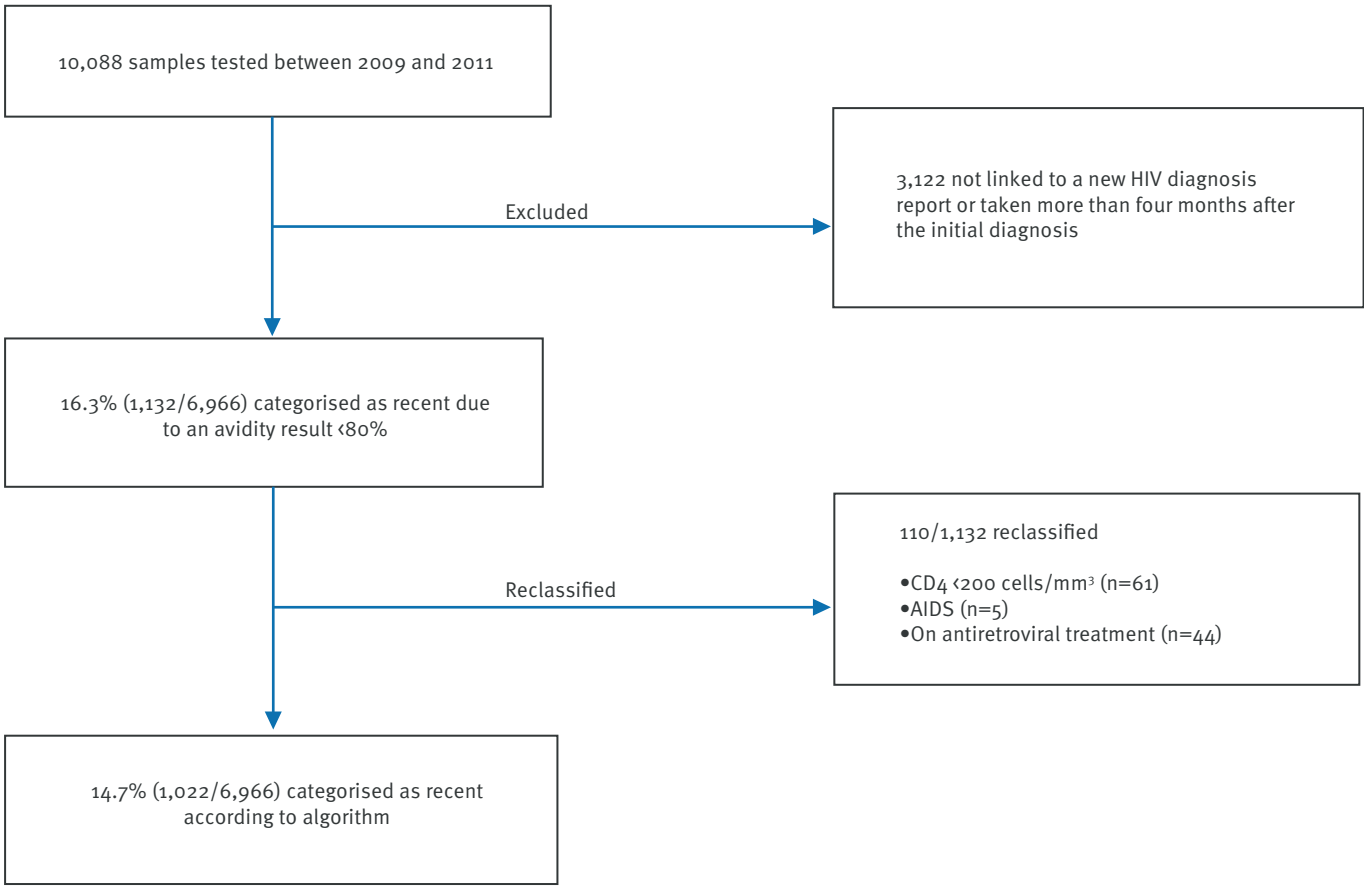
Among heterosexual men and women, the highest proportions of recent infection were among 15–24 year-old women (19.5%, 38/195) and 25–34 year-old men (6.4%, 15/234). Lower proportions were observed among persons born abroad (6.4%, 163/2,554 vs 13.8%, 84/610) and those reported to have acquired their infection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

Relationship between CD4 count and recent infection status

There was a strong association and a significant positive trend between CD4 counts >200 cells/mm^3 and recent infection classifications. Among MSM, only 11.4% (68/595) of individuals with a CD4 count between

Figure

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



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

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

Discussion

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

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

Table 2

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

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

CI: confidence interval; HIV: human immunodeficiency virus.

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

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

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

[c] CD4 data not available for all samples; the number of new diagnoses with CD4 count <200 cells/mm^3 was 4,621, of which 1,714 were tested for recent infection.

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

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

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

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

We found a positive association between recent infection and high CD4 count, both indicators of early-stage disease. Studies have shown that the mean CD4 count before seroconversion among MSM to be about 1,000 cells/mm^3, about 780 cells/mm^3 six months after infection and about 670 cells/mm^3 a year after infection, though with wide variations within and between individuals [19]. Among HIV-negative African populations, observations of median CD4 counts varied from 640 cells/mm^3 in Ethiopia [20] to 1,160 cells/mm^3 in Uganda [21,22]. Particularly among individuals with HIV infection, it is not uncommon for CD4 counts to double or halve within eight weeks of an initial count, with an average variation of 25% from the mean over this period [23]. Therefore, there is considerable uncertainty in the expected CD4 counts within the first six months or year of infection, which may explain why the proportion of likely recent infection is not higher among those with CD4 counts similar to persons who are HIV negative.

It is known that CD4 counts can drop during seroconversion [24]; if below 200 cells/mm^3, according to the algorithm used in this study, individuals would be reclassified as having a long-standing infection (n=61), potentially slightly underestimating the proportion of recent infection.

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

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

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

Acknowledgments

We gratefully acknowledge the continuing collaboration of clinicians, microbiologists, immunologists, public health practitioners, occupational health doctors and nurses and other colleagues who contribute to the surveillance of HIV and STIs in the UK, the HIV Incidence Advisory Group and Grace Mensah and Josephine Morris for performing the laboratory testing.

Conflict of interest

None declared.

Authors' contributions

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

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