Trends in undiagnosed HIV-1 infection among attenders at genitourinary medicine clinics, England, Wales, and Northern Ireland: 1990–6

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Objective: To describe trends in seroprevalence of undiagnosed HIV-1 infection among attenders at 15 genitourinary medicine clinics in England, Wales, and Northern Ireland between 1990 and 1996.

Method: Prospective, cross sectional sentinel serosurvey. Unlinked anonymous testing of remnant serum drawn for routine syphilis screening.

Results: In 1996, the seroprevalence of undiagnosed HIV-1 infection was 5% in homosexual men, 0.48% in heterosexual men, and 0.33% in heterosexual women. Between 1990 and 1996, there was a significant linear decrease in the seroprevalence of undiagnosed HIV-1 infection among homosexual and bisexual men within and outside London ($p<0.0001$; $p=0.0141$), equivalent to yearly decreases of 7.65% and 10.73% respectively. However, seroprevalence among homosexual and bisexual men under 25 years of age did not decline either inside or outside London. Seroprevalence among heterosexual men declined outside London ($p<0.005$), equivalent to an average annual decrease of 14.54%. There was a significant increase among male heterosexuals inside London ($p<0.05$) equivalent to a 8.09% increase per annum. Seroprevalence over time was unchanging among female heterosexuals both inside and outside London. Seroprevalence was significantly higher among those who injected drugs than those who did not report injecting in the following groups: homosexual and bisexual males within London ($p<0.005$), male heterosexuals both within and outside London ($p<0.05$; $p<0.05$) and female heterosexuals within London ($p<0.05$).

Conclusions: The study highlights a significant burden of undiagnosed HIV-1 infection more than 15 years since the HIV epidemic began. Methods of offering HIV testing need to be reassessed to extend the practice of routinely testing for HIV in GUM clinics. HIV transmission among young homosexual and bisexual men continues. The contrasting trends between homosexual and bisexual men, injecting drug users, and heterosexuals attending GUM clinics indicate these groups should be considered separately. The substantial HIV seroprevalence in each group indicates that they should be priorities for targeted HIV prevention.

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Introduction

In England, Wales, and Northern Ireland, 83% (23 660 of the 28 361) of HIV cases reported up to the end of 1997 were attributed to sexual transmission.[1] Consequently, UK health campaigns have focused on safer sex as the key to HIV prevention.[2] The seroprevalence of HIV-1 infection among heterosexual women attending genitourinary medicine (GUM) services is four times that seen among pregnant women.[3] This, together with the increasing burden of sexually transmitted infections (STIs) seen in GUM clinics, indicate that many attenders remain behaviourally vulnerable to HIV infection.[4–6] Attenders at GUM clinics are thus a prime sentinel group for monitoring HIV.

The survey of HIV seroprevalence among GUM clinic attenders, set up in 1990 as part of the unlinked anonymous prevalence monitoring programme,[7] uses an unlinked anonymous methodology to minimise participation bias and records previously diagnosed infections. The seroprevalence of undiagnosed HIV-1 infection can thus be estimated. This analysis was confined to undiagnosed HIV-1 infection

for a number of reasons. Quality control studies and preliminary analyses indicated that diagnosed HIV-1 infection was increasingly managed in specialist HIV care outside routine GUM services during the course of the study. Consequently there was a marked decrease in the seroprevalence of diagnosed HIV-1 infection. This bias prevents comparison of the seroprevalence of diagnosed and undiagnosed HIV-1 infection and thus the study was confined to undiagnosed HIV-1 infection which was unaffected by this source of bias.

Previous analyses of this dataset have shown that undiagnosed HIV-1 infection accounts for a substantial proportion of HIV-1 infections seen in GUM clinics and that patients with undiagnosed HIV-1 infection are more likely to have a newly acquired STI that those with diagnosed HIV-1 infection.[8] HIV infection in people unaware of their HIV positive serostatus is thus an important public health problem, as they are unable to benefit from recent advances in HIV care, and may be the source of ongoing transmission.[8] The analysis of undiagnosed infection among GUM clinic attenders repre-

Table 1   Seroprevalence of HIV-1 infection among homosexual and bisexual men

	London			Outside London		
	% HIV-1 infected (total)	Adjusted OR* (95% CI)	p Value	% HIV-1 infected (total)	Adjusted OR* (95% CI)	p Value
Age group			<0.0001			0.1239
<20	4.95 (364)	0.82 (0.50–1.36)		0.92 (435)	0.44 (0.16–1.25)	
20 to 24	5.83 (3226)	1.00		2.16 (1624)	1.00	
25 to 34	9.06 (10 504)	1.71 (1.45–2.01)		2.70 (3038)	1.27 (0.85–1.90)	
35 to 44	9.06 (4061)	1.77 (1.47–2.12)		2.78 (1373)	1.30 (0.81–2.07)	
45+	6.99 (1802)	1.35 (1.07–1.71)		2.19 (866)	1.02 (0.58–1.80)	
IDU						
Yes	13.05 (452)	1.65 (1.24–2.19)	0.0019	1.79 (112)	0.68 (0.17–2.77)	0.6713
No	8.12 (18 314)	1.00		2.42 (7060)	1.00	
NA/NR†	8.82 (1191)	1.17 (0.94–1.45)		3.05 (164)	1.39 (0.56–3.47)	
Year						
1990–1	9.90 (475)	1.00	0.0004	4.30 (93)	1.00	0.1462
1990–2	12.24 (915)	1.05 (0.73–1.52)		2.88 (278)	0.62 (0.18–2.13)	
1991–1	10.07 (1420)	0.85 (0.60–1.21)		2.88 (312)	0.56 (0.16–1.89)	
1991–2	9.69 (1104)	0.87 (0.61–1.26)		4.38 (274)	0.83 (0.26–2.71)	
1992–1	10.49 (915)	0.93 (0.64–1.35)		1.25 (401)	0.20 (0.05–0.80)	
1992–2	9.70 (1381)	0.83 (0.58–1.18)		2.94 (544)	0.49 (0.15–1.57)	
1993–1	9.84 (1138)	0.84 (0.58–1.21)		2.30 (740)	0.41 (0.13–1.30)	
1993–2	8.31 (1071)	0.71 (0.49–1.03)		3.57 (729)	0.62 (0.20–1.93)	
1994–1	8.33 (1212)	0.74 (0.51–1.07)		1.93 (624)	0.35 (0.10–1.16)	
1994–2	8.31 (1806)	0.79 (0.56–1.12)		2.20 (682)	0.39 (0.12–1.27)	
1995–1	6.83 (2256)	0.66 (0.47–0.93)		2.58 (638)	0.45 (0.14–1.43)	
1995–2	6.80 (2237)	0.67 (0.47–0.94)		1.44 (619)	0.33 (0.10–1.10)	
1996–1	6.52 (2332)	0.63 (0.44–0.89)		1.85 (703)	0.30 (0.09–1.01)	
1996–2	6.08 (1695)	0.58 (0.40–0.83)		1.77 (679)	0.31 (0.09–1.01)	

*Adjusted for age, IDU, time (as a factor), and centre.
†Not asked or not recorded.

sents a measure of the underlying prevalence of HIV infection. The prevalence of HIV infection in people under 25 years of age approximates to recent transmission of infection.[9] The aim of this analysis was thus to investigate differences and trends in undiagnosed HIV-1 infection by exposure category using data collected between 1990 and 1996.

Patients and methods
Between 1990 and 1994, 15 clinics were recruited, seven in London and eight outside London[10]; the data management and laboratory methods have been described previously.[3 7 10] For each attender, the first specimen tested for syphilis serology within each calendar quarter was eligible for inclusion. Data items collected included the following: sexual orientation, age group (<20, 20–24, 25–34, 35–44, and 45 and over), known to be infected with HIV before the clinic visit, injecting drug use (IDU), HIV-1 test result from residual specimen, clinic, and quarter and year of attendance. Cases with diagnosed HIV-1 infection (that is, those known to be HIV infected before attendance) were removed from the analysis. The data were stratified by exposure category (homosexual and bisexual male, heterosexual male, and heterosexual female). Data were analysed and presented according to whether clinics were inside or outside London.[10] The data were aggregated to 6 month periods. A separate analysis was undertaken for those under 25 years of age.

The three exposure categories were analysed separately using a logistic regression model in GLIM4.[11] All two way interactions between the independent variables were investigated and the smallest adequate model fitted. The baselines for odds ratio calculation were: age 20–24, not known to be an IDU, and the first half of 1990. Trends in prevalence over time were investigated by fitting suitable polynomials to a model that included time as a variable. Where overdispersion was found, rescaling was used in the subsequent analyses.

Results
A total of 315 477 attenders were included in the analysis, 2805 of these were found to have undiagnosed HIV-1 infection. Only 1795 (0.6%) of attenders objected to the study. These were evenly distributed among the exposure categories, were unlikely to have biased the results, and were excluded from the analysis.[12] Seroprevalence of undiagnosed HIV-1 infection by exposure category with adjusted odds ratios (OR) (adjusted by age, IDU, time, and centre) together with 95% confidence intervals (CIs) are shown in tables 1, 2, and 3. In 1996, the seroprevalence of undiagnosed HIV-1 infection was 5% in homosexual men. 0.48% in heterosexual men, and 0.33% in heterosexual women.

ASSOCIATION WITH AGE GROUP
After adjustment for other factors, significant differences in HIV-1 seroprevalence by age group were seen in all exposure categories. For homosexual and bisexual males within London, seroprevalence of undiagnosed infection was significantly higher than the baseline (the 20–24 year age group) in those aged 25 and over (p<0.0001). Outside London no difference was seen between age groups. For heterosexual men, there were significant differences in HIV-1 seroprevalence by age group both within and outside London (p<0.0001; p<0.001), highest seroprevalence being seen in those aged 25 or more. For heterosexual women, the seroprevalence inside London was significantly lower in the under 20 age group (p<0.0001), whereas outside London it was significantly higher in the 25–34 year age group (p<0.0001).

Table 2   Seroprevalence of HIV-1 infection among heterosexual men

	London			Outside London		
	% HIV-1 infected (total)	Adjusted OR* (95% CI)	p Value	% HIV-1 infected (total)	Adjusted OR* (95% CI)	p Value
Age group						
<20	0.23 (2196)	0.52 (0.21–1.30)	<0.0001	0.08 (6483)	1.26 (0.46–3.46)	0.0001
20 to 24	0.46 (10 005)	1.00		0.06 (24 711)	1.00	
25 to 34	0.96 (24 882)	2.08 (1.51–2.85)		0.18 (37 247)	2.97 (1.70–5.20)	
35 to 44	1.30 (8667)	2.08 (2.04–4.07)		0.18 (14 316)	3.09 (1.63–5.83)	
45+	0.80 (4265)	1.78 (1.14–2.77)		0.17 (6443)	3.06 (1.45–6.43)	
IDU						
Yes	2.01 (944)	1.92 (1.20–3.06)	0.0451	0.52 (953)	3.86 (1.56–9.53)	0.0396
No	0.85 (44 400)	1.00		0.14 (87 582)	1.00	
NA–NR†	0.88 (4671)	1.05 (0.73–1.51)		0.06 (1665)	0.54 (0.08–3.62)	
Year						
1990–1	0.79 (632)	1.00	0.0123	0.25 (1612)	1.00	0.2540
1990–2	0.72 (1249)	0.76 (0.25–2.29)		0.29 (3841)	0.98 (0.31–3.11)	
1991–1	0.81 (1599)	0.84 (0.30–2.38)		0.18 (3804)	0.61 (0.17–2.12)	
1991–2	1.23 (1377)	1.36 (0.50–3.72)		0.16 (3723)	0.51 (0.14–1.83)	
1992–1	0.72 (1112)	0.80 (0.26–2.45)		0.18 (5105)	0.62 (0.19–2.08)	
1992–2	0.46 (1971)	0.51 (0.17–1.52)		0.17 (7085)	0.52 (0.16–1.68)	
1993–1	0.70 (2413)	0.90 (0.33–2.48)		0.10 (8789)	0.29 (0.08–0.98)	
1993–2	1.15 (3305)	1.47 (0.57–3.78)		0.11 (7909)	0.30 (0.09–1.04)	
1994–1	1.16 (4121)	1.54 (0.60–3.92)		0.13 (7181)	0.33 (0.10–1.15)	
1994–2	0.95 (5781)	1.40 (0.55–3.57)		0.15 (7833)	0.41 (0.12–1.35)	
1995–1	0.77 (6499)	1.16 (0.46–2.96)		0.08 (7463)	0.23 (0.06–0.84)	
1995–2	0.65 (6820)	0.99 (0.39–2.54)		0.13 (8618)	0.34 (0.10–1.14)	
1996–1	0.90 (6913)	1.35 (0.53–3.40)		0.10 (8981)	0.27 (0.08–0.92)	
1996–2	1.01 (6223)	1.56 (0.62–3.94)		0.13 (8252)	0.36 (0.11–1.18)	

*Adjusted for age, IDU, time (as a factor), and centre.
†Not asked or not recorded.

ASSOCIATION WITH INJECTING DRUG USE

A comparison was made between those known to have injected drugs and those who did not report injecting (baseline). Seroprevalence was significantly higher than the baseline among those who injected in the following exposure categories: homosexual and bisexual males within London (p<0.005), male heterosexuals both within and outside London (p<0.05; p<0.05), and female heterosexuals within London (p<0.05).

TRENDS IN SEROPREVALENCE OF UNDIAGNOSED INFECTION, 1990–6

For homosexual and bisexual men, there was a significant linear decrease over time in undiag-nosed HIV-1 infection both inside and outside London (p<0.001; p<0.05), equivalent to yearly decreases of 7.65% (95%CL 5.09% to 10.14%) and 10.73% (95% CL 2.21% to 18.51%) respectively. There was also a signifi-cant linear decrease among male heterosexuals outside London (p<0.005), equivalent to an annual decrease of 14.54% (95% CL 4.85% to 23.25%). However, inside London, there was a significant linear increase in HIV-1 seropreva-lence among male heterosexuals (p<0.05), equivalent to an 8.09% (95% CL 1.63% to 14.96%) increase per annum. No trend in HIV-1 seroprevalence was seen for female het-erosexuals within or outside London.

Table 3   Seroprevalence of HIV-1 infection among heterosexual women

	London			Outside London		
Factor	% HIV-1 infected (total)	Adjusted OR* (95% CI)	p Value	% HIV-1 infected (total)	Adjusted OR* (95% CI)	p Value
Age group						
<20	0.22 (6040)	0.44 (0.24–0.78)		0.01 (13 329)	0.14 (0.02–1.01)	
20 to 24	0.46 (19 856)	1.00	<0.0001	0.05 (24 945)	1.00	<0.0001
25 to 34	0.61 (32 555)	1.31 (1.01–1.68)		0.14 (26 880)	2.79 (1.48–5.24)	
35 to 44	0.46 (8784)	0.96 (0.66–1.40)		0.10 (9160)	1.92 (0.82–4.49)	
45+	0.21 (2803)	0.45 (0.20–1.02)		0.11 (3617)	2.21 (0.72–6.77)	
IDU						
Yes	1.39 (717)	2.77 (1.47–5.22)		0.28 (354)	3.43 (0.48–24.65)	
No	0.48 (63 438)	1.00	0.0243	0.08 (751 265)	1.00	0.5670
NA/NR†	0.58 (5883)	1.08 (0.73–1.60)		0.08 (2451)	1.29 (0.30–5.49)	
Year						
1990–1	0.48 (421)	1.00	0.9274	0.31 (329)	1.00	0.0971
1990–2	0.41 (2193)	0.72 (0.15–3.34)		0.05 (2099)	0.08 (0.00–1.44)	
1991–1	0.50 (2408)	0.86 (0.19–3.84)		0.16 (3113)	0.30 (0.03–2.75)	
1991–2	0.41 (2172)	0.81 (0.17–3.76)		0.20 (3021)	0.34 (0.04–3.03)	
1992–1	0.59 (2019)	1.13 (0.25–5.07)		0.02 (4320)	0.05 (0.00–0.86)	
1992–2	0.43 (3012)	0.73 (0.16–3.25)		0.13 (5940)	0.28 (0.03–2.51)	
1993–1	0.58 (3789)	0.90 (0.21–3.86)		0.11 (7459)	0.21 (0.02–1.86)	
1993–2	0.32 (4337)	0.56 (0.12–2.45)		0.07 (7131)	0.13 (0.01–1.24)	
1994–1	0.51 (5337)	0.79 (0.18–3.34)		0.05 (6446)	0.09 (0.01–0.93)	
1994–2	0.45 (7857)	0.73 (0.17–3.07)		0.03 (7033)	0.05 (0.00–0.63)	
1995–1	0.47 (8875)	0.81 (0.19–3.39)		0.13 (6925)	0.25 (0.03–2.24)	
1995–2	0.50 (9453)	0.83 (0.20–3.47)		0.05 (7935)	0.09 (0.01–0.95)	
1996–1	0.59 (9558)	0.97 (0.23–4.05)		0.06 (8477)	0.11 (0.01–1.08)	
1996–2	0.53 (8607)	0.87 (0.21–3.65)		0.10 (7703)	0.17 (0.02–1.58)	

*Adjusted for age, IDU, time (as a factor), and centre.
†Not asked or not recorded.

Table 4   Seroprevalence of HIV-1 infection among homosexual and bisexual men aged 25 or less

	London			Outside London		
	% HIV-1 infected (total)	Adjusted OR* (95% CI)	p Value	% HIV-1 infected (total)	Adjusted OR* (95% CI)	p Value
Age group						
<20	4.95 (364)	0.80 (0.48–1.32)	0.3698	0.92 (435)	0.43 (0.15–1.23)	0.0822
20 to 24	5.83 (3226)	1.00		2.16 (1624)	1.00	
IDU						
Yes	12.26 (106)	2.13 (1.15–3.94)	0.0645	0.00 (40)	0.00‡	0.2527
No	5.44 (3293)	1.00		1.88 (1967)	1.00	
NA/NR†	7.33 (191)	1.29 (0.72–2.32)		3.85 (52)	2.10 (0.46–9.67)	
Year						
1990–1	4.17 (96)	1.00	0.1117	8.33 (24)	1.00	0.5461
1990–2	10.92 (238)	2.15 (0.72–6.45)		3.37 (89)	0.49 (0.07–3.32)	
1991–1	6.48 (293)	1.30 (0.42–3.96)		2.13 (94)	0.29 (0.04–2.33)	
1991–2	8.21 (207)	1.79 (0.58–5.50)		5.32 (94)	0.66 (0.11–4.06)	
1992–1	10.00 (150)	2.22 (0.71–6.95)		0.77 (130)	0.09 (0.01–1.08)	
1992–2	7.90 (291)	1.59 (0.53–4.79)		1.27 (157)	0.17 (0.02–1.42)	
1993–1	5.16 (194)	1.04 (0.31–3.45)		0.47 (214)	0.07 (0.01–0.84)	
1993–2	4.86 (185)	0.97 (0.29–3.30)		2.07 (193)	0.29 (0.04–2.02)	
1994–1	5.50 (182)	1.15 (0.35–3.81)		1.56 (192)	0.24 (0.03–1.77)	
1994–2	4.06 (345)	0.89 (0.28–2.81)		1.65 (182)	0.24 (0.03–1.72)	
1995–1	4.33 (416)	0.97 (0.32–2.99)		1.68 (179)	0.24 (0.03–1.74)	
1995–2	3.34 (359)	0.74 (0.23–2.39)		1.97 (152)	0.28 (0.04–2.09)	
1996–1	4.66 (386)	1.12 (0.36–3.45)		2.54 (197)	0.32 (0.05–2.08)	
1996–2	4.44 (248)	0.95 (0.29–3.11)		1.23 (162)	0.15 (0.02–1.27)	

*Adjusted for age, IDU, time (as a factor), and centre.
†Not asked or not recorded.
‡Adjusted OR estimate very low with confidence interval ($-\infty$, $+\infty$) as no IDU was HIV positive.

HOMOSEXUAL AND BISEXUAL MEN AGED UNDER 25 YEARS

There was no difference in prevalence between the under 20 and the 20–24 year olds either inside London (4.95% and 5.83% respectively) or outside London (0.93% and 2.16% respectively) and, over the 7 year period, there was no trend in seroprevalence either inside or outside London (table 4). Although seroprevalence of undiagnosed HIV-1 infection was twice as high in those who injected drugs, this difference was not significant (p=0.06).

Discussion

Undiagnosed HIV-1 infection is important both to public health and to the surveillance of HIV. Identifying undiagnosed infections enables individuals to benefit from advances in treatment and care, and reduces the risk of transmission to HIV negative partners. However, it has been suggested that detection of HIV infection in UK clinics may be lower than in some other European countries.[13] This analysis provides evidence that many infections remain undiagnosed after individuals have attended a GUM clinic. This is disturbing and supports the view that voluntary confidential testing should be strengthened in GUM clinics to increase the chance of early diagnosis.[14]

Over the period studied there was no indication of infection spreading beyond known risk groups. The contrast between London and other areas in terms of detected prevalence also indicates that infection has not diffused beyond the London area since the early 1990s. The HIV epidemic is focused on homosexual and bisexual men, the highest seroprevalences of undiagnosed HIV-1 infection were seen in this exposure category. The substantial burden of undiagnosed HIV-1 infection indicates that homosexual and bisexual men continue to place themselves at risk of HIV-1 infection despite public health campaigns, an observation which has been made in behavioural and

seroprevalence studies both in the United Kingdom and elsewhere.[15–17] The acquisition of STIs by homosexual and bisexual men who are aware of their HIV infection, indicates that knowledge of HIV infection status does not eliminate behaviour associated with continuing risk of HIV transmission.[7 10 16–18]

The seroprevalence of undiagnosed HIV-1 infection could have been influenced by variations in study selection procedure but no evidence was found in any of the survey's audit studies. Similarly, the seroprevalence of both diagnosed and undiagnosed HIV-1 infection could have been influenced by variations in testing practice but this is unlikely to have occurred as no changes were made to national testing policy during the period included in this analysis.

The reduction in seroprevalence of undiagnosed HIV-1 infection in homosexual and bisexual men needs to be carefully interpreted. Declines have been seen in other countries but, as most studies do not record diagnostic status, these observations could be accounted for by variations in diagnosis and care.[16 17 19] Since this study is based on undiagnosed infection, variations in case management (that is, the opening of specialist services attached to clinics taking part in the study) cannot account for the fall. Nor can it be explained by increasing diagnoses as the proportion of recognised infections has not changed in recent years.[10] This study shows continuing transmission and incidence, indicated by the consistent, substantial seroprevalence of undiagnosed HIV-1 infection among homosexual and bisexual men under 25 years of age and data from voluntary confidential HIV-1 testing and incidence studies.[20] Younger men are thought to have unsafe sex because they are less experienced in personal and/or sexual negotiation.[16 18 21] Clearly, HIV prevention needs to target this group. Variations in transmission in older age groups remains unclear but the use of tests to distinguish

recently acquired infection may be able to provide more information in this area.[14]

Although seroprevalence of undiagnosed HIV-1 among heterosexuals was lower than homosexual and bisexual males, the significant increase among heterosexual males inside London and the stable seroprevalence among females is of particular concern. Sex between men and women accounted for 16% of AIDS cases and 20% of diagnosed HIV-1 infections to the end of 1997,[1] but heterosexual transmission is considered uncommon in England and Wales. Sixty five per cent of AIDS case reports probably acquired through sexual intercourse between men and women have been associated with exposure in Africa, the majority were reported from London.[1] Country of birth data would allow a more comprehensive analysis of the heterosexual data but is only available for two of the seven years of the study and consequently was not included in this analysis. However, analysis of the available country of birth data indicates there was no difference in the proportion of undiagnosed HIV-1 infection by world region of birth for homosexual and bisexual men or heterosexual men or heterosexual women.[22]

This study highlights the continuing problem of undiagnosed HIV-1 infection among attenders at GUM clinics, a problem which has also been recognised in pregnant women.[23] Methods of offering HIV testing need to be reassessed if awareness to the benefits of HIV testing is be improved.

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