Increase in diagnosed newly acquired hepatitis C in HIV-positive men who have sex with men across London and Brighton, 2002–2006: is this an outbreak?

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ABSTRACT

Objectives: To determine the incidence of diagnosed newly acquired hepatitis C virus (HCV) in HIV-positive men who have sex with men (MSM) across London and Brighton in order to inform public health interventions.

Methods: Cases were defined as MSM attending London and Brighton HIV/genitourinary medicine clinics from January 2002 to June 2006, with HCV PCR RNA or antibody positive, and a negative HCV test in the previous three years. The yearly number of cases and HCV screening policy in MSM were examined. A negative binomial regression model was used to estimate HCV incidence density rate ratio and 95% CI.

Results: 20 out of 38 clinics provided information, covering 84% of the HIV-positive MSM workload in London and 100% in Brighton. The estimated overall incidence was 9.05 per 1000 HIV-positive MSM patient-years. It increased from 6.86 per 1000 in 2002 to 11.58 per 1000 during January–June 2006. Incidence at clinics ranged from 0 to 15.4 (median 6.52) per 1000 HIV-positive MSM patient-years. There was some evidence of difference in the incidence and trend ($p = 0.02$) in each clinic. The average annual rise in incidence of HCV was 20% (95% CI 4% to 39%, $p = 0.001$). There was little evidence of such transmission among MSM with negative or unknown HIV status.

Conclusions: HCV incidence clearly increased among HIV-positive MSM in London and Brighton during January 2002 to June 2006. Prospective enhanced surveillance of HCV in MSM, including HIV status and behavioural risk factors, is recommended to help inform control measures and better determine the frequency of transmission in all MSM.

Recent reports from genitourinary medicine (GUM) clinics in the south east of England suggested a sudden rise in hepatitis C virus (HCV) in HIV-positive men who have sex with men (MSM).[1–4] HCV infection, which may lead to symptomatic chronic liver disease after many years of asymptomatic infection, has been identified as a major public health issue in the United Kingdom.[5] Treatment for chronic infection is available. The efficacy for most genotypes remains low, however, with specific problems in HIV-positive individuals.[6–8] The main risk factor in the United Kingdom is injecting drug use.[9 10] Historically, using data from heterosexual HCV discordant couples, the risk of sexual transmission was considered to be low. Recent clinic reports of acute HCV in HIV-positive MSM in the south east of England were mirrored in other European countries where sexual transmission was being postulated as the primary mode of HCV transmission, in contrast to conventional routes.[11–13]

In the United Kingdom there are several shortcomings in the current national surveillance systems for HCV.[14–15] Risk factors are poorly recorded (less than a third of the laboratory reports contain this information) and reports are often incomplete, particularly in London.[16] The prevalence of HIV/HCV co-infection in MSM was estimated at the clinic level[17] but little is known about the burden of disease at a wider level and about the incidence of HCV infection. The nature and scale of the observed rise, and whether it was London-wide or extended to Brighton where there is a large MSM community, was therefore unclear.

The aim of this investigation was to determine the extent and trends in the incidence of diagnosed newly acquired hepatitis C in MSM in London and Brighton in order to inform public health interventions.

METHODS

Diagnosed newly acquired hepatitis C was defined as HCV RNA positive on PCR or HCV antibody positive and a documented HCV-negative test in the previous three years. A list of all HIV and GUM clinics in the London region and Brighton area (East Sussex) was drawn up. It comprised 35 London clinics and three major East Sussex clinics (ie Brighton, Eastbourne and Hastings).

A questionnaire was sent to leading consultants at each clinic. In HIV-positive MSM, questions were posed about the numbers of new cases of HCV diagnosed each year between January 2002 and June 2006, liver function tests (LFT) and HCV screening policies (ie frequency of screening and targeted patients). In MSM with negative or unknown HIV status, questions included the number of new cases diagnosed each year between January 2002 and June 2006, and HCV screening policy.

Estimates of denominators

Yearly denominators of HIV-positive MSM patients at each clinic were derived from the Health Protection Agency (HPA) Centre for Infections Survey of Prevalent HIV Infections

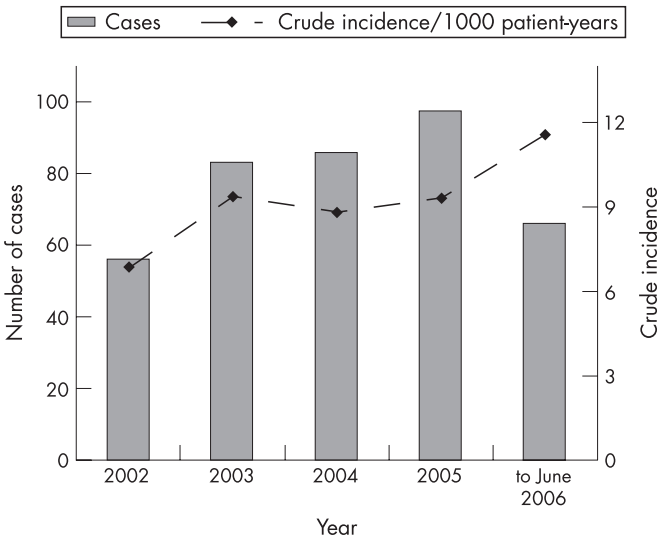

Figure 1 Number of cases and estimated incidence of diagnosed newly acquired hepatitis C in HIV-positive men who have sex with men per 1000 patient-years, reported by London and Brighton HIV/genitourinary medicine clinics January 2002–June 2006.

Diagnosed (SOPHID) data [18] from 2002 to 2005. Denominators for the first half of 2006 were derived for each clinic from the 2005 data multiplied by the estimated percentage change between 2004 and 2005 (+7% on average).

Statistical analysis

Initially a Poisson regression analysis was performed to assess whether there was an "apparent increase" in cases over the time period, controlling for the effect of take-up of routine HCV screening, and whether the incidence differed between London clinics. This model did not fit the data, as there was more variation than would be expected if it had arisen from a Poisson process. To allow for the extra Poisson variance, a negative binomial regression model was used. Any evidence of non-linearity was assessed using the likelihood ratio test. To compare incidence between clinics, Chelsea & Westminster was chosen as the reference because it saw the most patients over the years. The natural logarithm of the number of MSM HIV-positive patient-years in each clinic in each year was used as an offset in the regression model to normalise the results for differences in the patient-years "at risk".

It was difficult to assess the effect of routine HCV screening as it is intrinsically associated with the year and there was a clear temporal trend of HCV incidence. The effect of routine screening was explored by comparing each year separately for the incidence across clinics performing and not performing routine HCV screening. As there was no evidence of a difference, routine screening was not considered as a covariate in the regression model.

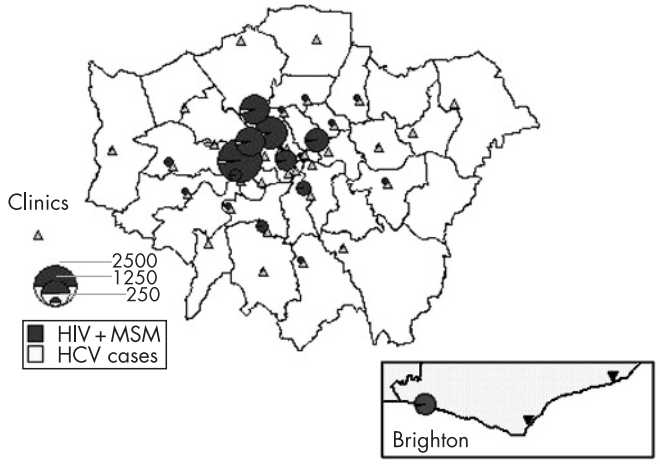

Figure 2 HIV/genitourinary medicine clinics, caseload of HIV-positive men who have sex with men (MSM) patients (SOPHID 2004 data) and reported diagnosed newly acquired hepatitis C virus (HCV) cases as a proportion of the total. London and Brighton, January 2002–June 2006.

RESULTS

Response rate

Twenty centres out of 38 returned the questionnaire, including 17 in London and three in East Sussex. The majority (17 out of 20) provided both HIV and GUM services; two were exclusively HIV clinics (at North Middlesex Hospital and the Ian Charleston Centre at the Royal Free Hospital) and one was exclusively a GUM clinic, seeing no HIV patients (Marlborough Clinic at the Royal Free Hospital). Seventeen of the 19 HIV clinics reported the number of newly acquired HCV cases seen in HIV-positive MSM during the survey time period. Based on SOPHID data these clinics cared for 84% of the total number of HIV-positive MSM attending London HIV clinics and 100% of HIV-positive MSM attending the Brighton HIV Clinic in 2005. Thirteen of the 18 GUM clinics reported the number of diagnosed newly acquired HCV cases seen in MSM who were HIV negative or of unknown HIV status.

Screening

By 2006, routine HCV screening was carried out in HIV-positive MSM patients in all 19 responding HIV clinics, increasing from five before 2000, to nine before 2003 and 16 before 2005. The majority (13 of the 19 responders) repeated HCV screening annually, two more often and four less often. Regarding HCV screening in MSM with unknown or negative HIV status, 16 clinics responded, of which five routinely screened for HCV and two of those started in 2006.

LFT in HIV-positive MSM were carried out on a quarterly basis in 17 of the 19 HIV clinics responding, and less often (four to six-monthly) in the other two clinics. One clinic reported performing LFT less than once a quarter for HIV-positive MSM patients not on highly active antiretroviral therapy. Of the 15 clinics that specified which HIV-positive MSM patients had routine LFT, 14 clinics responded that testing was carried out on all HIV-positive MSM patients, whereas one clinic reported testing only patients on highly active antiretroviral therapy. Of the nine clinics that provided information on the date of introduction of routine LFT testing, all nine did so before 2002.

Cases among HIV-positive MSM

Clinics reported a total of 389 diagnosed newly acquired HCV cases among HIV-positive MSM, including 352 in London and 37 in Brighton. Reports increased from 56 cases in 2002, to 86 in 2004 and 66 in the first six months of 2006 (fig 1).

Estimated incidence rate of diagnosed newly acquired HCV infection in HIV-positive MSM

For London and Brighton, 389 diagnosed newly acquired HCV cases arose from a total of 42 985 HIV-positive MSM patient-

Table 1 Reports of diagnosed newly acquired hepatitis C virus infections and estimated incidence per 1000 patient-years among HIV-positive men who have sex with men, by HIV/genitourinary medicine clinic in London and Brighton, January 2002–June 2006

HIV clinics	Total diagnosed newly acquired HCV infections in HIV-positive MSM	Total patient-years	Incidence rate per 1000 patient-years
Royal Sussex County Hospital Brighton	37	3453	10.72
Eastbourne	0	158	0.00
Hastings	0	68	0.00
Beckenham Hospital	1	143	6.99
Central Middlesex Hospital	1	158	6.33
Charing Cross Hospital	6	1406	4.27
Chelsea & Westminster Hospital*	70	12 112	5.78
Mortimer Market Centre (UCH)	78	7139	10.93
North Middlesex Hospital	1	449	2.23
Royal Free Hospital HIV Clinic	73	5429	13.45
Royal London Hospital	33	2144	15.39
St George's Hospital	4	1074	3.72
St Mary's Hospital	53	5457	9.71
Guys and St Thomas'	30	3115	9.63
West Middlesex Hospital	2	298	6.71
Queen Elizabeth Woolwich Hospital	0	382	0.00
Total	389	42 985	9.05

HCV, Hepatitis C virus; MSM, men who have sex with men; UCH, University College Hospital.
*Joint two clinics.

years, an overall incidence of 9.05 HCV cases per 1000 patient-years. Incidence increased from 6.86 per 1000 patient-years in 2002 to 11.58 per 1000 patient-years during January–June 2006. The highest incidences were mainly in central London and large HIV clinics, as well as in Brighton. The estimated incidence across the clinics ranged from 0 to 15.39, the median being 6.52 per 1000 HIV-positive MSM patient-years (table 1). Of the clinics that reported numbers of cases, nine reported six or fewer cases (table 1, fig 2).

Incidence rate ratio

A likelihood ratio test for non-linearity of the time trend was not significant, chi square test statistic 0.27 (3 degrees of freedom, $p = 0.96$), thus a linear time trend was assumed. The estimate of the annual increase in incidence of HCV in HIV-positive MSM was 20% each year (95% confidence interval 4% to 39%, $p = 0.01$). The incidence at the Royal Free and Royal London during 2002 to 2006 was more than twice that of the reference clinic (Chelsea & Westminster; table 2).

There was some evidence that the incidence of HCV differed between clinics ($p = 0.02$). In addition, when clinics with two or fewer cases were excluded because small numbers made the estimated trends uncertain, there was strong evidence that the temporal trend of HCV incidence did differ between clinics (chi square test statistic 36.3 on 8 degrees of freedom, $p<0.0001$). There was no difference in incidence between clinics with and without routine screening when each year was analysed separately. Also, the clinics with the greatest estimated annual

Table 2 Estimated incidence rate ratio of diagnosed newly acquired hepatitis C virus infection in HIV-positive men who have sex with men patients by HIV/genitourinary medicine clinic, 95% CI and p value estimated from the negative binomial regression model, January 2002–June 2006, London and Brighton

Factor	HIV clinics	Estimated incidence rate ratio	95% CI	p Value
Clinic	Royal Sussex County Hospital Brighton	1.67	0.80 to 3.47	0.02
	Eastbourne	0	–	
	Hastings	0	–	
	Beckenham Hospital	1.13	0.14 to 8.96	
	Central Middlesex Hospital	1.02	0.13 to 8.08	
	Charing Cross Hospital	0.67	0.24 to 1.88	
	Chelsea & Westminster Hospital*	Reference		
	Mortimer Market Centre (UCH)	1.84	0.93 to 3.64	
	North Middlesex Hospital	0.36	0.05 to 2.83	
	Royal Free Hospital HIV Clinic	2.27	1.14 to 4.49	
	Royal London Hospital	2.35	1.12 to 4.92	
	St George's Hospital	0.56	0.17 to 1.83	
	St Mary's Hospital	1.52	0.75 to 3.09	
	Guys and St Thomas'	1.38	0.65 to 2.93	
	West Middlesex University Hospital	1.00	0.21 to 4.66	
	Queen Elizabeth Woolwich Hospital	0	–	
Year		1.20	1.04 to 1.39	0.01

UCH, University College Hospital.
*Joint two clinics.

increase were those that had routine screening in place throughout the study. It would thus appear that the progressive introduction of routine screening during the study period did not have an undue effect on the observed rise in incidence.

Cases with unknown or negative HIV status

Only three clinics reported cases with unknown or negative HIV status in MSM (total of six cases, including three cases at one clinic routinely screening all MSM patients for HCV).

DISCUSSION

This investigation provides evidence of ongoing and increasing diagnosed newly acquired HCV infection in HIV-positive MSM across most major clinics in the London and East Sussex regions since 2002. The documented increase does not appear to be associated with the progressive implementation of HCV screening for HIV-positive MSM.

We believe that this study provides confirmation at a regional level that HCV is circulating at high and increasing levels among HIV-positive MSM and represents a possible outbreak. This adds to the evidence from epidemiological and molecular studies describing clusters and suggesting a sustained chain of transmission in the HIV-positive MSM population at the clinic level.[2 3] We have not confirmed individual sexual or other epidemiological links between cases and further work is needed to confirm the existence of a London-wide outbreak.

Our survey was not designed to collect individual characteristics (eg timing of any HIV co-infection) and behavioural information (eg injecting or other drug use or sexual practices including number of partners and unprotected sex). There were differences in incidence and in trends in incidence between clinics, possibly related to variations in case mix, with patients presenting different behavioural risk factors, but we could not confirm the contribution of such risk factors to the caseload at any clinic or their contribution to the observed differences. The mechanism of HCV transmission among MSM is not yet fully understood, although it has been postulated that mucosal trauma during rough sexual practices (eg fisting) and group sex in conjunction with recreational drug use may facilitate transmission among HIV-positive MSM.[3 19 20] Information on risk factors should be considered in longer-term prospective enhanced surveillance.

It is possible that response bias could have led to an overestimation of the incidence as non-responders may have been more likely to have fewer cases. The clinics that did respond, however, were major centres covering the large majority of HIV-positive MSM patients under care.

We found little evidence to indicate the frequent occurrence of diagnosed newly acquired HCV in MSM with negative or unknown HIV status. There have been reports from a study in Brighton suggesting that transmission was not confined to HIV-positive MSM.[21] In that study, however, HIV-positive men were found to be approximately 13 times more likely to have a new HCV diagnosis compared with HIV-negative men. It is also possible that the specificity of our case definition itself may have led to bias. As documented evidence of a previously negative test within the past three years was required, HIV-positive MSM may have been more likely to be reported because they have had previous HCV tests. In addition, although we did not ask if the reported cases were diagnosed through LFT or not, there is a possible detection bias: HIV-positive MSM patients have routine LFT in all clinics, which may make them more likely to be diagnosed when infected with HCV. This could change should the frequency of follow-up at clinics reduce as the number of patients increases. It was noteworthy, however, that at those London clinics where HCV screening was reportedly being carried out routinely among all MSM patients (including those with unknown or negative HIV status), only three cases were reported.

Although HIV-positive MSM attending HIV services do constitute a well-monitored cohort and may be more likely to be diagnosed if HCV infected, there are also data from community-based behavioural surveys to show that HIV-positive MSM report more high-risk sexual behaviours and recreational drug use than HIV-negative men.[22 23] Furthermore, sexually transmitted infections (STI) have been associated with more high-risk sexual behaviours in MSM and there have been recent reports of other outbreaks in HIV-positive MSM in the United Kingdom and in London, including syphilis, lymphogranuloma venereum and *Shigella sonnei* outbreaks [24–27]. This suggests a considerable and increasing burden of various STI among HIV-positive MSM, highlighting the need for targeted primary prevention and harm minimisation initiatives.

In the era of antiretroviral therapy the number of people living with HIV is steadily increasing, including those continuing with high-risk behaviours. The number of HIV-positive MSM who are resident in London and seen for HIV-related healthcare increased by 50% from 6800 in 2000 to 10 200 in 2005.[16] Chronic HCV/HIV co-infection may compromise the response to treatment and has important implications for the prognosis and treatment of both conditions.[7 8 28–30] The ongoing transmission of HCV among HIV-positive MSM may have a significant impact for health service provision and costs in the future. The National Institute for Health and Clinical Excellence (NICE) has estimated drug treatment costs for mild chronic HCV of approximately £14 000 for 48 weeks of treatment. Little cost information is available for the treatment of co-infected patients[6] and average costs are difficult to estimate. These are likely to be much higher as a result of longer treatment cycles and greater complexity; although the lower response rate as well as potential drug interactions may also cause more patients to terminate their treatment early.

Key messages

- This study provides evidence of a 20% year on year increase in the incidence of diagnosed newly acquired HCV infection in HIV-positive MSM across major clinics in London and Brighton, from January 2002 to June 2006
- Little evidence was found on the occurrence of diagnosed newly acquired HCV infection in MSM with negative or unknown HIV status
- Enhanced surveillance of diagnosed newly acquired HCV in MSM is recommended to monitor spatial and time trends and to inform public health interventions

CONCLUSION

This survey has shown evidence of ongoing and increasing transmission of HCV infections in HIV-positive MSM across the London and East Sussex regions. Yet there are gaps in our understanding, especially regarding the relative contribution of different risk factors and the burden of disease for all MSM. Our findings endorse British HIV Association recommendations for regular HCV testing among HIV-positive patients and among those with unexplained liver transaminase elevation, especially in patients with potential risk factors (ie MSM with sexual

risks). Testing MSM of unknown or negative HIV status should also be recommended when there are specific risk factors (group sex participation, other high-risk sexual behaviours, or recreational drug use). The survey strongly supports the recent research findings on diagnosed newly acquired HCV infection in HIV-positive MSM[1 2 15] and confirms the need for better information about new HCV infections among all MSM.

An enhanced surveillance system for newly acquired HCV infection could provide useful information on the number of new cases, temporal and spatial trends, as well as risk factors, in order to refine harm minimisation strategies and the public health response.

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Contributions: IG designed the questionnaire, organised the data collection and data management, reviewed the literature and wrote the paper. MR usefully drafted discussion points, facilitated the data collection at some clinics and extensively commented on the drafts. HM led the study and supervised both MR and IG and extensively commented on drafts. JT, RG, MF and SB provided data and usefully commented on drafts. AC supervised and verified the data analysis and guided on reporting the statistical results. HM with support from FN initiated the joint HPA–BASH–BHIVA study. MJ and SB contributed to the questionnaire design and were indispensable in their support and promotion of the study with clinicians.

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Commentary

Giraudon *et al* corroborate that herpes C virus (HCV) is circulating among HIV positive men who have sex with men (MSM) in South East England.[1] Earlier reports noted evidence of acute sexually transmitted infections among HIV positive men and of HCV infection among HIV positive men in other countries.[2-4] Giraudon's study is based on reports of HCV screening (of people with a history of HCV antibody tests) by 20 of 38 genitourinary clinics in London, Brighton and elsewhere in South East England, and an estimated denominator of person years at risk derived from routine surveillance of prevalent HIV infections from these clinics.[1] The clinics reported 389 newly acquired HCV infections over 4.5 years yielding an estimated incidence of 9/1000 person years, which varied greater than threefold by clinic and may have increased over time. The hypothesis raised by Giraudon *et al* that incidence has increased requires further corroboration given that the analysis did not have data on the number of HCV antibody tests conducted in