HCV reinfection incidence and treatment outcome among HIV-positive MSM in London

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Objective: Liver disease secondary to hepatitis C virus (HCV) infection in the context of HIV infection is one of the leading non-AIDS causes of death. Sexual transmission of HCV infection among HIV-positive men who have sex with men (MSM) appears to be leading to increased reports of acute HCV infection. Reinfection after successful treatment or spontaneous clearance is reported among HIV-positive MSM but the scale of reinfection is unknown. We calculate and compare HCV reinfection rates among HIV-positive MSM after spontaneous clearance and successful medical treatment of infection.

Design: Retrospective analysis of HIV-positive MSM with sexually acquired HCV who subsequently spontaneously cleared or underwent successful HCV treatment between 2004 and 2012.

Results: Among 191 individuals infected with HCV, 44 were reinfected over 562 person-years of follow-up with an overall reinfection rate of 7.8/100py (95%CI 5.8–10.5). Eight individuals were subsequently reinfected a second time, with a rate of 15.5/100py (95% CI 7.7–31.0). Combining all reinfections, 20% resulted in spontaneous clearance and treatment SVR rates were 73% (16/22) for genotype 1/4 and 100% (2/2) for genotype 2/3.

Among 145 individuals with a documented primary infection, the reinfection rate was 8.0 per 100 person-years (95%CI 5.7–11.3) overall, 9.6/100py (95%CI 6.6–14.1) among those successfully treated and 4.2/100py (95%CI 1.7–10.0) among those who spontaneously cleared. The secondary reinfection rate was 23.2/100py (95%CI 11.6–46.4).

Conclusion: Despite efforts at reducing risk behaviour, HIV positive MSM who clear HCV infection remain at high risk of reinfection. This emphasizes the need for increased sexual education, surveillance and preventative intervention work.

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AIDS 2013, **27**:000–000

Keywords: coinfection, HCV, hepatitis C virus, HIV, human immunodeficiency virus, reinfection

INTRODUCTION

Following the introduction of effective anti–retroviral therapy (ART), liver disease has become the leading non-AIDS cause of death among HIV positive patients in the resource rich world [1]. The majority of liver disease in HIV positive patients is caused by coinfection with the hepatitis C virus (HCV) [1–3]. Coinfection with HIV

and HCV is associated with accelerated liver fibrosis, shorter time to progression to cirrhosis and hepatic decompensation when compared to those with HCV monoinfection [4−8].

Over the past decade, an epidemic of sexually transmitted HCV among HIV positive men who have sex with men (MSM) in Europe, the USA and Australia has been reported [9−17]. Phylogenetic analyses of circulating HCV strains in European countries suggest sexual transmission occurring since the mid-90 s [10,18]. The incidence of HCV infection among HIV-positive MSM is increasing with recent reports of rates as high as 2−5 per 100 person years [18−21]. Identified risk factors for transmission include ulcerating genital infections, unprotected anal intercourse and high-risk sexual activity such as toy use, group sex, fisting and recreational drug use [9,17,21−23].

Reinfection with HCV following either treatment or spontaneous clearance has been demonstrated in animal models, people who inject drugs (PWID) and, more recently, HIV positive MSM [24−27]. Among PWID, weak evidence exists to suggest that individuals who spontaneously clear HCV monoinfection are at lower risk of developing chronic reinfections. This lower risk may in part be explained by the development of partial immunity leading to a higher probability of spontaneous clearance of reinfection. However, study results are highly heterogeneous and conflicting results may in part be explained by variable testing intervals during follow up [24,28]. One retrospective study in the Netherlands revealed an alarmingly high HCV reinfection rate of 15.2 per 100 person years among HIV-positive MSM who had previously been treated for acute HCV infection [29]. No studies to date have investigated the rate of reinfection among HIV-positive MSM in the UK, and whether there are differing reinfection rates among those who spontaneously clear their infections and those who are successfully treated.

We therefore calculated and compared the HCV reinfection rate among individuals who had either been treated for acute or chronic HCV infection, or who had spontaneously cleared their HCV infection within a cohort of over 8000 HIV infected individuals attending clinic at Chelsea and Westminster Hospital in London, UK.

Methods

Study population
All HIV-positive MSM who had a positive HCV antibody result between January 2004 and April 2012 who attended the dedicated HIV clinic at Chelsea and Westminster Hospital were identified. Individuals were excluded if their primary documented mode of transmission was via contaminated blood products or injecting drug use. The following subgroups were extracted for inclusion within the study:

Successfully treated HCV infection with results indicating a sustained viral response (SVR) defined as undetectable viral replication 24 weeks following end of treatment and at least 1 subsequent HCV PCR measurement.

Spontaneously cleared HCV infection with evidence for undetectable HCV PCR for at least 24 weeks following infection and at least 1 subsequent HCV PCR measurement.

Spontaneously cleared or treated HCV infection who were subsequently reinfected with a different HCV genotype from their previous infection but within the 24-week period required to formally reach SVR.

Data Collection
All HCV PCR results subsequent to the first identified HCV infection were collected. Basic HIV infection and patient characteristics were collected from medical files including age, HIV viral load, CD4 lymphocyte subset count, anti-retroviral therapy (ART) details, HCV genotype and peak ALT levels. Behavioural data was not routinely collected at the centre and was therefore unavailable for our study.

Case definitions
HCV reinfections were defined as any newly detectable HCV PCR following SVR for treated infections or 24 weeks after spontaneous clearance. In addition, cases were defined as reinfection if patients had detectable HCV viraemia within 24 weeks of end of treatment or spontaneous clearance if there was an HCV genotype switch.

Patients were subdivided depending on whether it was possible to determine that the initial infection was their primary infection (shown by a negative HCV antibody within a year prior to positive HCV antibody detection), or that the nature of the initial infection was uncertain (no previous antibody result available or previously HCV antibody positive).

Data analysis
For those individuals who underwent HCV antiviral treatment, the commencement of follow-up was taken from the end-of-treatment date. For those who spontaneously cleared their HCV infection, start of follow-up was the midpoint between the last positive and first negative HCV PCR. The date of reinfection for all patients was taken as the midpoint between the last undetectable HCV PCR and the first positive HCV PCR.

Reinfection rates were calculated by dividing the number of reinfections by the total number of patient–years of follow-up. Kaplan-Meier survival curves were created to assess the proportion reinfected over time. Comparisons of median testing intervals, age and peak ALT levels were performed using Kruskal-Wallis rank test. Analysis of proportion of patients on ART was performed using Fisher's exact test. Equality of variances were assessed using Bartlett's test. All statistical calculations were performed using Stata 10.0.

Results

858 individuals were identified with a positive HIV and HCV antibody result. Of these, 191 HIV-positive MSM with HCV who fulfilled our inclusion criteria were identified, representing 562 patient years of follow up. Among these patients, 145 had a documented primary infection and 46 had uncertain initial infection details. The stratification of patients is summarized in Fig. 1.

Among the 145 who had either spontaneously cleared or had been successfully treated for their primary HCV infection, there were 400 person-years of follow-up with a median follow-up time of 2.1 years. The median testing intervals during follow up were 105 and 173 days among those successfully treated and those who spontaneously cleared their primary infection, respectively. The difference in testing interval was statistically significant (p < 0.0001). The median age of patients included was 41 years. Group characteristics and follow-up details are summarised in Table 1.

Of the 145 patients with documented primary infection, 32 reinfections occurred yielding a HCV reinfection rate of 8.0/100py (95% confidence interval (CI) 5.7−11.3). Among the 114 who had been successfully treated for their primary HCV infection, 27 reinfections occurred at a reinfection rate of 9.6/100py (95% CI 6.6−14.1). 25% of patients treated for HCV virus infection became reinfected within 2 years of follow up. Among the 31 individuals who spontaneously cleared their primary HCV infection, 5 reinfections occurred yielding a reinfection rate of 4.2/100py (95% CI 1.7−10.0). The difference in reinfection rate between those treated successfully and those who spontaneously cleared their primary infections did not reach significance (p = 0.15). The Kaplan-Meier curve giving proportion of patients free from reinfection is shown in Fig. 2 for the two groups. 17 of the 32 reinfected patients spontaneously cleared or were successfully treated of which 8 had a subsequent second reinfection over 34 person-years of follow-up yielding a second reinfection
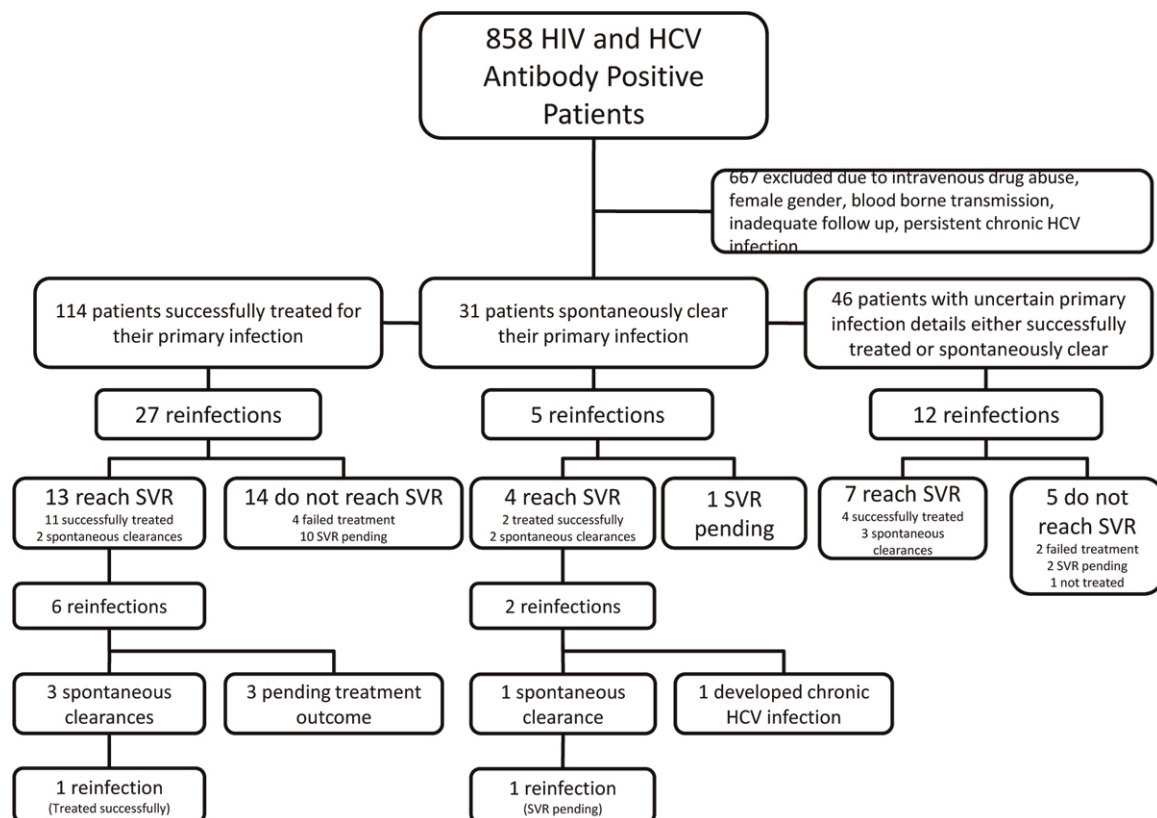

Fig. 1. Flow schematic of patients included in the study.

Table 1. Group characteristics divided by HCV infection status during initial primary infection and during follow-up post primary infection.

	All patients	Treated HCV Infection		Spontaneously cleared HCV infection	
		Non-reinfected	Reinfected	Non-reinfected	Reinfected
Incident infection					
Total	145	87	27	26	5
Median age (IQR)		41 (38–47)	41 (37–43)	39 (34–43)	36 (35–42)
Incident Genotype (%)					
1	97	67 (77)	22 (82)	7 (27)	1 (20)
2	1	1 (1)	0 (0)	0 (0)	0 (0)
3	6	5 (6)	0 (0)	1 (4)	0 (0)
4	18	13 (15)	4 (15)	0 (0)	1 (20)
Unknown	23	1 (1)	1 (1)	18 (69)	3 (60)
Median peak ALT of incident infection (IQR)		476 (251–1014)	414 (216–832)	359 (145–755)	95 (54–327)
Follow-up					
Median testing interval, days (IQR)		112 (62–224)	106 (62–210)	99 (55–161)	99 (63–247)
cART use during follow-up (%)	129 (89)	82 (94)	22 (81)	21 (81)	4 (80)
Median peak ALT during follow up (IQR)		38 (26–55)	254 (140–892)	58 (35–125)	226 (168–499)
Median CD4 at last negative HCV RNA PCR/first positive HCV RNA (IQR)		547 (444–681)	429 (379–624)	531 (392–687)	397 (280–710)
Reinfection genotype (%)					
1		22 (69)	19 (70)		3 (60)
2		0 (0)	0 (0)		0
3		1 (3)	1 (4)		0
4		2 (6)	1 (4)		1 (20)
Unknown		7 (22)	6 (22)		1 (20)

rate of 23.2/100py (11.6−46.4). Median follow-up time per patient following second reinfection was 1.5 years.

There was no evidence of a difference in CD4 cell count, age, use of ART or peak ALT during primary infection between patients who underwent reinfection and those who did not or between those who were treated and those who spontaneously cleared their infection. Use of ART during follow-up was high (89%) and did not differ between groups (p = 0.11). Peak ALT levels did not significantly differ between primary infection and primary reinfection. However, peak ALT among patients who were reinfected was significantly higher than peak ALT during follow-up of patients who had no reinfection (median 253 vs 41 U/L, p < 0.0001).

When including those with uncertain incident infection details, the overall reinfection rate was similar at 7.8/100py (95% CI 5.8−10.5). Among the 191 patients there were 44 reinfections of whom 7 (16%) spontaneously cleared their infection. 17 were successfully treated and the remainder failed therapy [6], opted out of treatment [1] or are pending final SVR results [13].

24 patients had available HCV PCR results following successful treatment or spontaneous clearance of their first reinfection. Among these patients there were 8 second-reinfections yielding a second-reinfection rate of 15.5/100py (95% CI 7.7−31.0). From these 8, 4 (50%) spontaneously cleared their infection, one opted out of treatment developing chronic infection and three were treated with results pending. From the four patients who

spontaneously cleared their second reinfection, 2 patients underwent a third reinfection: one was successfully treated and the other is pending SVR. A summary of the eight patients who were reinfected more than once is shown in Fig. 3.

Combining first, second and third reinfections, there were 54 reinfections in total. 32 (59%), 1 (2%), 2 (4%), 7 (13%) and 12 (22%) were genotype 1, 2, 3, 4 and unknown genotype respectively. From the 54 reinfections, 11 patients (20%) spontaneously cleared HCV. Among patients who spontaneously cleared their reinfections, the median time to achieve undetectable viraemia was 43 days (IQR 28−76.5) and the median number of positive HCV PCRs per infection was 1 (IQR 1−3). A total of 63% (34 of 54) of those with reinfection underwent treatment. Following reinfection, the median period until treatment was initiated was 57 days (IQR 38−112). The SVR rate among reinfections was 73% (16 of 22) for genotype 1/4 and 100% (2 of 2) for genotype 2/3. 10 patients are pending SVR results.

Discussion

Our results demonstrate a high risk of HCV reinfection among HIV-positive MSM who are either treated for or who spontaneously clear their initial HCV infection. As many as 25% of individuals treated for HCV will become reinfected within 2 years. These results emphasize the need for effective sexual education for HIV-positive
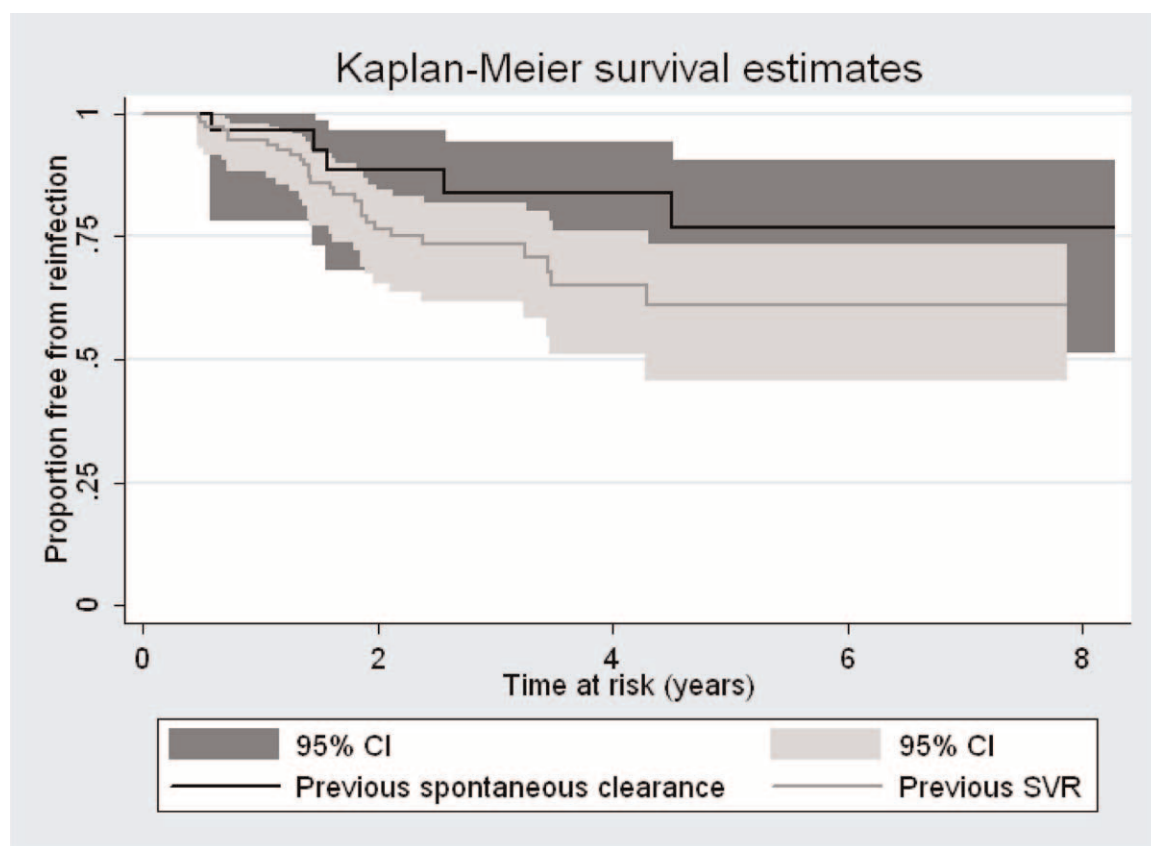
Fig. 2. Kaplan-Meier curves of survival free from reinfection for patients who were either spontaneously cleared or achieved SVR for their primary infection.

MSM presenting with primary HCV infection and the implementation of preventative interventions to reduce the risk of reinfection. Given their high risk, we recommend enhanced surveillance of previously infected individuals to enable the early detection and treatment of any reinfections. New UK guidelines have been updated to reflect this by recommending HCV PCR testing every 3–6 months among individuals who remain at risk following incident infection clearance [30].

Our rate of reinfection among spontaneous clearers was lower than treated individuals (4.2/100py vs 9.6/100py); however, the evidence for a difference lacked power (p = 0.15) and may have been influenced by different median testing intervals in the two groups (105 vs. 173 days, p < 0.0001) therefore providing only weak evidence for protective immunity [24,28]. The rate of reinfection among spontaneous clearers was high overall and this group should therefore be followed up with regular HCV PCR testing as for individuals who have been previously treated for their HCV infection.

SVR rates for individuals treated for their HCV reinfection were generally high (73% for genotype 1 + 4 and 100% for genotype 2 + 3). The majority of reinfections were treated in the acute phase of the

infection (median time to treatment following first positive HCV PCR was 43 days) and SVR rates were consistent with studies treating acute HCV infections in HIV-positive MSMs [31].

Our spontaneous clearance rate of reinfection (11 of 54 reinfections, 20%) is consistent with spontaneous clearance rates of primary HCV infection in HIV-positive MSM (5–40%) [32–36]. The true spontaneous clearance rate of reinfection is likely to be higher, though, as spontaneously cleared infections may have been missed due to variable testing intervals (median 112 days, IQR 62–224). This study provides the first large cohort estimates of spontaneous clearance of HCV reinfection among HIV-infected individuals and supports monitoring for spontaneous clearance of reinfection before initiating treatment as for primary infection with HCV.

Our reinfection rate following treatment for HCV infection (9.6/100py 95% CI 6.6–14.1) is comparable to that found by Lambers et al (15.2/100py 95% CI 8.0–26.5) [29]. Strengths of our study in comparison to Lambers et al. are the considerably larger sample size (191 patients and 562 person-years follow-up vs 56 patients and 72 person-years follow-up), the inclusion of spontaneous clearers in the analysis and the analysis of
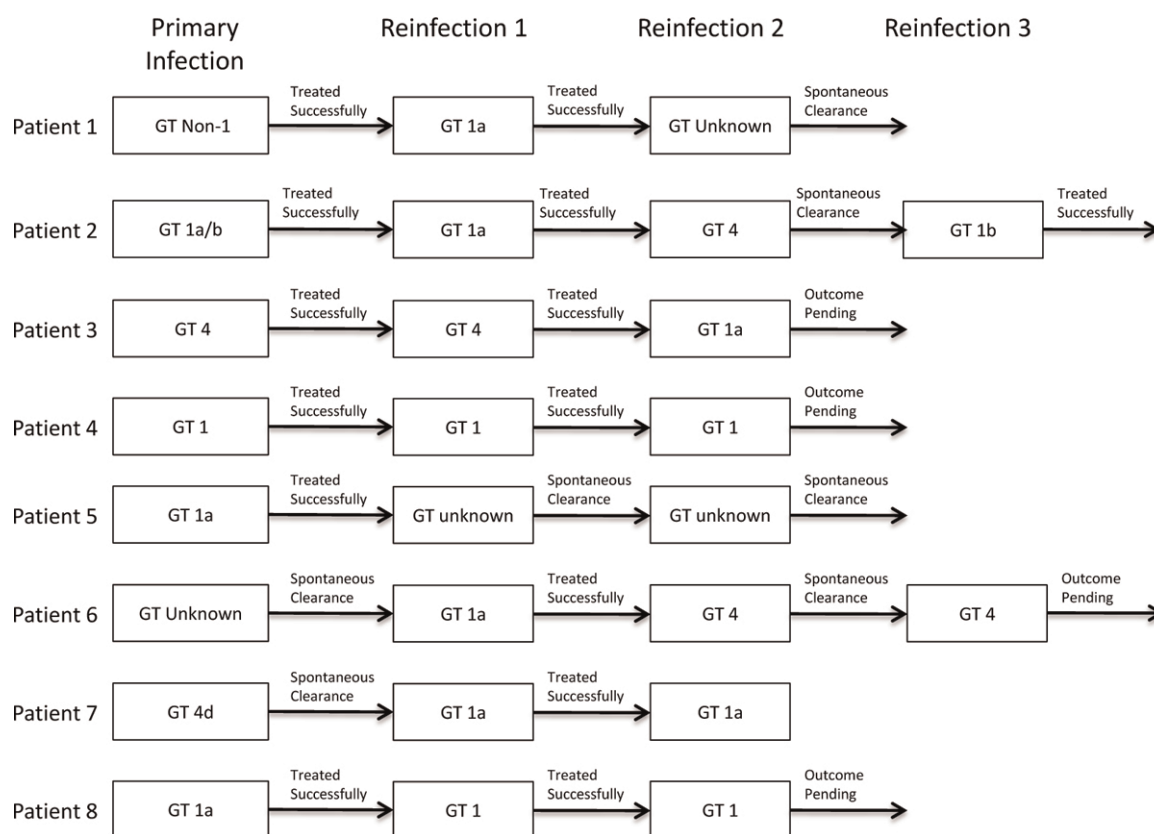
Fig. 3. Flow chart of 8 individuals with more than 1 reinfection.

individuals who subsequently had multiple reinfections. The higher incidence of reinfection found by Lambers et al. may be explained by their inclusion of patients who underwent reinfection with the same genotype but different phylogeny within the 24 weeks required for definitive SVR and also shorter testing intervals during follow up (median 91 days, IQR 58–130 vs. 112 day, IQR 62–224) [28].

Limitations of our study include its retrospective nature, the absence of behavioural data and the lack of phylogenetic analysis to prove reinfection in cases where reinfection was with the same genotype. The true reinfection rate in our cohort is likely to be higher for the following reasons: (i) the testing interval post primary infection was variable and long in comparison to the duration of possibly missed spontaneous clearances; (ii) we excluded patients who developed recurrent viraemia within the 24 weeks required for SVR whereas previous phylogenetic studies have shown a proportion of these 'relapses' to, in fact, be true reinfections.

Unfortunately, it remains difficult, as in previous studies, to definitively say that the reappearance of viraemia following treatment is not the emergence of a non-dominant quasispecies or superinfection after treatment of a dominant HCV strain [32,37]. However, we believe the re-emergence of viraemia is most likely to represent reinfection in our study, supported by the long duration to reinfection in most cases with multiple negative HCV PCR results between infections and the excellent response of reinfection to treatment. Finally, the patients included in our study were all from a single HIV clinic and as such our results may not be representative of other areas in London, the UK or Europe.

In conclusion, our results show high HCV reinfection rates for HIV positive MSM who have previously cleared the infection either spontaneously or through treatment. We recommend enhanced surveillance of patients who have cleared HCV infection to allow the early detection and treatment of any reinfection. In addition, we recommend directed education and prevention interventions to HIV positive MSMs with HCV infection. Future work will include evaluation of interventions and prospective studies to evaluate further protective immunity in this population.

Contributions

TM designed the study, collected and analysed the data and wrote the paper. NM contributed to the study design, statistical analysis and paper editing. MH and PV contributed to study design, analysis and paper editing.

Conflicts of interest

None declared.

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