Hepatitis C Virus (HCV) Antibody Dynamics Following Acute HCV Infection and Reinfection Among HIV-Infected Men Who Have Sex With Men

Joost W. Vanhommerig,1,2 Xiomara V. Thomas,1 Jan T. M. van der Meer,3 Ronald B. Geskus,2,4 Sylvia M. Bruisten,2 Richard Molenkamp,1 Maria Prins,2,3 and Janke Schinkel1; for the MOSAIC (MSM Observational Study for Acute Infection with hepatitis C) Study Group

1Department of Medical Microbiology, Section of Clinical Virology, Academic Medical Center, 2Cluster of Infectious Diseases, Public Health Service of Amsterdam, 3Department of Internal Medicine, Division of Infectious Diseases, Academic Medical Center, Center for Infection and Immunity Amsterdam (CINIMA), and 4Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, Amsterdam, The Netherlands

(See the Major Article by Freiman et al on pages 1686–93, and the Editorial Commentary by Reiberger on pages 1694–5.)

Background. A decline of hepatitis C virus (HCV) antibody titers (anti-HCV), ultimately resulting in seroreversion, has been reported following clearance of viremia in both acute and chronic HCV infection. However, frequency of seroreversion remains unknown in human immunodeficiency virus (HIV)/HCV-coinfected patients. We describe anti-HCV dynamics among HIV-infected men who have sex with men (MSM) following acute HCV infection and reinfection.

Methods. Primary acute HCV infection was assumed when a subject was anti-HCV negative prior to the first positive HCV RNA test. Anti-HCV was measured at least annually in 63 HIV-infected MSM, with a median follow-up of 4.0 years (interquartile range [IQR], 2.5–5.7 years). Time from HCV infection to seroconversion, and from seroconversion to seroreversion, was estimated using the Kaplan–Meier method. Longitudinal anti-HCV patterns were studied using a random-effects model to adjust for repeated measures.

Results. Median time from HCV infection to seroconversion was 74 days (IQR, 47–125 days). Subjects who cleared HCV RNA (n = 36) showed a significant decrease in anti-HCV levels (P < .001). Among 31 subjects with sustained virologic response (SVR), anti-HCV became undetectable during follow-up in 8; cumulative incidence of seroreversion within 3 years after seroconversion was 37% (95% confidence interval, 18%–66%). Eighteen subjects became reinfected during follow-up; this coincided with a subsequent increase in anti-HCV reactivity.

Conclusions. A decline of anti-HCV reactivity was associated with HCV RNA clearance. Seroreversion was very common following SVR. Upon reinfection, anti-HCV levels increased again. Monitoring anti-HCV levels might therefore be an effective alternative for diagnosis of HCV reinfection.

Keywords. acute HCV; HIV/HCV co-infection; men who have sex with men; HCV reinfection.

Hepatitis C virus (HCV) is a major cause of liver disease. Globally an estimated 2%–3% of people are infected [1, 2]. Following acute infection, the majority of HCV-infected individuals will develop chronic HCV infection and are at risk for long-term sequelae, including liver cirrhosis and hepatocellular carcinoma [3]. Major risk factors for contracting HCV infection are injection drug use, blood transfusions from unscreened donors, and unsafe medical procedures [2]. The risk...
of sexual transmission of HCV in monogamous heterosexual couples is considered negligible [4]. Since the mid-1990s, an epidemic of HCV infection has emerged among human immunodeficiency virus (HIV)-infected men who have sex with men (MSM) in high-income countries [5–8]. These men denied injection drug use, and phylogenetic analyses of circulating HCV strains have revealed the presence of multiple MSM-specific clusters, thereby demonstrating that sex may be an alternative transmission route [9–11].

The window period between HCV infection and detectable HCV antibody (anti-HCV) has been estimated to range from 34 to 70 days in studies among HIV-negative recipients of blood products [12–15] and HIV-negative injection drug users [16, 17]. A delayed anti-HCV response was reported among HIV-infected MSM with acute HCV, suggesting an important role for coinfection with HIV [18]. The reported median time to seroconversion in that study was 91 days, and 158 days in a subset of 8 men sampled more frequently.

A decline in anti-HCV reactivity, ultimately followed by seroreversion, has been reported following spontaneous or treatment-induced clearance, mostly in the absence of HIV infection and only after long-term follow-up [19–27]. The available literature seems to agree that seroreversion may occur in cases of profound immunodepression [28]. Only a few reports have described seroreversion among HIV-coinfected patients [27, 29–31]. Therefore, the frequency of HCV seroreversion among HIV-coinfected patients remains unknown. The objectives of the current study were to examine dynamics of anti-HCV reactivity following acute HCV infection among HIV-infected MSM. The high incidence of HCV reinfection in this population [32, 33] also allowed us to study anti-HCV dynamics following reinfection.

METHODS

Participants

Participants eligible for this study included HIV type 1–infected MSM, aged ≥18 years, diagnosed with acute HCV infection at the Academic Medical Center HIV outpatient clinic in Amsterdam. The majority of study subjects (42/63 [66.7%]) participated in MOSAIC (MSM Observational Study for Acute Infection with hepatitis C), a multicenter open prospective cohort study in the Netherlands that was initiated in 2009 [32]. For the present study, strict inclusion criteria were applied with respect to the maximum interval between HCV RNA–negative and –positive visits (ie, maximum of 6 months). Primary HCV infection was assumed when a subject was anti-HCV negative prior to the first positive HCV RNA test. Sociodemographic, clinical, and virological data, including age, use of combination antiretroviral therapy (cART), HIV load, CD4 cell count, concentrations of alanine aminotransferase (ALT), HCV load, and HCV treatment data were retrieved from medical files.

Laboratory Methods

To determine the interval between the last negative and the first positive HCV RNA test, blood samples collected at earlier visits were tested retrospectively. HCV RNA tests were performed using either transcription-mediated amplification (Versant, Siemens; limit of detection [LOD], 5–10 IU/mL) or COBAS AmpliPrep/COBAS TaqMan (Roche Diagnostics; LOD, 15 IU/mL). Anti-HCV reactivity was tested at least every 6 months in the first year following infection (and reinfection), followed by annual testing. Anti-HCV testing was performed using a commercial microparticle enzyme immunoassay (AxSYM HCV 3.0, Abbott Laboratories). A positive anti-HCV test was defined as having a sample-to-cutoff (S/CO) value of ≥1.00. When a subsequent negative anti-HCV test was recorded (ie, S/CO <1.00), this was considered seroreversion. Date of seroreversion was estimated as the midpoint between the first negative anti-HCV test after seroconversion and the preceding sample. HCV genotype was determined by sequencing a 340-bp fragment of the NS5B region [34].

Definition of HCV Reinflection

Reinflection was defined as the presence of a different genotype compared with primary infection. To investigate the possibility of reinfection with the same genotype in patients without a genotype switch, consecutive E2/HVR1 sequences were analyzed as previously described [32]. Relapse was defined as a positive HCV RNA result after a negative HCV RNA test at the end of treatment with the same viral strain.

Statistical Analysis

The midpoint between the last negative and the first positive RNA test, and the midpoint between the last anti-HCV–negative and the first anti-HCV–positive test was estimated to be the dates of infection and seroconversion, respectively. When the last negative HCV RNA test coincided with the last negative anti-HCV test, and the first positive HCV RNA result coincided with the first positive anti-HCV test, the estimated dates of infection and seroconversion were estimated at the one-third and two-thirds time point between the last negative HCV and first positive HCV test, respectively.

First, we estimated the cumulative incidence and median time (1) from acute HCV infection to seroconversion and (2) from seroconversion to seroreversion, through Kaplan–Meier survival estimates. Univariable Cox proportional hazards analysis was used to evaluate associations of age, HCV genotype, CD4 cell count before infection, and nadir CD4 cell count before infection, on time to seroconversion. Associations of these variables were also evaluated on time to seroreversion.
addition, peak level of anti-HCV was examined in analysis of the latter. Second, differences in peak levels of ALT concentration and anti-HCV reactivity between primary HCV infection and reinfection were compared using the nonparametric Wilcoxon matched-pairs signed-rank test. Third, anti-HCV signal patterns were estimated from the time of primary infection until end of follow-up. Sequential anti-HCV measurements were corrected for within-subject correlation using a random-effects model with random intercept. A random slope was added to the model 6 months after estimated infection; restricted cubic splines allowed for smoothly varying trends. In the analyses of primary HCV infection, measurements during treatment were included, but were censored at HCV reinfection. The statistical software packages Stata Intercooled 13.1 (Stata Corp, College Station, Texas) and R 3.0.1 [35] were used for analysis.

RESULTS

General Characteristics
Sixty-three HIV-infected MSM were diagnosed with acute HCV infection and included in this study (Table 1). Median age at the estimated date of infection was 42 years (interquartile range [IQR], 35–47 years), and the majority (87.3%) had Dutch nationality. Genotype of primary HCV infection was most frequently genotype 1a (39/63 [61.9%]) or 4d (15/63 [23.8%]); other genotypes were 1b (n = 5), 2b (n = 3), and 3a (n = 1). Anti-HCV reactivity was measured during a median observation time of 4.0 years following acute infection (IQR, 2.6–5.8 years), with a median test interval of 0.5 years (IQR, 0.2–1.0 years). Median time between the estimated date of infection and initiation of treatment was 6.7 months (IQR, 3.7–8.7 months), or 4.4 months (IQR, 1.8–7.5 months) after the first RNA-positive visit. Sampling intervals around HCV infection were wider in the group that did not clear HCV, compared with those who did (123 vs 89 days; P = .015). During follow-up, 18 of 63 subjects became reinfected; 16 were reinfected once, 1 was reinfected twice, and 1 was reinfected 3 times. Two out of 21 reinfections (9.5%) were cleared spontaneously. Remarkably, these 2 patients also spontaneously cleared their primary HCV infection. Treatment outcomes during follow-up of all primary infections and reinfections are shown in Figure 1.

Seroconversion Window
All subjects (63/63 [100%]) seroconverted during the observation period. Median time from infection to seroconversion was 74 days (IQR, 47–125 days; Figure 2). The cumulative incidence of seroconversion was 59% (95% confidence interval [CI], 47%–71%) at 3 months, 73% (95% CI, 62%–83%) at 4 months, and 98% (95% CI, 93%–100%) at 12 months. In univariable Cox regression, time to seroconversion was not significantly associated with age (hazard ratio [HR], per 10-year increment: 1.15; 95% CI, .82–1.59), genotype (1 vs non-1: HR, 1.06; 95% CI, .62–1.83), CD4 cell count (HR per 100 cells/µL increment: 1.03; 95% CI, .92–1.12), or nadir CD4 cell count before infection (HR per 100 cells/µL increment: 1.01; 95% CI, .86–1.18).

Dynamics of Anti-HCV Reactivity Following Primary HCV Infection
Upon seroconversion, anti-HCV reactivity increased to peak levels well above the detection limit, with a median S/CO

Table 1. Characteristics of 63 HIV-Infected Men Who Have Sex With Men by Hepatitis C Virus Status After Primary Infection

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (N = 63)</th>
<th>Persistent Viremia (n = 27)</th>
<th>Viral Clearance (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at primary HCV infection, y</td>
<td>42 (35–47)</td>
<td>41 (36–45)</td>
<td>42 (35–49)</td>
</tr>
<tr>
<td>Dutch nationality, No.</td>
<td>55 (87)</td>
<td>22 (81)</td>
<td>33 (92)</td>
</tr>
<tr>
<td>Genotype of primary infection, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>39 (62)</td>
<td>17 (63)</td>
<td>22 (61)</td>
</tr>
<tr>
<td>1b</td>
<td>5 (8)</td>
<td>3 (11)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>2b</td>
<td>3 (5)</td>
<td>1 (4)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>3a</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>4d</td>
<td>15 (24)</td>
<td>6 (22)</td>
<td>9 (25)</td>
</tr>
<tr>
<td>CD4 cell count before primary infection, cells/µL</td>
<td>495 (350–660)</td>
<td>475 (320–680)</td>
<td>505 (380–660)</td>
</tr>
<tr>
<td>Nadir CD4 cell count before primary infection, cells/µL</td>
<td>260 (130–410)</td>
<td>275 (190–445)</td>
<td>230 (80–370)</td>
</tr>
<tr>
<td>On cART at first HCV-positive visit, No. (%)</td>
<td>41 (65)</td>
<td>15 (56)</td>
<td>26 (72)</td>
</tr>
<tr>
<td>HIV RNA load at first HCV-positive visit, copies/mL</td>
<td>&lt;50 (40–17590)</td>
<td>99 (&lt;50–33680)</td>
<td>&lt;50 (&lt;40–9916)</td>
</tr>
<tr>
<td>Anti-HCV reactivity at first anti-HCV-positive visit, S/CO</td>
<td>60.5 (12.9–85.1)</td>
<td>61.5 (21.0–85.2)</td>
<td>50.6 (12.5–84.2)</td>
</tr>
<tr>
<td>Days between last negative and first positive HCV RNA test</td>
<td>107 (80–133)</td>
<td>123 (98–140)</td>
<td>89 (71–119)</td>
</tr>
</tbody>
</table>

Reported values are median (interquartile range), unless indicated otherwise.

Abbreviations: anti-HCV, hepatitis C virus antibody; cART, combination antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; S/CO, sample-to-cutoff value.

* Twenty-seven had persistent viremia; 36 cleared HCV (5 spontaneously cleared infection, and 31 cleared infection after treatment).
ratio of 89.4 (IQR, 58.6–115.3). Two distinct patterns of anti-HCV dynamics emerged 6 months postinfection; Figure 3 shows the modeled estimates for anti-HCV reactivity. Of 27 subjects who were persistently viremic (ie, untreated subjects, nonresponders, and relapers), all but 1 showed a stable serological profile; 80% of all anti-HCV measurements in this group were above an S/CO ratio of 50. After HCV clearance, either spontaneously (n = 5) or following treatment (n = 31), anti-HCV reactivity decreased significantly (P < .001). The median peak and subsequent nadir S/CO ratios were 89.4 (IQR, 58.6–115.3) and 5.4 (IQR, 1.3–50.8), respectively.

Incidence of Seroreversion
Full seroreversion was observed in 8 of 31 subjects with sustained virologic response (SVR) following primary HCV infection. Among those who spontaneously cleared HCV, partial seroreversion (ie, a decrease, but not complete loss of anti-HCV signal) was observed. The cumulative incidence of seroreversion was 37% (95% CI, 18%–66%) within 3 years after seroconversion (Figure 4), or 51% (95% CI, 27%–81%) within 3 years after reaching SVR. The CD4 cell count at the visit before seroreversion was 490 cells/µL (IQR, 440–775), and the nadir CD4 cell count at that visit was 305 cells/µL (IQR, 140–380). In univariable Cox regression, seroreversion was significantly associated with lower peak anti-HCV levels during primary infection (HR, per 10 S/CO lower: 1.6; 95% CI, 1.1–2.3; P = .014). None of the other studied risk factors were significantly associated with seroreversion: age (HR, per 10-year increment: 0.88; 95% CI, .38–1.07), genotype 1 vs non-1 (HR, 2.62; 95% CI, .59–11.8), CD4 cell count before HCV infection (HR, per 100 cells/µL increment: 1.25; 95% CI, .79–1.97), and nadir CD4 cell count before HCV infection (HR, per 100 cells/µL increment: 1.18; 95% CI, .81–1.70).

Anti-HCV and ALT During HCV Reinfection Versus Primary Acute Infection
During follow-up, 21 reinfections were observed among 18 subjects. Reinfection occurred either following SVR (13 reinfections), before SVR was reached (3 reinfections), or following spontaneous clearance (4 reinfections), or without intermittent negativity (1 reinfection; possible superinfection). Table 2
shows that peak anti-HCV reactivity levels (S/CO) were significantly higher during reinfection (median, 119.6; IQR, 103.4–146.6) compared with primary infection (median, 72.9; IQR, 57.1–105.5; P = .014). Anti-HCV reactivity of the subject who had 3 reinfections is shown in Figure 5 to illustrate what may be observed during a course of multiple infections.

At the first RNA-positive date during primary infection, ALT concentrations were elevated (ie, >2 times the upper limit of normal; ≥80 U/L) in 13 of 18 (72.2%) of cases, with a median of 119 U/L (IQR, 56–470 U/L). ALT levels were less pronounced upon reinfection, with a median of 66 U/L (IQR, 26–222 U/L). Moreover, ALT concentrations were elevated in only 8 of 18 (44.4%) cases at the first RNA-positive date of reinfection (Table 2).

**DISCUSSION**

In this study, dynamics of HCV-specific antibodies were studied among HIV-infected MSM with acute HCV infection. Our main findings were that (1) the seroconversion window in this population was comparable to the seroconversion window reported among HIV-uninfected subjects; (2) seroreversion was very common following successful antiviral treatment; and (3) after an initial decrease in anti-HCV levels following SVR, levels
increased following reinfection to levels reached during primary infection (or higher).

The median time to seroconversion in our study was 74 days and comparable to the HCV seroconversion window reported for HIV-uninfected subjects [12–17]. However, in contrast to our study, in a group of HIV-infected MSM, a delayed or even absent antibody response against HCV following acute infection was reported by Thomson et al [18]. In our study, in a sensitivity analysis among subjects with narrower testing intervals around primary infection, estimates were comparable to the seroconversion window we obtained in the full dataset (data not shown). Also, in our study, all men seroconverted within the observation period, whereas in the Thomson et al report, no anti-HCV antibodies were detected in 4 of 43 subjects at the end of follow-up [18]. As 2 of these subjects had spontaneously cleared HCV, se

Table 2. Maximum Observed Values for Hepatitis C Virus Antibody and Alanine Aminotransferase Concentrations During Primary Infection and Subsequent Reinfection for 18 HIV-Infected Men Who Have Sex With Men Who Were Reinfected During Follow-up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Anti-HCV</th>
<th>ALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactive/elevated at first HCV RNA+ visit during primary infection, No. (%)</td>
<td>6/15 (40)</td>
<td>13/18 (72)</td>
</tr>
<tr>
<td>Reactive/elevated at first HCV RNA+ visit during reinfection, No. (%)</td>
<td>13/14 (93)</td>
<td>8/18 (44)</td>
</tr>
<tr>
<td>Peak following primary HCV infection, median (IQR)</td>
<td>72.9 (57.1–106.5)</td>
<td>470 (336–840)</td>
</tr>
<tr>
<td>Peak following HCV reinfection, median (IQR)</td>
<td>119.6 (103.4–146.6)</td>
<td>223 (164–482)</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; anti-HCV, hepatitis C virus antibody; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range.


d Measurements are shown from the first HCV RNA positive (+) visit following primary infection, and reinfection. During primary and reinfection, no anti-HCV result was available from the first HCV RNA+ sample for 3 of 18 and 4 of 18, respectively.

Sample-to-cutoff value.

Anti-HCV reactivity (S/CO)

Figure 5. Hepatitis C virus (HCV) antibody (anti-HCV) sample-to-cutoff levels and qualitative RNA measurements in 1 HIV-infected man who has sex with men. After resolving a primary HCV-4d infection after treatment; after spontaneous HCV clearance, we expect that

normalize within the serodiagnostic window. As a result, acute infections in patients with normal ALT levels and an HCV-seronegative status may still be missed. ALT levels may not always be elevated following HCV (re)infection, and when elevated, do not always indicate recent HCV infection [32]. Indeed, in our study, 72.2% of reinfected subjects had elevated ALT levels at the first RNA-positive date of primary infection, whereas only 44.4% of them had elevated ALT at the first RNA-positive date of reinfection. This further emphasizes the need for HCV RNA testing in patients at risk for reinfection.

Seroreversion (ie, loss of antibodies) following HCV clearance was relatively common in our study, being 37% at 3 years after seroconversion. To our knowledge, we are the first to have systematically addressed the occurrence of seroreversion among HIV-infected patients with acute HCV infection. The observed incidence of seroreversion in our study is very high, especially when compared to the frequency of seroreversion reported after treatment of chronic HCV [19,20,22,23,25,26,26,36]. One explanation for the high seroreversion rate may be that in our study, treatment was initiated early in the course of infection, resulting in lower peak anti-HCV levels, as a loss of HCV RNA coincided with decline in anti-HCV levels.

Seroreversion was observed only among those who cleared HCV following treatment; after spontaneous HCV clearance, only partial seroreversion was observed, most likely because 4 of 5 subjects who had spontaneously cleared their primary infection became reinfected during follow-up. We expect that
seroreversion is also likely to occur after spontaneous clearance of HCV, as the observed slope of decline in anti-HCV was comparable to the slope in those who cleared following antiviral treatment. For the same reason, peak anti-HCV reactivity probably influenced the time to seroreversion.

The rapid decrease of anti-HCV reactivity, indicating loss of specific anti-HCV-producing plasma cells in this population, may be partly due to the presence of HIV coinfection, although most men were on cART and had relatively high CD4 cell counts. During HIV infection, the total B-cell number and number of memory B cells may be significantly reduced [37]. Whereas use of cART is associated with a normalization of the absolute number of B cells, the memory B-cell subset is unlikely to be restored [37]. Also, plasma cell disorders are reported more frequently among HIV-infected patients, but the exact mechanisms that drive this are still unclear [38]. An additional explanation for the rapid decline in anti-HCV reactivity following HCV clearance may be that humoral responses during antiviral therapy in patients with acute HCV infection differ from patients with chronic infection; the rapid decrease in viral antigen, required for stimulation of B cells, and interferon therapy itself, may inhibit B-cell proliferation. Indeed, loss of anti-HCV reactivity has also been reported after treatment of acute HCV among HIV-negative individuals by Wiegand et al [36].

Interestingly, following initial decrease in anti-HCV reactivity after HCV clearance, a subsequent increase in anti-HCV reactivity was observed in all reinfection cases. To our knowledge, this finding of “seroreconversion” is unique and may supplement current screening strategies for HCV reinfection in this population. This may be especially helpful because ALT levels are not always elevated during reinfection.

The level of anti-HCV reactivity might be a marker for the presence of neutralizing antibodies (nAbs) after infection, as has been proposed by Mizukoshi et al [39]. In addition, nAbs generally are thought to develop only after initial control of viremia [40]. If this is indeed the case, nAb titers may remain low when treatment is initiated early after primary infection. To some extent, this could even explain the high rates of reinfection reported among HIV-infected MSM [32, 33].

Our study has a number of limitations. All subjects were identified at an HIV outpatient clinic; this may have led to selection bias because symptomatic patients may have a higher frequency of visits. Average testing intervals around infection were wider among subjects not treated for HCV compared with those who were, suggesting that patients who are willing to undergo HCV treatment are more compliant to clinical visits. We did not correct for the uncertainty of the estimated dates of infection, seroconversion, and seroreversion in our analyses. Instead, we applied a strict inclusion criterion of maximum 6 months between the last negative and the first positive HCV RNA test. Another limitation is that our study did not incorporate subjects with chronic HCV infection. However, the literature suggests that decline of anti-HCV occurs rarely following treatment of chronic HCV infection [19, 20, 22, 23, 25, 26, 36]. Finally, the results of this study may only apply for the antibody assay used, an assay with sufficient linear range. Our results may be less applicable when assays with a more narrow linear range are used.

In conclusion, we have shown that the seroconversion window among HIV-infected individuals is comparable to that of HIV-uninfected individuals. Still, the median time to seroconversion was 74 days. Screening for acute HCV infection is thus still ideally performed using nucleic acid testing. Seroreversion was common following HCV clearance, and may cause misclassification of a reinfection as an initial infection in clinical practice. Finally, anti-HCV levels increased again following HCV reinfection to levels reached during primary infection. Although the antibody assay used is not a quantitative assay, a clear association existed between anti-HCV reactivity and viremia within subjects following acute HCV infection. Monitoring antibody dynamics following SVR could thus be a useful and inexpensive alternative and additional tool for evaluation and diagnosis of HCV reinfection in the HIV-infected MSM population.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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