

# Spontaneous Clearance of Hepatitis C Virus Infection Among Human Immunodeficiency Virus–Infected Men Who Have Sex With Men

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We assessed spontaneous clearance in 27 human immunodeficiency virus–infected men who have sex with men (MSM) who seroconverted for hepatitis C virus (HCV). In contrast with a recent estimate of 45.8%, we found a spontaneous clearance rate of 11.1% (95% confidence interval = 2.4–29.2). This finding suggests that treatment deferral to await spontaneous clearance might not be justified for MSM with sexually acquired HCV.

**Keywords.** hepatitis C virus; men who have sex with men (MSM); spontaneous clearance.

Most studies examining spontaneous clearance following acute hepatitis C virus (HCV) infection have been conducted among symptomatic individuals because acute HCV infection is usually asymptomatic and therefore rarely diagnosed unless systematic HCV screening is performed. Estimates of spontaneous HCV clearance rates derived from these studies are subject to bias because those with symptoms at acute infection are more likely to clear [1]. Recently, Seaberg et al found that 46% of men who have sex with men (MSM) and 40% of those who were infected with human immunodeficiency virus (HIV) spontaneously cleared acute HCV infection [2]. This estimate was derived from the prospective Multicenter AIDS Cohort Study (MACS), in which all participants were systematically screened for HCV, and is therefore likely to be unbiased. The authors suggest that both the amount of viral inoculum and

the immune mechanism involved with a successful response to acute HCV differ by mode of virus acquisition. The rectal mucosa provides both a physical and immunological barrier, which might lead to higher spontaneous clearance rates of HCV after sexual exposure when compared with percutaneous exposure. However, the high estimate is surprising because it is almost 3-fold the estimate reported in 2 previous systematic reviews [1, 3]. We therefore reexamined the spontaneous clearance rate of sexually acquired HCV among HIV-infected MSM because we had the unique opportunity, like Seaberg and colleagues, to provide an unbiased estimate using data from 2 cohorts.

## METHODS

The Amsterdam Cohort Studies (ACS) on HIV among MSM is a prospective cohort initiated in 1984 [4], with participants returning every 3–6 months for follow-up. Human immunodeficiency virus–positive and HIV negative MSM were recruited through announcements in the gay press, advertisements, and by word of mouth and entered the cohort at the Public Health Service of Amsterdam. The HCV status of each participant has been retrospectively determined, as described previously [5, 6]. We selected MSM who seroconverted for HCV during follow-up (the seroconversion date was estimated as the midpoint between the first positive and last negative HCV antibody [anti-HCV] test). We restricted our analysis to those who seroconverted for HCV before January 1, 2006, to minimize the probability that patients were treated for HCV shortly after seroconversion, which may bias the estimate of spontaneous clearance due to uncertainty about subsequent spontaneous clearance if treatment had not been initiated. Treating acute HCV infections became common practice around 2006 [7], when the first reports of an HCV outbreak among MSM were published [8]. We extended our study population with a cohort of HIV-infected MSM in clinical care at the Academic Medical Center (AMC) in Amsterdam, who were systematically screened for HCV in a cross-sectional study between 2007 and 2008 [9]. If anti-HCV–positive, the moment of HCV seroconversion was determined retrospectively using stored sera. Not all patients who visited the outpatient clinic in the study period were invited to participate due to logistical restrictions. The same inclusion criteria as described above were applied to the participating patients. Spontaneous clearance was defined as being HCV RNA–negative at least 2 years after the estimated seroconversion date to make the estimate comparable with the MACS, for which the outcome was also clearance within 2 years of infection. The few patients who had initiated HCV treatment within 2 years after HCV seroconversion were excluded from

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the analysis. Descriptive statistical analyses were performed using Stata (Stata Statistical Software: Release 13; StataCorp LP).

## RESULTS

In the ACS cohort, 11 MSM, all HIV-infected, seroconverted for HCV between October 1984 and January 1, 2006, and fulfilled the inclusion criteria. From the AMC, we selected 16 HIV-infected MSM with a documented HCV seroconversion, making for a total of 27 MSM for the analysis. The characteristics of the study population at the time of HCV seroconversion are shown in Table 1. The median year of seroconversion was 2002 (interquartile range [IQR] = 2001–2005), the median age was 40 years (IQR = 35–43), and 72.0% of the participants had a Dutch nationality. Sixteen MSM (59.3%) were on combination antiretroviral therapy (cART). The median CD4 cell count and HIV RNA levels measured around seroconversion were 585 cells/ $\mu$ L (IQR = 360–810) and 50 copies/mL (IQR = 50–6042), respectively. Nadir CD4 cell count was 220 cells/ $\mu$ L (IQR = 90–360), and 2 participants had a positive hepatitis B surface antigen (HBsAg). None of the ACS participants reported injection drug use at study entry; data on drug use were not available for the AMC patients.

One patient from the ACS and 2 from the AMC (total = 3 of 27 MSM) had spontaneously cleared the acute HCV infection (11.1%; 95% confidence interval [CI] = 2.4%–29.2%) within 2 years after seroconversion. These MSM seroconverted for HCV in 1992, 2002, and 2003; were aged 41, 38, and 35 years; and were all on cART. Two of them were HBsAg-positive, compared with none of the 24 MSM who did not spontaneously clear HCV ( $P = .009$ , Fisher's exact test). Other variables were not significantly associated with clearance.

**Table 1. Characteristics of the Study Population at Hepatitis C Virus Seroconversion**

Characteristic	All Patients (n = 27)	ACS (n = 11)	AMC Patients (n = 16)
Age, y	40 (35–43)	40 (34–43)	39 (35–44)
Dutch nationality	72.0% <sup>a</sup>	72.7%	71.4% <sup>a</sup>
Calendar year of HCV seroconversion	2002 (2001–2005)	2001 (2000–2005)	2002 (2001–2004)
CD4 cell count, cells/ $\mu$ L	585 (360–810) <sup>b</sup>	450 (290–580) <sup>b</sup>	690 (425–945)
HIV RNA, copies/mL	50 (50–6042) <sup>b</sup>	525 (50–1290) <sup>b</sup>	50 (50–8833)
On cART	59.3%	54.6%	62.5%
CD4 nadir, cells/ $\mu$ L	220 (90–360) <sup>a</sup>	185 (50–330) <sup>b</sup>	290 (120–410) <sup>b</sup>
HBsAg-positive	7.4%	9.1%	6.3%
History of injecting drug use	NA	0%	NA

Data are median (IQR) unless otherwise noted.

Abbreviations: ACS, Amsterdam Cohort Studies; AMC, Academic Medical Center; cART, combination antiretroviral treatment; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NA, not available.

<sup>a</sup>Two missing values.

<sup>b</sup>One missing value.

## DISCUSSION

Despite a similar study design, the spontaneous HCV clearance rate among MSM in our cohort (11.1%) is substantially lower than the spontaneous clearance rate reported in the MACS (45.8%). Although our study is limited by a small sample size and thus resulted in a wide 95% confidence interval around our clearance rate (95% CI = 2.4%–29.2%), the estimate from the MACS does not fall within this confidence interval. Our spontaneous clearance rate is in line with a recent systematic review and meta-analysis (15.4%) among HIV-infected MSM [3], although the design of most reports included was cross-sectional.

Being uninfected with HIV and aged <30 years were independently associated with spontaneous clearance in the MACS. In our study population, all patients were infected with HIV, and nearly all patients were aged  $\geq$ 30 years. However, the MACS clearance rates for HIV-infected patients (40.0%) and patients aged  $\geq$ 30 years (34.3% for patients aged 30–49 years and 58.8% for patients aged  $\geq$ 50 years) remain much higher than our estimate. In the MACS analyses restricted to HIV-infected men aged  $\geq$ 30 years, older age, taking highly active antiretroviral therapy (HAART), and not having unprotected anal intercourse in the last 6 months were independently associated with spontaneous clearance. The median age in our study was comparable with that in the MACS, but the proportion of HIV-infected MSM taking HAART was higher (59.3% vs 22.3%). These factors are, therefore, unlikely to explain the lower spontaneous clearance rate in our study. As we did not have data available on unprotected anal intercourse, we were unable to compare this. In line with another study [10], we found an association between HBsAg positivity and HCV clearance, which was not found in the MACS. However, the proportion of patients with a positive HBsAg was comparable (7.4% vs 8.9% in the MACS). Also, other factors that are known to be associated with spontaneous clearance, such as an IFNL3 (IL28B) CC genotype, infection with HCV genotype 1, or female sex [11], are either not applicable to the MACS (female sex) or were not associated with spontaneous clearance (IFNL3 and HCV genotype 1) in the MACS and therefore cannot explain the high clearance rate. A limitation of our study is that an initially spontaneously cleared HCV infection followed by an HCV reinfection could have been misclassified as a nonspontaneously cleared initial HCV infection. However, the same limitation holds for the MACS.

The largest difference between our cohort and the MACS is that 60% of the MACS seroconverted for HCV between 1985 and 1994, whereas >90% of MSM in our study seroconverted after 1994. In both studies, the majority of HCV infections were attributed to sexual exposure. However, the timeframe of the HCV epidemic among MSM in the MACS (with highest incidence between 1985 and 1994 [12]) precedes the start of the

HCV epidemic among HIV-infected MSM described in most Western countries [8]. Could false-positive test results partly explain the high rate of spontaneous clearance observed in the MACS? Based on literature [13] and our experience in the ACS, retrospective testing of anti-HCV in “aged stored” samples is associated with weak aspecific anti-HCV reactivity, which is often negative when confirmed by immunoblot. In the MACS, anti-HCV reactivity was not confirmed by immunoblot, and despite regular follow-up visits every 3–6 months, HCV RNA was not detected (not at the last anti-HCV–negative visit nor the first anti-HCV–positive visit) in 36 of 45 (80%) of MSM with spontaneous clearance in the MACS. Thus, only 20% of MSM with spontaneous clearance in the MACS had at least 1 HCV RNA–positive sample during the course of their HCV infection. In our cohort, all 3 MSM with spontaneous clearance had at least 1 HCV RNA–positive sample, comparable with a previous cohort study on spontaneous HCV clearance among people who inject drugs (PWID) [14, 15], in which HCV RNA could be detected at either the last anti-HCV–negative or first anti-HCV–positive visit in 62% of the PWID who spontaneously cleared HCV. Seaberg and colleagues did try to minimize inclusion of false-positive test results by defining incident HCV infection by an anti-HCV–negative visit followed by 2 consecutive anti-HCV–positive visits. However, aspecific reactivity can persist for a substantial period of time.

To conclude, our study showed a much lower spontaneous HCV clearance rate than the study of Seaberg and colleagues. Therefore, although we are unable to fully explain the difference, the final recommendation of Seaberg et al that “MSM who develop acute HCV infections should be carefully monitored for spontaneous clearance before treatment is initiated” should be treated with caution, especially because treatment deferral may enhance onward HCV transmission [16].

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