

**Shedding of Hepatitis C Virus Into the Rectum of HIV-infected
Men Who Have Sex With Men**

Andrew L. Foster, Michael M. Gaisa, Rosanne M. Hijdra, Samuel S. Turner, Tristan J. Morey,
Karen B. Jacobson, and Daniel S. Fierer

Division of Infectious Diseases, Icahn School of Medicine at Mount Sinai (New York, NY), USA

Corresponding Author: Dr. Daniel Seth Fierer, Icahn School of Medicine at Mount Sinai,
1 Gustave L. Levy Place, Box 1009, New York, NY 10029. E-mail: daniel.fierer@mssm.edu;
tel: (212) 824-7413; fax: (212) 824-2312

Short title: Rectal HCV Shedding in HIV-infected MSM

Brief summary: HCV was shed in non-blood rectal fluid of 47% of HIV-infected MSM, with a range of 2.6 to 5.5 log₁₀ IU/mL. The presence and magnitude of rectal HCV shedding was strongly associated with magnitude of blood VL.

Abstract

Background

For over a decade we have known of an epidemic of sexually-transmitted hepatitis C virus (HCV) infection among HIV-infected men who have sex with men (MSM), but there still remains significant controversy over which bodily fluid(s) are responsible for HCV transmission in these men.

Methods

We enrolled HIV-infected MSM with recent and chronic HCV infection and quantified HCV from rectal fluid obtained by blind swab. We compared the rectal HCV viral load (VL) with paired blood HCV VL.

Results

We found rectal HCV shedding in 20 (47%) of 43 men, only one (2%) of whom had visible bleeding. Detection of rectal HCV shedding was associated with blood VL $> 5 \log_{10}$ IU/mL ($p = 0.01$), and 85% with blood VL $> 5 \log_{10}$ IU/mL had rectal shedding. The HCV VL of the rectal fluid ranged from 2.6 to 5.5 \log_{10} IU/mL. Based on the median rectal fluid VL, the surface of an average human penis would be exposed to at least 2,300 IU of HCV for the duration of anal intercourse.

Conclusion

This study provides the first direct evidence that a sufficient quantity of HCV is shed into the rectum in HIV-infected men with HCV infection to directly infect an inserted penis, or be passed indirectly through fomite-like transmission to the rectum of sex partner. We must develop an appropriate public health campaign to educate MSM about these routes of HCV infection to reverse the HCV epidemic among HIV-infected MSM.

Keywords: hepatitis C virus (HCV); HIV-infected MSM; sexual transmission; rectum; shedding

The epidemic of sexually-transmitted hepatitis C virus (HCV) infection among HIV-infected men who have sex with men (MSM) was first identified over a decade ago[1–3]. Despite seven case-control studies that confirmed sexual transmission since these initial reports[4–10], there are only a few consistent, albeit not uniformly accepted, findings[11]. In our study in New York City (NYC), we found that receptive anal intercourse without a condom and with ejaculation into the rectum of the partner was the only sexual risk factor for acquiring HCV infection[5]. Similarly, Witt et al. [8], also in the US, found unprotected receptive anal intercourse to be one of the significant sexual risk factors. In contrast, a German group[6] did not find that anal intercourse was associated with HCV infection, and was the only study of the seven to find rectal bleeding (“rectal trauma with bleeding frequently or always”) as a risk factor. Overall, the most frequently identified risk factors for HCV acquisition were unprotected anal intercourse (five of seven studies), fisting (four of five studies), and group sex (three of five studies). The most plausible explanation for the significant variability in the risk factors found in different studies, in addition to the limited statistical power of these relatively small studies, is that sex practices are likely to be different among HIV-infected MSM across the cities of the US and Europe. This variability also demonstrates, however, that although more “traumatic” acts such as fisting or even vigorous penile insertion may be *sufficient* for HCV acquisition, they are not necessary. Neither fists nor penises bleed during insertion into the rectum, and so the HCV-containing fluid that infects anal receptive partners is most plausibly semen[12, 13]. HCV in semen could be absorbed through the rectal mucosa that was mildly abraded by the action of the inserted penis in the absence of more serious rectal trauma, possibly enhanced by changes induced by rectal douching, and possibly further enhanced by the mucosa compromised by the CD4⁺ T-cell depletion caused by primary HIV infection[14]. However, epidemiological evidence and experience from our patients (Fierer DS, unpublished data) suggest that all HCV acquisitions cannot be explained by seminal HCV, and further suggests fomite/fomite-like transmission through, or direct infection of unprotected penises or fists. Without more concrete data about the mechanisms of HCV transmission during sex, we cannot provide clear advice to MSM about how to prevent HCV infection.

The rectal vault contains approximately 2-3 mL of neutral pH mucus[15]. Hepatitis B virus (HBV) and HIV, both acquired during sex by MSM, have been detected in this rectal fluid[16–18]. We therefore hypothesized that HCV is also present in this fluid in the rectal vault and undertook to measure HCV shedding into this fluid in the rectal vault in HIV-infected MSM with

recent and chronic HCV infection.

Methods

HIV-infected MSM referred to the Mount Sinai Medical Center for the management of recent and chronic HCV infections were enrolled in this study. Written informed consent was obtained with approval of the Institutional Review Board of the Icahn School of Medicine at Mount Sinai ("Mount Sinai School of Medicine" at the time of enrollment of some participants) in accordance with the Helsinki Declaration of 1975, as revised in 2000. Criteria for eligibility were being HIV-infected MSM with documented HCV viremia.

The date of clinical onset of HCV infection was defined as the date of the first-noted ALT elevation, date of HCV antibody (Ab) seroconversion, or date of first-noted HCV viremia, whichever came first. In this study, recent HCV was defined as the 1-year period after HCV seroconversion, while chronic HCV infection was defined as the time after this 1-year period. We did not study seronegative acute HCV. Testing for sexually-transmitted infections (STI) was performed for syphilis (rapid plasma reagin [RPR], Mount Sinai Clinical Laboratory) and rectal *Chlamydia* (Ct) and *N. gonorrhoea* (GC) (APTIMA COMBO 2 Assay, Gen-Probe Inc, San Diego, CA) on the day of or within a week before the rectal fluid specimen was collected.

Detection of HCV in rectal fluid was performed by blindly inserting a moistened polyester-tipped swab (Puritan) gently into the anal canal until the tip was approximately 7 cm past the anal verge just beyond the dentate line and rotated gently. No other instrumentation of the rectum was performed before the swab was inserted. After being withdrawn, each swab was inspected carefully for visible blood. The swab was then placed in a conical tube containing 2mL of Hank's balanced salt solution (BSS), vortexed vigorously for 10 seconds (Vortex-Genie, Scientific Industries), was pressed against the side of the tube to express the excess fluid, and then removed. The supernatant was assayed for HCV VL immediately, or was frozen and assayed the next day. High resolution anoscopy (HRA) was performed after the swab procedure for the first 30 patients, allowing visualization of the region for the presence of blood or other abnormalities. A blood specimen was obtained for HCV viral load (VL) on the day that the rectal swab was performed (paired specimens).

HCV VL analysis of paired rectal fluid and blood was performed using the Roche COBAS Ampli-Prep/COBAS TaqMan CAP/CTM and CAP/CTM v2.0 systems [lower limit of quantification

(LLOQ) 43 IU/mL and 15 IU/mL, respectively]; the later version was introduced midway through the study. The lower limit of detection (LLOD) of both assays is 7 IU/mL for genotype 1 HCV (Roche Cobas 2013 Ampli-Prep/TacMan Package insert). Rectal HCV VL measurements below LLOQ but below the LLOD were assigned the value of 7 IU/mL, the LLOD of the assays.

Two adjustments to the raw measurements of HCV VL from rectal fluid were necessary to obtain the estimated HCV VL of *in situ* rectal fluid. First, the dilution by the Hanks buffer into which the swabs were placed after adsorbing rectal fluid was experimentally determined, assuming complete saturation of a dry swab with rectal fluid, and further adjusted for the total volume of the supernatant assayed. This dilution adjustment factor was determined to be 1 or $2 \times 1.08 \log_{10}$ depending on the volume of supernatant assayed. Second, the efficiency of both HCV adsorption to and elution from the polyester tip of the rectal swab was experimentally determined by exposing moistened swabs to serial dilutions of sera containing known concentrations of HCV over a 5-log_{10} range. These swabs were processed and assayed in the same manner as the rectal swabs. The efficiency adjustment factor was calculated from the mean of two experiments. This efficiency adjustment factor was determined to be $1.01 \log_{10}$. Each measured HCV VL was therefore adjusted by the combined dilution and efficiency factors to obtain the estimated HCV VL of *in situ* rectal fluid for each man.

Statistical analysis was performed using SPSS version 20 (IBM). Group comparisons were made between those who had rectal HCV detected versus those who did not. Fisher's Exact and Chi-Square tests were used for categorical variables, and the non-parametric Mann-Whitney-U test was used for continuous data. The Freeman-Halton extension of the Fisher's Exact test was used for extending the number of categories analyzed. The Spearman's Rho test was used to generate a correlation coefficient between the blood and rectal HCV viral loads (two non-parametric variables). P-values < 0.05 were considered to be statistically significant.

Results

We enrolled 45 HIV-infected MSM with HCV infection (40 with primary HCV infection and five with HCV re-infection) and obtained rectal fluid samples between May 2012 and November 2014. The median age was 43 years and 60% were white. All but two were prescribed combination antiretroviral therapy (cART), although not all were fully adherent, with 22 (51%) of 43 who were prescribed cART without complete virologic suppression (Table 1). The median

CD4 count was 582 cells/ μ L; none had CD4 count < 200 cells/ μ L, but 10 (22%) had a history of AIDS.

At the time of this study, it was our clinical practice to perform HRA on all men with sexually-acquired HCV infection due to concerns of their being at heightened risk for HPV-related disease (manuscript in preparation). HRA performed on the first 30 (67%) patients found no evidence of injury due to the swab procedure nor of other relevant pathology above the dentate line, and HRA was then not routinely performed on the one third of patients enrolled subsequently. One man from this later group did undergo HRA to investigate his complaints of rectal pain, bleeding, and tenesmus. His swab from before HRA showed visible blood, and was the only swab among the 45 that showed the presence of visible blood. HRA confirmed the presence of proctitis, with diffuse bleeding in the rectal vault that was deemed not to have been caused by the swab procedure. Two (4%) specimens failed HCV VL quantification due to PCR inhibition, resulting in 43 evaluable rectal fluid specimens.

HCV in rectal fluid was detected in 20 (47%) of the men with evaluable rectal fluid specimens (Table 2). The median rectal fluid HCV VL was 2.9 \log_{10} IU/mL. The blood HCV VL was much higher in men with HCV detected in rectal fluid compared to those in whom it was not detected [VL 6.4 (IQR 6.3-6.9) \log_{10} IU/mL compared to 4.0 (IQR 2.9-5.6) \log_{10} IU/mL, respectively; $p < 0.001$] (Figure 1). The median difference between blood and rectal HCV VL was 3.3 \log_{10} IU/mL. Shedding of HCV into rectal fluid was strongly associated with blood HCV viral load > 5 \log_{10} IU/mL ($p = 0.01$) and even more strongly associated with blood HCV viral load > 6 \log_{10} IU/mL ($p < 0.001$). Further, 85% of those with blood HCV VL > 5 \log_{10} IU/mL, and 90% of those with blood HCV VL > 6 \log_{10} IU/mL, the typical VL range in HIV-infected patients with chronic HCV infection[19], shed HCV into their rectal fluid (Table 2).

We found a significant positive correlation between the magnitude of the VL in rectal fluid and the magnitude of the VL in blood (Figure 2). High-level rectal fluid shedding of 4 to 5 \log_{10} IU/mL was found in five (25%) of those with blood VL > 6 \log_{10} IU/mL. The man with the highest rectal fluid VL of 5.2 \log_{10} IU/mL had concurrent bloody proctitis, as demonstrated by HRA. Rectal shedding of HCV was not qualitatively or quantitatively associated with simultaneous rectal GC or Ct infection, having a reactive test for syphilis (RPR), or any other measured demographic characteristic (Table 2).

Discussion

This study provides the first direct evidence that HCV is shed into the rectum of HIV-infected men. We found HCV at substantial levels in the rectal fluid of almost half the HIV-infected men we studied. The proportion of all HIV-infected men who shed HCV into rectal fluid is actually likely to be much higher than half, as the percentage of men shedding HCV and the quantity of virus in the rectum was positively correlated with the amount of HCV in the blood. Since most of our subjects in this study were still within the early phase of HCV infection, they had lower blood HCV VL than men with chronic HCV[13].

Even with the overall lower blood HCV VL of men in our study compared to those with chronic HCV, our data show that an inserted penis (average surface area 185 cm²)[20] would be exposed to at least 2,300 IU HCV in rectal fluid for the duration of anal intercourse. This amount could be higher in the case of fluid extravasation locally due to the friction of intercourse. As few as 10-20 HCV particles delivered parenterally are sufficient to establish infection[21], and our study enumerating founder HCV virions in HIV-infected MSM with sexually-acquired HCV found just a single founder virus in eight of nine sexually-acquired infections[22]. It is therefore plausible that a penis or other fomite such as a sex toy could carry enough HCV to another rectum to result in transmission. That mode could be more efficient for transmission if the rectum were abraded by insertion of the fomite. In addition, while the surface of the penis is dry epithelium composed of stratified squamous cells[23] and therefore relatively impermeable to HCV when intact, in the setting of the of continuous friction of intercourse, this magnitude of exposure could result in adsorption of HCV. Alternatively, the external urethral meatus, composed of non-keratinized, pseudo-columnar epithelium[23], which is a portal of entry for HIV and most sexually-acquired bacterial pathogens, could also be a portal of entry for HCV. These results support the accumulating epidemiological evidence that rectal bleeding is not required for transmission of HCV infection among HIV-infected MSM, and may be the explanation for the epidemiological associations found in some studies between HCV acquisition and group sex or fisting.

Our study has a number of weaknesses. As discussed, we enrolled mostly men with early HCV, whose blood HCV VL is significantly lower than that of chronic HCV. The large majority of HIV-infected MSM who have HCV infection have chronic HCV and we therefore expect a higher proportion of men overall to shed HCV into their rectums, and at higher concentration. We performed blind sampling of the rectal fluid; if the rectal fluid were poorly sampled, by the swab

not reaching the rectal mucosa, for instance, we could have underestimated the prevalence and magnitude of HCV shedding. We determined that pre-wetted polyester swabs are relatively inefficient at both adsorbing and allowing elution of HCV, resulting in loss of over 2 log₁₀ of sensitivity of our assay, and thereby likely underestimating the prevalence of low-level shedding. Future studies are planned to correct these deficiencies. Only 16% of men had concomitant rectal GC or Ct, so although there was no significant difference in HCV shedding among men with or without these rectal STI, the statistical power of this comparison was low, and it seems likely that concomitant infection with these organisms could increase rectal HCV shedding. Finally, the detection of HCV RNA in the rectum does not prove its infectivity. Detection of HCV RNA in body fluids has been correlated with infectiousness[24], however, and we suggest that for clinical and public health purposes, finding of HCV RNA in rectal fluid should be taken as evidence of infectiousness until proven otherwise. In addition to performing more direct and efficient collection techniques, future studies should be done to determine the origin of the HCV in the rectal fluid. It is likely that HCV is extravasated along with the locally-produced rectal fluid, similarly to that of cervicovaginal fluid[25]. Alternatively, or in addition, some HCV could originate as proximally in the gut as the bile[26]. There has been a recent intriguing report of high HCV levels in stool[27], suggesting HCV could exist throughout the GI tract.

In conclusion, this study provides the first direct evidence that HCV is shed into the rectum in HIV-infected men with HCV infection. HCV is present at titers high enough to to be transferred through fomite-like transmission into the rectum of another sex partner or mediate infection of an inserted penis. Taken together with the majority of epidemiological evidence as well as our recent work demonstrating that HCV is shed into semen[13], also at levels sufficient to transmit HCV during sex among MSM, we believe that semen and rectal fluid, rather than frank blood from the rectum, are likely the fluids that mediate most HCV infections in this epidemic. With this preponderance of evidence, we suggest it is now time to readjust the paradigm of HCV transmission requiring significant rectal trauma or bleeding, which misleads both susceptible MSM as well the research community. Finally, we must develop an appropriate public health campaign to educate MSM about these routes of HCV infection to reverse the HCV epidemic among HIV-infected MSM.

Notes

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Disclosures

The authors have no reported conflicts of interest.

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Figure Legends:

Figure 1. Detection of HCV in rectal fluid as a function of HCV VL in blood.

Abbreviations: HCV, hepatitis C virus; n, number; VL, viral load; IU, international units

Figure 2. Correlation between HCV VL in blood and rectal fluid.

Abbreviations: HCV, hepatitis C virus; n, number; VL, viral load; IU, international units

Table 1. Baseline characteristics of 45 HIV-infected men with HCV infection

Characteristic	HIV-infected MSM with HCV infection n = 45
Median age (IQR), years	43 (33-49)
Ethnicity (%)	
White	27 (60)
Black	7 (16)
Hispanic	8 (18)
Other	3 (7)
MSM (%)	45 (100)
HCV status (%)	
Primary infection (%)	40 (89)
Re-infection (%)	5 (11)
HCV genotype (%)	
1a	39 (87)
1b	6 (13)
Underwent HRA (%)	31 (69)
Median blood HCV VL (IQR), log ₁₀ IU/mL	5.9 (3.9-6.5)
HIV parameters	
Median CD4 count (IQR), cells/μL	582 (446-738)
History of AIDS (%)	10 (22)
Receiving cART (%)	43 (96)
Detectable HIV viremia (%)	22 (49)

Abbreviations: n, number; IQR, interquartile range; HCV, hepatitis C virus; IU, international units; RPR, rapid plasma reagin; STI, sexually transmitted infection; MSM, men who have sex with men; HRA, high resolution anoscopy; VL, viral load; cART, combination antiretroviral therapy

Table 2. Factors associated with detection of HCV shedding into rectal fluid of 43 HIV-infected men with HCV infection.

	Rectal HCV Detected n=20	Rectal HCV Not Detected n=23	p value
Blood HCV VL > 5 log IU/mL (%)	17 (85)	11 (48)	0.01
Blood HCV VL > 6 log IU/mL (%)	18 (90)	3 (13)	<0.001
Rectal STI present (%)	4 (20)	3 (13)	0.7
RPR reactive	9 (45)	9 (39)	0.9
High-grade dysplasia (%) present unknown	5 (25) 7 (35)	9 (39) 7 (30)	0.6
HIV viremia at baseline (%) (n=42)	12 (60%)	8 (40%)	0.2
History of AIDS (%)	6 (30)	4 (17)	0.5
Median blood HCV VL (IQR), log ₁₀ IU/mL	6.4 (6.3-6.9)	4.0 (2.9-5.6)	<0.001

Abbreviations: n, number; IQR, interquartile range; HCV, hepatitis C virus; IU, international units; RPR, rapid plasma reagin; STI, sexually transmitted infection; MSM, men who have sex with men; VL, viral load

Figure 1

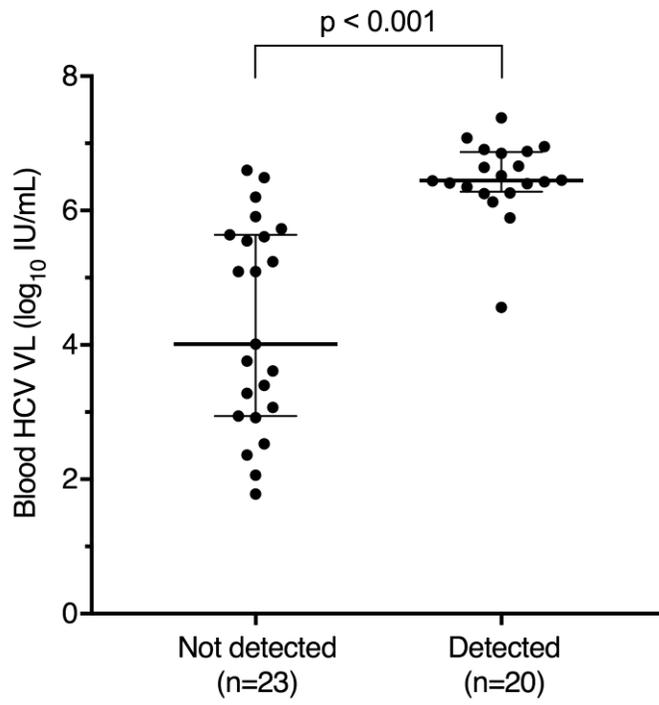


Figure 2

