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Assessing HCV Acquisition Routes in HIV-infected MSM Using Single Genome Sequencing – A Pilot Study

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ABSTRACT

Background: The international epidemic of hepatitis C virus (HCV) infection is in its second decade among HIV-infected men who have sex with men (MSM) but little is known about mechanisms of transmission. Our prior case control study in New York City found unprotected receptive anal intercourse as the main risk factor for acquisition, but studies in England and Germany suggest that group sex or anal trauma are the main risk factors. We sought to understand whether significant disruption of the anorectum is required for HCV acquisition among HIV-infected MSM.

Methodology: We used single genome sequencing (SGS) to identify and enumerate transmitted HCV genomes to test the hypothesis that sexual transmission would be associated with few transmitted genomes, parenteral infection through injection would be associated with many, and bloody or traumatic sex would be associated with an intermediate number of transmitted genomes. Detailed sex and drug histories and plasma were obtained during acute HCV infection in HIV-infected MSM.

Results: Eight men with acute HCV underwent SGS of their plasma virus RNA from the earliest available visits. All had precise and unambiguous identification and enumeration of transmitted HCV genomes. Six of 8 men were productively infected by single HCV genomes; none had rectal bleeding associated with sex nor were they exposed to blood of others; one had injected methamphetamine but without sharing injection equipment, and then had sex. Two men were infected by >10 genomes; one had shared injection equipment and then had sex, and the other denied any injection, rectal trauma, or bleeding with sex. None had an intermediate number of infecting genomes.

Conclusions: Most HCV infections of HIV-infected men were caused by a single transmitted virus, suggesting that HCV infection of MSM is due to a limited exposure to infecting virus across a relatively intact mucosal barrier. In contrast, the one man who had shared injection equipment was infected by a high number of viruses. These patterns of HCV infection parallel both sexual and parenteral acquisition of HIV, where most infections are caused by a single versus a higher number of transmitted HIV genomes, respectively. Larger prospective risk factor studies are needed using SGS to provide novel epidemiological insights to better characterize HCV acquisition in HIV-infected MSM.

BACKGROUND

1) Case-controlled studies of HCV acquisition:

New York (Fierer MMWR 2011)	London (Danta AIDS 2007)	Germany (Schmidt PLoS One 2011)
Receptive UAI with ejaculation (AOR 23.0)	Group sex with receptive or insertive UAI	Rectal trauma with bleeding, frequently or always (AOR 6.2)
Sex while high on crystal methamphetamine (AOR 28.6)	Or receptive or insertive fisting (AOR 9.2 to 23.5)	Frequent receptive fisting without gloves (AOR 5.7)
		Nasal drug use (AOR 3.3)

2) Transmitted HCV in anonymous blood donors (no risk-factor data) (Li 2012)

ID#	Max. Diversity	No. transmitted HCV viruses
10051	0.08%	1
10021	0.14%	1
10025	0.15%	1
9055	0.10%	1
105431	0.40%	2
105686	0.70%	2
10012	3.49%	3
10062	0.71%	3
6213	6.83%	3
10004	4.56%	3
6222	0.57%	4
110069	0.80%	4
10017	1.03%	6
10024	1.32%	7
10029	3.15%	9
10020	0.27%	10
10002	3.22%	12
10016	0.36%	13
10003	0.35%	17
106889	1.22%	>33

HYPOTHESIS

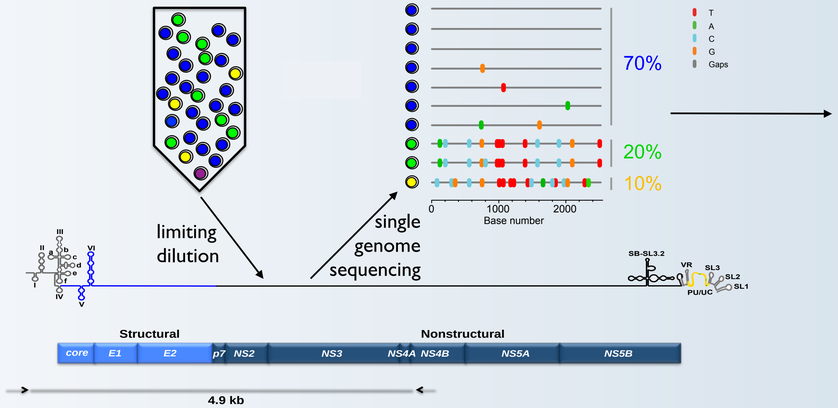
- Sexual transmission of HCV can be distinguished from other routes based on number of transmitted viruses:
- Sex would result in few transmitted viruses; percutaneous transmission in multiple; and bloody sex in an intermediate number

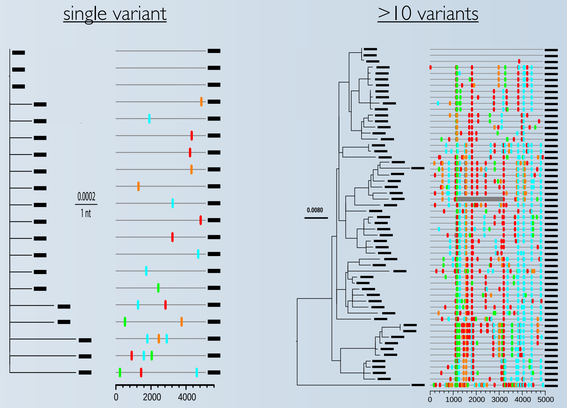
MATERIALS, METHODS, AND SCHEMA

Study subjects
We enrolled and followed HIV-infected MSM with new HCV infection. Written informed consent was obtained from all patients.

Clinical protocol
New HCV infection was defined as new ALT elevation with HCV viremia and seroconversion. Serum and plasma were obtained serially, starting at the earliest possible time points. A structured interview was performed to assess sex and drug use

Single genome sequencing
Analysis by SGS and phylogenetic reconstruction were done as previously described (Li, et al, PLoS Path 8:e1002880, 2012).

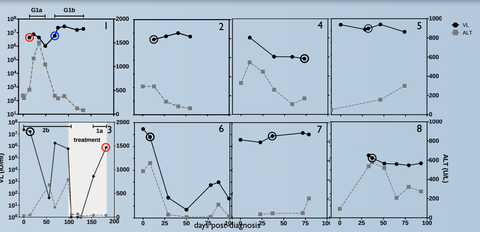




RESULTS

Study subjects (sex and drug history):

- Eight HIV-infected men who have sex with men (MSM) from NYC had 10 acute HCV infections
  - All 8 had unprotected receptive anal intercourse, some continuing after their initial infection
  - None had rectal pain or bleeding associated with sex
- Two men reported IDU with crystal methamphetamine:
  - One (#5) *did not share* injection equipment, and then had sex.
  - One (#7) did share injection equipment, and then had sex



ID#	HCV Ab	HCV VL	Genotype	No. of 5' half sequences	Max. Diversity	No. Transmitted viruses	transmission risk(s)
1-first ⊙	pos	7,630,000	1a	93	0.28%	**1**	sex only
1-second ⊙	n.a.	5,880,000	1b	117	0.12%	**1**	sex only
2	neg	2,740,000	1b	65	0.16%	**1**	sex only
3-first ⊙	neg	23,492,010	2b	53	0.32%	**1**	sex only
3-second ⊙	n.a.	760,793	1a	46	0.69%	**1**	sex only
4	neg	2,636,512	1a	28	0.41%	**>10**	sex only
5	neg	31,434,330	1a	65	0.17%	**1**	IDU *no share*+sex
6	unkn	2,875,900	1a	20	0.12%	**1**	sex only
7	neg	3,626,615	1a	57	2.0%	**>10**	shared IDU+sex
8	neg	157,504	1a	45	0.18%	**1**	sex only

CONCLUSIONS

- Most MSM with no percutaneous exposures were infected by a single virus
  - Suggests that HCV infection of MSM during sex occurs across relatively intact mucosa
- Not all those with IDU are infected through their IDU
  - Irony: the public health message that HCV is only transmitted by needle sharing is so clear that we have men who have "safe" IDU, yet despite these efforts get HCV through unsafe sex, a route that is not officially acknowledged