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BRIEF REPORT

Sexually Acquired Hepatitis C Infection in HIV-Uninfected Men Who Have Sex With Men Using Preexposure Prophylaxis Against HIV

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Sexually acquired hepatitis C virus (HCV) infections among human immunodeficiency virus (HIV)-uninfected men who have sex with men (MSM) have been rare. With the introduction of preexposure prophylaxis (PrEP) against HIV, we hypothesized that these infections would increase. Between 2013 and 2018, we diagnosed 15 likely sexually acquired HCV infections among 14 MSM using PrEP. Most (87%) were asymptomatic, detected by routine alanine transaminase (ALT) or HCV monitoring. Half reported increasing sex partners and drug use after starting PrEP; 5 reported injection of methamphetamine. Interventions are needed to prevent sexually acquired HCV infections by MSM using PrEP. Centers for Disease Control and Prevention guidelines for monitoring during PrEP should include regular ALT and HCV testing.

Keywords. acute hepatitis C virus; men who have sex with men; preexposure prophylaxis; sexual transmission; methamphetamine.

Hepatitis C virus (HCV) is not considered to be efficiently transmitted during sex; blood exposure, particularly associated with injection drug use (IDU), is responsible for the overwhelming majority of HCV infections worldwide [1]. Somewhat over a decade ago, however, the first reports appeared from Europe, Australia, and the United States of an emerging epidemic of HCV infections in human immunodeficiency virus (HIV)-infected men who have sex with men (MSM) who did not engage in IDU (reviewed in [2]). But despite an increase in HCV incidence among HIV-infected MSM in many countries, HCV infection of HIV-uninfected MSM was seen rarely [3], including in our cohort in New York City (NYC), where only approximately 1 in 50 sexually acquired HCV infection was in an HIV-uninfected MSM (D. S. Fierer unpublished data).

We have previously hypothesized [2] that the relative rarity of HCV infections among HIV-uninfected MSM compared to HIV-infected MSM was largely due to 2 factors: serosorting, the HIV risk-reduction practice of choosing partners with concordant HIV serostatus with whom to have sex without a condom; and stochasticity. Once HCV entered the population of HIV-infected MSM, serosorting, without condom use, would result in a higher HCV prevalence within this group. Then, in the setting of HIV- and HCV-discordant partnering, the likelihood of MSM becoming HIV-infected before HCV-infected through unprotected sex with HIV and HCV coinfected MSM is stochastic, resulting in a ratio of HIV to HCV infections roughly corresponding to the differential infectivity between HIV and HCV during anal sex.

There may also be an additional element of biological susceptibility to HCV infection in those with HIV, due to the massive and nearly permanent memory CD4 cell depletion from the colonic mucosa during acute HIV infection, resulting in a significantly more porous barrier to small molecules [4], which could include HCV that was introduced into the rectum in semen [5] or rectal fluid coating the penis, fist, or object inserted [6].

The FDA approval of emtricitabine/tenofovir as preexposure prophylaxis (PrEP) against HIV infection in July 2012 changed both the serosorting and the stochastic portions of the equation. HIV-uninfected MSM, relying less on serosorting and condom use to prevent HIV and more on PrEP [7], have become increasingly exposed to the semen and rectal fluid of HIV-infected MSM, who have a higher prevalence of HCV infection. And with the effectiveness of PrEP in preventing HIV, these men could then become HCV-infected while remaining HIV-uninfected, somewhat the converse of the situation of those not using PrEP. We present here a report of 14 MSM using PrEP who remained uninfected by HIV while becoming infected with HCV, including 1 man who was reinfected after clearance of his primary HCV infection.

METHODS

HIV-uninfected MSM using PrEP with suspected sexually acquired HCV infection were referred to the Mount Sinai Medical Center, NYC, and the University of California, San Francisco (SF). The study was approved by the institutional review boards of each of these institutions.

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The criteria for diagnosis of primary HCV infection were detection of HCV viremia in the setting of HCV antibody seroconversion. For HCV reinfection, there was an additional criterion of documentation of a period of at least 12 weeks of aviremia after either treatment-induced or spontaneous clearance. Plasma HCV RNA levels were quantified by assays providing lower limits of quantification of 12 or 15 IU/mL. HCV genotyping was performed by commercial assays.

Behavioral changes after PrEP initiation, risk factors for HCV acquisition, time on PrEP in NYC or SF, laboratory data at the time of HCV diagnosis, and HCV treatment outcomes were obtained through patient report and/or review of electronic medical records.

RESULTS

Fourteen HIV-uninfected MSM on PrEP were diagnosed with HCV infection from 2013 to 2018, 1 of whom became reinfected (1 case 2013, 2 cases 2014, 4 cases 2015, 3 cases 2016, 2 cases 2017, 3 cases 2018). Eleven (79%) of the men lived in NYC. The median age of the 14 men at the time of their primary HCV infections was 35 years, and they had been taking PrEP for a median of 12 months before their primary HCV diagnoses (Table 1). Half reported an increase in behaviors that could result in exposure to HCV after starting PrEP, the most common being decreased condom use and an increase in number of sexual partners.

Thirteen (87%) of the 15 HCV infections were asymptomatic, diagnosed during routine laboratory screening, either due to alanine transaminase (ALT) levels (60%) or HCV surveillance testing with HCV antibody or HCV RNA (27%) (Table 2). Only 2 (13%) were symptomatic. Recreational drug use in the past 6 months, primarily of crystal methamphetamine, was reported by 10 (67%), 5 of whom reported injection use, all of which was methamphetamine. All of the men engaged in receptive anal intercourse, with 12 (80%) reporting at least 10 sexual partners during the 3 months prior to the HCV diagnosis. Six (40%) men had a bacterial sexually transmitting infection (STI) at the time of HCV diagnosis.

Most (80%) HCV infections were genotype 1a. Three (20%) of the HCV infections cleared spontaneously, as determined by multiple undetected HCV RNA measurements over 12 weeks. The remainder of infections were either treated and cured (n = 8, 53%), referred for treatment with unknown outcome (n = 1), or are currently undergoing treatment (n = 3). The 1 man who was reinfected had spontaneously cleared his primary genotype 1a HCV infection and presented 71 weeks later with new genotype 4d HCV viremia and elevated ALT after a trip to Europe that included sex while in Germany; he spontaneously cleared this infection as well.

Table 1. Characteristics of Study Population

Characteristic	Value (N = 14)[a]
Age, y, median (IQR)	35 (31–44)
City of residence, No. (%)	
New York City	11 (79)
San Francisco	3 (21)
Race, No. (%)	
White	9 (64)
Hispanic	2 (14)
Asian	2 (14)
Black	1 (7)
Year of PrEP initiation, median (range)	2015 (2011–2017)
Behavior change after PrEP initiation, No. (%)	
Increased risk	7 (50)
Decreased condom use	6
Increase in number of partners	6
Drug use during sex	1
Changed from top to bottom partner	1
Decreased risk (increased condom use)	1 (7)
No change	3 (21)
Unknown	3 (21)
Time from PrEP initiation to HCV diagnosis, mo, median (IQR)	12 (10–17)
Time from seroconversion to HCV antibody positive, mo, median (IQR)[b]	9 (4–11)

Abbreviations: HCV, hepatitis C virus; IQR, interquartile range; PrEP, preexposure prophylaxis.

[a]Characteristics of first (primary) infection; 1 man had reinfection.

[b]Refers to time from seroconversion from HCV antibody negative to HCV antibody positive.

DISCUSSION

In the decade before the FDA approval of emtricitabine/tenofovir for PrEP in 2012, sexual acquisition of HCV infection was rare in HIV-uninfected MSM compared to HIV-infected MSM. However, since the FDA approval and the increasing prescription of PrEP in our regions we have now documented 15 sexually acquired HCV infections among 14 HIV-uninfected MSM after their initiation of PrEP.

A few other groups have also reported sexually acquired HCV infections in MSM using PrEP. The first report of sexual acquisition of HCV in men using PrEP was from the SF area [8] at about the time the first such infections were seen in NYC. With the subsequent approval of emtricitabine/tenofovir in Europe, a French consortium reported sexually acquired HCV among 10 MSM using PrEP (including 2 who were reinfected), across 13 sites between January 2016 and June 2017, for an overall incidence rate of 1.2 per 100 person-years [9]. Interestingly, this HCV incidence rate was numerically the same as the contemporaneous rate among HIV-infected MSM [9]. Sexually acquired HCV may also have occurred during PrEP use in a placebo-controlled study of PrEP in France, but the report did not specify the distribution between the PrEP and placebo groups of the 5 incident HCV infections [10]. Another French group also recently reported sexually acquired HCV infection among 6 HIV-uninfected MSM, although only 1 of them was using PrEP at the time of the HCV infection [11]. This group also found that the HCV isolates from the HIV-uninfected MSM were

Table 2. Characteristics of Incident HCV Infections

Characteristic	Value, No. (%) (N = 15)[a]
Clinical presentation	
Asymptomatic ALT elevation	9 (60)
HCV screening	4 (27)
Symptomatic	2 (13)
Drug use	10 (66)
Meth ± other drugs	8 (53)
Injection drug use[b]	5 (33)
Other (ecstasy, poppers, THC, LSD, cocaine, ketamine, GHB)	2 (13)
Alcohol use	4 (27)
Anal intercourse during the 3 months prior to HCV diagnosis	
Anal receptive solely	8 (53)
Anal receptive and insertive	7 (47)
Number of sexual partners during 3 months prior to HCV diagnosis	
<10	3 (20)
10–50	7 (47)
>50	5 (33)
STI at time of HCV diagnosis	6 (40)
Syphilis	2
Rectal gonorrhea	2
Rectal *Chlamydia*	3
Rectal spirochetosis	1
Nonrectal *Chlamydia*	2
HCV genotype	
1a	12 (80)
4d	2 (13)
Unknown	1 (7)
HCV treatment	
Spontaneously cleared	3 (20)
Treated and cured	8 (53)
Referred for treatment	1 (7)
Treatment ongoing	3 (20)

Abbreviations: ALT, alanine transaminase; GHB, gamma hydroxybutyrate; HCV, hepatitis C virus; LSD, lysergic acid diethylamide; Meth, methamphetamine; STI, sexually transmitting infection; THC, tetrahydrocannabinol.

[a]Includes 1 man with reinfection.

[b]Injection use was crystal methamphetamine.

phylogenetically closely related, clustering with HCV isolates from HIV-infected MSM, lending evidence to the supposition that MSM using PrEP likely acquired HCV from HIV-infected MSM. This observation of clustering of HCV isolates between HIV-uninfected and HIV-infected MSM had been previously reported among MSM entering a PrEP program, in Amsterdam, in which a surprisingly high 18 out of 375 (4.8%) had current or prior HCV infection [12]. In contrast, however, a similarly sized program in NYC found no HIV-uninfected MSM with serological evidence of HCV among 381 entering a PrEP program [13], possibly suggesting a difference in the threshold in sexual risk behaviors at which men sought PrEP in Amsterdam compared to NYC.

Our study has a few important limitations. We could not determine the incidence rate of HCV infection among MSM using PrEP in our regions as we do not know the number of MSM using PrEP in our referral networks. We also do not know whether all MSM using PrEP in our areas were screened for HCV, that all diagnosed were referred to us, or that all those infected chose to attend the referral visit. Nonetheless, as this is, to our knowledge, the largest number of HCV infections among users of PrEP reported so far, and as these factors would have led to an underestimate of the number of HCV infections, the number of actual HCV infections among MSM using PrEP in SF and NYC is likely higher. We also have not performed a phylogenetic analysis of the HCV isolates in comparison to HCV infections among HIV-infected MSM in our areas, but we have no reason to believe, given the studies from France and the Netherlands, that the situation would be different in US cities.

We would like to note a few other important issues that we determined from clinical history among these men. Most had increases in sexual and drug use behaviors that made them more likely to encounter HCV, but also the more common and infectious bacterial STI. Emtricitabine/tenofovir is as poor in preventing these STI it is at preventing HCV, and therefore the non-HIV consequences of sex without a condom among MSM using emtricitabine/tenofovir are not insignificant, both to these men individually and to the public health. Preventing HIV is crucial, and PrEP is a critical but not sole element of the strategy. We need to develop prevention messages to help decrease the risks of sexual acquisition of HCV in addition to the STI more commonly encountered with the larger-scale adoption of PrEP. We would also note that aside from 1 man who had spontaneous clearance twice, the rate of clearance in this group of HIV-uninfected men was low. To prevent further transmission of HCV, including into HIV-uninfected MSM who are not using PrEP, we therefore suggest that treatment of HCV in HIV-uninfected men be initiated quickly.

Finally, almost all of the HCV infections that we have reported were asymptomatic and detected only through regular laboratory screening during PrEP, which included measurements of ALT and/or HCV antibody. While baseline HCV screening among MSM prior to PrEP initiation is recommended by the Centers for Disease Control and Prevention (CDC) and baseline ALT is often performed, neither of these tests are part of the CDC recommendations during follow-up PrEP visits [14]. In contrast, the American Association for the Study of Liver Diseases/ Infectious Diseases Society of America (AASLD/IDSA) HCV guidelines recommend HCV testing at least annually at follow-up PrEP visits, with more frequent testing warranted depending on sexual or drug use behavior [15]. Hence, while most of the PrEP clinics involved in our cases series performed routine follow-up ALT or HCV testing, this practice was not uniform. As quarterly HIV testing is recommended during PrEP prescribing and elevated ALT is more sensitive than HCV antibody during acute infection, we strongly encourage incorporating ALT testing into this quarterly panel

to facilitate earlier HCV diagnoses. However, because mild ALT elevations may be caused by a number of factors besides HCV, ALT cutoffs to prompt HCV RNA testing among PrEP users are needed. Finally, we support the AASLD/IDSA guidelines to perform HCV antibody screening at least annually for all MSM using PrEP who report multiple sex partners to prevent what might otherwise become an undetected expansion of sexually transmitted HCV infection into HIV-uninfected MSM.

Notes

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