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BRIEF REPORT

Acute Hepatitis A Viral Infection in People With HIV With Previously Documented Hepatitis A Immunity or Appropriate Vaccination: A Case Series

Stephanie E. McLaughlin,[1] Jason D. Simmons,[1] Hilary Armstrong,[2] Elysia Gonzales,[2] Robert M. Rakita,[1] Jeffrey S. Duchin,[1,2] and Rena C. Patel[1,3]

[1]Division of Allergy and Infectious Disease, Department of Medicine, University of Washington, Seattle, Washington, USA, [2]Public Health - Seattle and King County, Seattle, Washington, USA, and [3]Department of Global Health, University of Washington, Seattle, Washington, USA

We describe 4 people with HIV (PWH) who acquired acute hepatitis A (HAV) infection during recent King County, Washington, outbreaks despite documented immunity and/or vaccination. HAV revaccination may be needed in PWH with risk factors for HAV infection regardless of preexisting immunity.

Keywords. hepatitis; HAV; HIV; vaccination.

Hepatitis A (HAV) infection is transmitted fecal-orally through either direct person-to-person contact or consumption of contaminated food or water [1]. HAV has historically caused self-limited symptoms and has resulted in few hospitalizations [1, 2]. However, more recently, hospitalizations have risen as numerous outbreaks have been noted throughout the United States [1, 3].

People with HIV (PWH) are at risk for adverse HAV outcomes, including more profound liver function dysfunction and prolonged viremia and viral shedding [4, 5]. They may also mount a less robust or durable vaccination response than their HIV-negative counterparts [6–8]. While 85% of vaccinated PWH had durable HAV seropositivity postvaccination in a study by Crum-Cianflone et al., the longevity of this HAV antibody response varied markedly from 6 to 10 years. Suppressed HIV viral load and higher CD4 cell counts at vaccination were associated with increased longevity of antibody titers [9].

The newest Centers for Disease Control and Prevention (CDC) guidance recommends vaccinating all PWH age >1 year for HAV [6]. The guidelines also suggest considering booster vaccination of PWH who do not demonstrate an adequate immune response or who later demonstrate an improvement in immune status [6]. However, it remains unclear if PWH who have adequate anti-HAV antibody titers and/or who were vaccinated with high CD4 cell counts should receive HAV booster vaccination, particularly during local HAV outbreaks [6, 10].

Since January 1, 2019, King County has identified 2 separate HAV outbreaks spreading mainly via person-to-person transmission: (1) a small outbreak primarily among men who have sex with men (MSM; November 2018–March 2019) and (2) a large outbreak beginning in April 2019, primarily among persons experiencing homelessness (PEH) or persons who use drugs (PWUD). In the 2 years of these outbreaks, there have been a total of 194 cases of HAV—compared with a previous 10-year range of 5 to 16 cases per year—including 119 (61.3%) hospitalizations and 2 (1.0%) deaths. Of these 194 cases, 68% were male, the median age (range) was 42 (9–78) years, 60.3% occurred among PEH and/or PWUD, and 8.2% occurred among MSM [11]. Beyond King County, Washington state also declared a statewide HAV outbreak among PEH and PWUD in July 2019. Nationally, 35 states have reported similar outbreaks since 2016 [3].

During these local King County outbreaks, we provided clinical care for 4 PWH who developed acute HAV infection despite documented prior immunity or history of vaccination. To better describe any shared risk factors and highlight the limitations of current [re]vaccination guidelines, we present a detailed case series of these 4 individuals.

METHODS

We identified patients with acute HAV infection during outbreak surveillance within the above noted outbreaks. Coauthors on this report initiated a discussion with local public health collaborators when some coauthors identified 2 of these cases through direct patient care at the county hospital. We gathered data from surveillance records, case report forms, and medical records via existing public health and electronic medical records data systems. The University of Washington Human Subjects Division (Institutional Review Board) considered this reporting exempt from human subjects research.

RESULTS

We identified 4 PWH who acquired acute HAV infection between January 2019 and June 2020 despite having no known prior HAV infection and reporting a remote HAV vaccination history (Patients A–C) and/or documented past immunity (via qualitative HAV immunoglobulin G [IgG] positivity years after vaccination; Patient D). All 4 required hospitalization due to

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Correspondence: Stephanie E. McLaughlin, MD, MPH, University of Washington, 1959 NE Pacific St., Box 356423, Seattle, WA 98195 (mclaus02@uw.edu).

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their HAV infection. Details of patient characteristics and their courses are listed in Table 1.

Patient A was a 65-year-old man with chronic kidney disease and chronic heart failure who presented with 1 week of increasing fatigue and myalgias. At the time of acute HAV infection, he denied drug use, was consistently engaged in care and stable on antiretrovirals (ARVs), and was housed in a private apartment.

Patient B was a 38-year-old man who presented with 2 weeks of fevers, severe myalgias, anorexia, and diarrhea. He was also consistently engaged in HIV care and adherent to ARVs. He was stably housed in a private apartment and reported a recent history of inhaled methamphetamine.

Patient C was a 48-year-old man who presented with 3 weeks of progressive abdominal pain, anorexia, and jaundice. Patient C had less consistent antiretroviral adherence than Patients A or B and had recently discontinued ARVs in the setting of gastrointestinal complaints. Patient C had previously experienced homelessness, but at the time of this illness he had supportive housing. He also reported recent inhaled methamphetamine use.

Patient D was a 55-year-old transgender woman, male sex at birth, who presented with 10 days of fatigue, headache, fevers, and dark urine. She was also consistently engaged in HIV care and adherent to ARVs. She also reported housing in a private apartment and denied drug use.

Patients A–D all indicated condomless sex with a new male partner during their exposure period. All patients' liver function and subjective symptoms improved quickly with supportive care. They were discharged to home and returned to their baseline health status.

DISCUSSION

All 4 PWH presented here acquired acute HAV requiring hospitalization despite documented immune response after vaccination and/or prior documentation of HAV vaccination at CD4 >200 cells/mL. Several factors may account for HAV infection despite presumed immunity. First, we know that protective immunity may wane over time and lead to disease acquisition and that immunosuppressed states, such as HIV, may predispose individuals to less durable immunity [4, 7, 10, 12]. Vaccination at a CD4 count >200 is thought to predict long-lasting immunity in PWH [10]. Despite that, the patients in our case series were either vaccinated at a CD4 count >200 (Patient D) or had well-controlled HIV with long-standing undetectable HIV viral loads at the time of HAV vaccination (Patients A–C). Therefore, it is unlikely that secondary failures correlate with profound immune suppression at the time of vaccination in these patients. Accordingly, the reliance on CD4 count alone as an indicator of who will benefit from an HAV booster vaccination is insufficient.

Second, a past or current positive HAV IgG titer may be an unreliable correlate of protection from acute HAV infection in PWH. Neutralizing anti-HAV IgG titers, which are thought to be associated with lifelong protection [13], are significantly lower after inactivated HAV vaccination as compared with natural infection [14]. Total HAV IgG titers are correlated with neutralizing antibody titers [14] where a level of >10 mIU/mL is considered a surrogate correlate of protection in vaccine trials [15]. However, a minimum anti-HAV IgG level that confers protection in real-world situations has not been established. Three patients in our series (A–C) had positive HAV IgG titers both at the time of acute HAV infection and 3–8 years prior, which is consistent with their prior vaccination, although, admittedly, acute infection may have boosted HAV IgG titers. Further study is required to define the mechanisms of these secondary failures and may inform whether the traditional surrogate markers of immunity (ie, ≥10 mIU/mL anti-HAV IgG) should be modified for PWH. Possible mechanisms of these "breakthrough" infections could include a large inoculum related to unprotected anal intercourse, particularly with oral–anal sex, or viral escape phenomenon overcoming any existing immunity. The latter possibility may be less likely given the viral fitness costs measured after mutations in viral capsid-neutralizing epitopes [16] but has been described in prior outbreaks associated with transmission among MSM [17].

Third, self-reported, and even well-documented, complete HAV vaccination may not be evidence of sufficient protection during an outbreak. A related case series detailed 6 male, previously HAV-vaccinated PWH who acquired acute HAV during a 2017–2018 Tennessee outbreak. In this series, over half of those infected had a documented partial or complete HAV vaccination series [18]. The Tennessee report, like ours, substantiates the concern that neither prior vaccination nor positive HAV IgG titers postvaccination can confidently predict protection from HAV infection in PWH during an outbreak.

Given the limitations of using CD4 monitoring, HAV IgG titers, and vaccination history to predict protection from acute HAV in PWH, we suggest that HAV booster vaccination be considered, especially during a local outbreak, based on risk factors for HAV acquisition irrespective of documented prior vaccination or immunity. The risk of HAV infection is higher in MSM [1]; as such, it is possible that anal intercourse, particularly anal–oral sex, delivers a larger HAV inoculum or at least increases rates of fecal–oral transmission as compared with other exposures. In our series, Patients A–C were MSM, and Patient D identified as a transgender woman (male at birth) with similar sexual risk factors for HAV infection. Of note, a limitation of our report is the lack of risk factor analysis with comparator groups, such as persons within the local HAV outbreak not living with HIV. However, no foodborne transmission risk factors were identified in the patients reported in this series. These 4 cases serve as "proof of concept" that some form of prior immunity is not protective against acute HAV infection during local outbreaks among PWH. As such, we posit that

Table 1. Sociodemographic and Clinical Characteristics of PWH who Contracted Acute HAV Infection Despite Previously Documented HAV Immunity or Immunization

		Patient A	Patient B	Patient C	Patient D
Age, y		65	38	48	55
Gender (sex at birth if differs from gender)		Male	Male	Male	Transgender woman (male sex at birth)
Sexual orientation		MSM	MSM	MSM	Sex with men
Housing		Stable, apartment with long-term male partner	Stable, single apartment	Stable, supportive group housing	Stable, single apartment
Illicit drug use		None	Current inhaled methamphetamine use, never IDU	Current inhaled methamphetamine use, past IDU >1 y ago	None
Occupation		Disabled	Ride-share driver	Technician for a meal service company	Unemployed
Year of HIV diagnosis (years between HIAV and HAV diagnosis)		8	14	6	28
CD4 cell count nadir HIV VL history		Unknown nadir UD VL since 2012	Unknown nadir UD VL since 2011	Nadir 736 cells/mL in 2018 Intermittently UD VL	Unknown nadir UD VL (since unknown date)
Antiretroviral medication (at time of HAV diagnosis)		Abacavir, lamivudine, raltegravir	Tenofovir, emtricitabine, bictegravir	Tenofovir, emtricitabine, dolutegravir	Abacavir, lamivudine, dolutegravir
HAV vaccination status (years before HAV diagnosis)		Self-reported prior vaccination (unknown date)	Self-reported prior vaccination (unknown date)	None documented	12, 6 (2-dose series 12 and 6 y prior)
CD4 cell count at HAV vaccination, cells/mL		Unknown	Unknown	Unknown	333
HAV IgG positivity (years before HAV diagnosis)		8	3	3	Not known
CD4 cell count and HIV VL (within year before HAV diagnosis), cells/mL, copies/mL		379, UD	803, UD	800, 1636	1013, UD
Likely source of acute HAV acquisition		Condomless sex with new male partner 2–3 wk prior (not long-term partner)	Condomless sex with new male partner 2 wk prior	Condomless sex with new male partner 2–3 wk prior	Condomless receptive anal sex with new, consistent male partner for 2 mo prior
LFT peak (AST/ALT, total bilirubin), units/L		2732/5049, 5.9	2493/5010, 6.7	1708/4531, 13.1	538/1090, 6.0
Radiologic findings		Normal liver US (no doppler)	Liver US: slightly echogenic liver parenchyma is suggestive of diffuse hepatocellular disease (no doppler)	Liver US with doppler: subtle hepatic parenchymal edema, typical for acute hepatitis, no vascular anomalies, thrombosis, or biliary obstruction	None
Other workup	HCV	HCV Ab and PCR neg	HCV Ab neg	HCV Ab neg	HCV Ab neg
	HBV	HBV sAb pos HBV sAg neg HBV PCR neg	HBV sAb pos HBV sAg neg	HBV sAb pos HBV sAg neg	HBV sAg neg
	CMV	PCR neg	IgM and IgG neg	PCR neg	Not known
	HSV	PCR neg	Reactive IgG	PCR neg	Not known
	Autoimmune	ANA neg (8 y prior)	ANA neg	ANA neg, anti-smooth muscle Ab pos 1:80	ANA neg (12 y prior)
STI testing at admission		Urine GC/CT NAATs neg	Syphilis neg	Syphilis neg Rectal and pharyngeal GC/CT NAATs neg	RPR pos (titer 1:32) Urine GC/CT NAATs neg
HAV IgM at admission (Ig level if known, g/L)		Pos[b]	Pos[b] (7.10)	Pos[b] (10.8)	Pos[b]
HAV IgG at presentation (Ig level if known, g/L)		Pos[a] (level unknown)	Pos[a] (3.9)	Pos[a] (3.8)	Not known
HAV PCR (at admission)		Pos	Pos	Pos	Pos

Abbreviations: Ab, antibody; ANA, antinuclear antibody; CMV, cytomegalovirus; CT, chlamydia; GC, gonorrhea; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; IDU, intravenous drug use; Ig, immunoglobulin; LFTs, liver function tests; MSM, men who have sex with men; NAAT, nucleic acid amplification test; PCR, polymerase chain reaction; RPR, rapid plasma regain; STI, sexual transmitted infection; TGNB, transgender and nonbinary; UD, undetectable; VL, viral load.

[a]Positive >1.21 (s/co).

[b]Positive >1.0 (s/co).

certain sexual behaviors historically associated with MSM, such as anal–penile sex or anal–oral sex, reported by PWH should prompt consideration of an HAV booster vaccination during a local outbreak.

HAV risk factors, such as homelessness (PEH), drug use (PWUD), and predisposing sexual behaviors, often coexist within individual patients and patient populations. A comprehensive social history, including a detailed history of drug use and specific sexual behaviors, will help clinicians identify PWH who may benefit from booster vaccination during an outbreak.

Single booster vaccination has been shown to generate sufficient immune response in PWH [6, 10, 12]. Nevertheless, future clinical guidelines should be informed by modeling and cost-effectiveness studies that evaluate both vaccine manufacturing and distribution costs as well as the high cost of HAV outbreak–associated hospital care [19]. Logistical considerations, such as supply or administration during the coronavirus disease 2019 pandemic, must also be accounted for in future public health policy regarding HAV booster vaccination.

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