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BRIEF REPORT

Continued Low Rates of Hepatitis C Virus (HCV) Recurrence in HCV/HIV- and HCV-Infected Participants Who Achieved Sustained Virologic Response After Direct-Acting Antiviral Treatment: Final Results From the AIDS Clinical Trials Group A5320 Viral Hepatitis C Infection Long-term Cohort Study (V-HICS)

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Final results from the long-term Viral Hepatitis C Infection Long-term Cohort Study (V-HICS) found low rates of hepatitis C virus (HCV) recurrence after direct-acting antiviral therapy in both HCV/human immunodeficiency virus (HIV)–coinfected (0.67/100 person-years) and HCV-infected (0.2/100 person-years) groups with >500 person-years of follow-up. Confirmed reinfections were in participants with HIV who reported high-risk behaviors.

Keywords. direct-acting antivirals; hepatitis C; HIV; recurrence.

Hepatitis C virus (HCV) recurrence after direct-acting antiviral (DAA) treatment may be due to relapse of the original infection or reinfection. Treatment failure (relapse) with modern DAA regimens is rare (<5%), particularly after a sustained virologic response (SVR) 12 weeks following therapy completion (SVR_{12}), where rates of late relapse are <0.5% [1, 2]. In contrast, rates of reinfection are variable and typically categorized based on the primary perceived risk behavior for initial acquisition. Persons living with human immunodeficiency virus (PLWH), particularly those who identify as men who have sex with men (MSM), and persons who inject drugs are the 2 groups often cited as having the highest rates of reinfection [3–6].

Data from prospective, long-term cohorts contemporaneously enrolling both human immunodeficiency virus (HIV)–infected and -uninfected groups after HCV DAA treatment are lacking. Additionally, most reports describing high rates of HCV recurrence in the setting of HIV are from cohorts primarily composed of MSM with acute HCV infection [7–9]. Additional data are needed for a balanced and accurate representation of HCV recurrence rates in the broad PLWH population. In a preliminary report representing a total of 478 person-years (PY) of follow-up in both HIV/HCV and HCV groups, we found low and similar rates of reinfection (0.35 and 0.52 per 100 PY, respectively) [10]. We now present recurrence data through the end of Viral Hepatitis C Infection Long-term Cohort Study (V-HICS) follow-up, which was up to 5 years.

METHODS

The AIDS Clinical Trials Group (ACTG) A5320 (V-HICS) was a prospective, long-term follow-up study that enrolled HCV/HIV-coinfected and HCV-infected participants within 1 year of completion of DAA-based HCV treatment in clinical trials or in practice. Participants were enrolled into 4 groups based on HIV coinfection status and HCV DAA treatment response (group A: HCV/HIV, non-SVR; group B: HCV non-SVR; group C: HCV/HIV, SVR; group D: HCV, SVR). Additional details of the study have been described previously [10].

Study visits were conducted every 6 months through a planned follow-up of up to 5 years. Annual visits included clinical assessments, a physical examination, and collection of basic laboratory parameters and imaging/fibrosis staging studies as well as phlebotomy for annual assessment of HCV RNA in groups C and D. Cirrhosis status was assigned based on medical history (at entry) and ongoing clinical diagnosis collected during follow-up. In addition, data for Fibrosis-4 Index for Liver Fibrosis (FIB-4) calculation was collected at every visit. Substance use history at any time prior to V-HICS entry was collected at baseline. Alcohol and behavioral risk assessments were conducted at annual visits including assessment of risk behaviors pertinent to HCV reinfection. Semiannual visits were limited to brief clinical assessment and phlebotomy for specimen banking.

For the final recurrence analysis, all participants in SVR groups C (HCV/HIV) and D (HCV) were included regardless of duration of follow-up. SVR was defined as having achieved HCV RNA less than the lower limit of quantification (LLOQ)

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at least 12 weeks after completion of DAA treatment with no known subsequent HCV RNA ≥ LLOQ prior to V-HICS entry. HCV recurrence was defined as newly quantifiable HCV RNA after study entry and expressed as recurrence per 100 PY of follow-up with a 2-sided 95% Poisson confidence interval (CI). Start of follow-up time was defined as the date of HCV treatment completion. HCV genotype determination (VERSANT HCV Genotype 2.0 assay [line probe assay], Siemens) on stored plasma samples at the time of recurrence was compared to genotype obtained prior to treatment. Additional stored samples were assayed (if available) to refine the timing of HCV recurrence.

RESULTS

From March 2014 to March 2018 a total of 332 participants were enrolled into the V-HICS study including 130 in HCV/HIV SVR and 125 in HCV SVR (Table 1). Planned accrual was completed into HCV/HIV in August 2016 and into HCV in December 2016. Given slow enrollment into the non-SVR groups (n = 77 combined), study follow-up was terminated in November of 2019.

Both SVR groups were predominantly male with similar proportion of Black race and minimal reported injection drug use (IDU) at enrollment (≤1%). Most participants initially had HCV genotype 1a and 11% reported cirrhosis. The HIV/HCV group was younger and had well-controlled HIV; longer follow-up and more frequent initial treatment in a clinical trial in the HCV/HIV group reflects rapid enrollment by ACTG sites that also participated in HCV/HIV DAA clinical trials when the V-HICS study opened to accrual. This was prior to amendment 2.0, which expanded to treatment in the clinical care setting.

The median duration of follow-up was 262 weeks in HCV/HIV and 225 weeks in HIV. Five confirmed HCV recurrences were observed during follow-up (Table 2), including 4 over 593.35 PY for HCV/HIV and 1 over 507.08 PY in HCV, resulting in recurrence rates of 0.67/100 PY (95% CI, .25–1.80) and 0.20/100 PY (95% CI, .03–1.40), respectively (Table 1). All participants with confirmed (genotype switch) or probable reinfections reported substance use/IDU or high-risk sexual behaviors during the study (Table 2).

A sixth participant (HCV group) was reported to have detectable HCV RNA at study week 104. Genotyping was unsuccessful

Table 1. Sustained Virological Response Group Characteristics and Recurrence Rates

Characteristic<?Char=Text?>	HCV/HIV Coinfection (n = 130)	HCV Infection (n = 125)
Age, y, median (min–max)	53 (19–69)	59 (23–83)
Male sex at birth	81%	74%
Non-Hispanic White/Black	34%/43%	44%/41%
HIV RNA less than the LLOQ	95% (n = 124)	NA
CD4 count, cells/μL, median (Q1, Q3)	700 (483, 890) (n = 115)	NA
Prior[a]/current IDU reported at V-HICS entry	43%/0%	47%/1%
Any prior[a] recreational drug use	77% (n = 117)	84% (n = 117)
Marijuana	66%	76%
Cocaine	51%	68%
Heroine	30%	36%
Amphetamines	23%	34%
Methamphetamines	17%	22%
Barbiturates	17%	33%
Other street drugs	15%	11%
Prescription drugs	31%	36%
Prior[a] methadone treatment		
Ever[a]	8%	20%
Never	84%	74%
Unknown/missing	8%	6%
Methadone treatment at V-HICS entry	2%	7%
IDU reported at any time on study	5%	6%
Pre-DAA genotype: 1a/3	67%/2%	61%/0% (n = 109)
FIB-4 score >3.25	6% (n = 127)	7% (n = 123)
Treated in a clinical trial	86%	39%
Median weeks since completion of therapy (min–max)	262 (23–343)	225 (39–327)
Follow-up since DAA completion, PY	593.35	507.08
HCV recurrences, No.	4	1
Incidence rate (95% CI)	0.67/100 PY (.25–1.80)	0.20/100 PY (.03–1.40)

Abbreviations: CI, confidence interval; DAA, direct-acting antiviral; FIB-4, Fibrosis-4 Index for Liver Fibrosis; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug use; LLOQ, lower limit of quantification; NA, not applicable; PY, person-years; Q1, quartile 1; Q3, quartile 3; V-HICS, Viral Hepatitis C Infection Long-term Cohort Study.

[a]Prior or ever refers to at any time before entering the V-HICS study.

Table 2. Detailed Characteristic of Recurrences

Group	Genotype (Initial/ Recurrence)	Initial DAA Regimen	Weeks Since DAA Completion	Cirrhosis	On-Study Self-Reported Risk Behaviors	Recurrence Type	Retreatment Outcome
HCV/HIV	1/ND	SOF + RBV 12 wk	176	No	MSM, multiple partners, anal receptive sex, sex toys/fisting	Probable reinfection	SOF/LDV 12 wk; SVR_{12}
HCV/HIV	1b/3a	SOF/LDV 12 wk	93	No	Drug use[a]; injection and noninjection	Definite reinfection	GLE/PIB 8 wk; SVR_{12}
HCV/HIV	1a/3	SOF + DCV 12 wk	277	Yes	Drug use[b]; injection and noninjection	Definite reinfection	NA
HCV/HIV	1a/1a	PTV/OBV/r + DSV + RBV 24 wk	168	Yes	MSM, multiple partners, anal receptive	Probable reinfection	NA
HCV	1a/1a	SOF + SIM 12 wk	37	Yes (decompensated)	None reported	Probable relapse	SOF/LDV + RBV 24 wk; SVR_{12}

Abbreviations: DAA, direct-acting antiviral; DCV, daclatasvir; DSV, dasabuvir; GLE, glecaprevir; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDV, ledipasvir; MSM, men who have sex with men; NA, not applicable; ND, not done; OBV/r, ombitasvir/ritonavir; PIB, pibrentasvir; PTV, paritaprevir; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; SVR_{12}, sustained virologic response 12 weeks following therapy completion.

[a]Substance use history questionnaire that captured specifics on the drugs was not completed.

[b]Substance use history questionnaire completed at study entry indicated prior use of marijuana, heroin, amphetamines, methamphetamines, other street drugs, and prescription drugs.

and a repeat HCV RNA on a backup sample yielded an HCV RNA of <15 IU/mL. HCV RNA at week 118 was also <15 IU/mL and the initial test was considered a false positive.

DISCUSSION

In this final analysis of HCV recurrence following SVR_{12} after DAA therapy in the V-HICS cohort, we found low rates of recurrent HCV infection regardless of HIV coinfection status. Given the small number of events in both groups, no significant difference in recurrence rates was found. Put into context, the low rates of recurrence seen in our cohort are in the range (0.3–0.5/100 PY) reported from population-based studies for HCV treated persons without IDU or HIV [3, 11]. The low and similar recurrence rates, regardless of HIV status, may be due in part to the unique nature of the V-HICS cohort. Under version 1.0 of the protocol, only persons treated in a clinical trial were eligible to enroll; this requirement was removed in version 2.0 and participants enrolled after June 2015 could have been treated for their HCV in clinical practice. Due to rapid enrollment of the HCV/HIV SVR group, 86% were treated in a clinical trial (only 39% in HCV SVR group). Clinical trial participants are a unique subset of patients seen in the clinic, and many early-stage HCV clinical trials excluded persons with ongoing substance use, biasing early enrollment against participants at higher risk for HCV reinfection. Additionally, while enrollment after treatment for acute HCV infection was not excluded, at the time few clinical trials were being conducted in acute HCV. Specific data on whether the initial treatment regimen was for acute infection was not collected; however, in the HCV/HIV group only 4 (3%) participants were in an acute HCV treatment trial. By definition, acute HCV infection is a high-risk condition for HCV reinfection and this has been shown to particularly be the case for HIV-infected MSM [7–9]. This population was underrepresented in V-HICS.

Despite the primary findings, recurrence rates were numerically higher in the HCV/HIV group, most being definite or probable reinfections. In contrast, the lone recurrence in the HCV group may have been a late relapse. While late HCV RNA relapse after DAA therapy is rare, this participant had a number of features suggestive of this phenomenon: a relatively short time from completion of DAA therapy to recurrence detection, disease characteristics increasing the risk for treatment failure (genotype 1a and decompensated cirrhosis), a suboptimal regimen in the setting of cirrhosis (sofosbuvir + simeprevir for 12 weeks), and lack of known risk factors for reinfection [1]. Without phylogenetic analysis, a definitive determination is not possible.

It should be noted that V-HICS was not specifically designed to assess risk factors for HCV recurrence, and collection of substance use data was limited. Furthermore, the small number of recurrences precluded further statistical analysis of risk for recurrence within the cohort. Despite these limitations, all

recurrences in the HCV/HIV group were related to either IDU or the interplay of HIV, high-risk sex practices in MSM, and substance use. These are not novel findings and support risks for reinfection identified in prior studies [5, 12, 13]. They highlight the need for improved support services for IDU, such as opiate agonist therapy and syringe service programs, to be provided in conjunction with widespread delivery of DAA therapy.

In summary, we found low rates of HCV recurrence after DAA treatment in a long-term prospective cohort of HIV-coinfected and HIV-uninfected participants regardless of HIV coinfection status. These data suggest that HIV infection itself probably plays a modest role in modulating risk for HCV reinfection, with HCV reinfection risk being dominated by behaviors that may be more prevalent in PLWH such as high-risk or traumatic sexual practices in MSM and substance use including IDU. The overall low recurrence rates in our study are encouraging for meeting World Health Organization elimination goals in PLWH as a microelimination group. However, the emergence of similar risk behaviors in the reinfections highlight challenges for elimination in subpopulations of PLWH, such as HIV-positive MSM with substance use. Developing more accessible and effective interventions to prevent HCV reinfections after DAA treatment in high-risk groups will be key to attaining HCV elimination in these populations.

Notes

Patient consent statement. The study protocol was designed, reviewed, and approved within the AIDS Clinical Trials Network. Local institutional review board approval was obtained at all network sites participating in the study. Written informed consent was obtained from all study participants.

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