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BRIEF REPORT

Similar Low Rates of HCV Recurrence in HCV/HIV- and HCV-Infected Participants who Achieved SVR After DAA Treatment: Interim Results From the ACTG A5320 Viral Hepatitis C Infection Long-term Cohort Study (V-HICS)

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Hepatitis C virus (HCV) recurrence rates were similar between those with HCV/HIV co-infection (0.35/100 person-years) and HCV infection (0.42/100 person-years). Low rates of recurrence likely represent enrollment of an HIV population at low risk for recurrence. Care should be taken not to label all HCV/HIV co-infected patients as being at high risk for HCV recurrence.

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

Hepatitis C virus (HCV) infection is prevalent in persons with HIV due to shared routes of transmission. In particular, high-risk sexual practices appear to be associated with significant rates of HCV transmission in HIV-positive men who have sex with men (MSM), as demonstrated by several outbreaks [1–3]. Risk factors for incident HCV infections in these studies have included anal receptive sex, multiple partners, the use of sex toys, and the use of noninjection recreational drugs [4, 5]. Although these studies focused on incident HCV infection, these same risk behaviors may also lead to re-infection with HCV after clearance—either spontaneous or antiviral therapy induced.

Direct-acting antiviral (DAA) regimens are widely available and have been shown to be equally effective in HIV co-infected persons achieving sustained virologic response (SVR) in excess of 95%. However, eradication of HCV in an individual through drug therapy does not offer any significant protection from re-infection if prior risk behaviors are not altered. A high rate of re-infection could negate the benefits of HCV treatment at both an individual and community level. A number of studies have demonstrated increased rates of hepatitis C virus (HCV) recurrence after SVR in HCV/HIV co-infected persons [6–9]. However, several of these studies are limited by inclusion of population almost exclusively consisting of HIV+ MSM with acute or recent HCV infection [6–8].

In the setting of limited data on the rates of and risk factors for HCV re-infection after DAA treatment in those with HIV, the potential to label all patients with HIV and HCV co-infection at "high-risk" for re-infection exists and could lead to stigmatization and withholding treatment. Additional data are needed to better estimate the HCV recurrence risk in those with HIV co-infection and, if possible, delineate risk factors for recurrence. We sought to assess the rate of HCV recurrence after SVR in the Viral Hepatitis C long-term Infection Cohort Study (V-HICS) using interim data.

METHODS

The AIDS Clinical Trails Group (ACTG) is a network of linked clinical research sites that execute research protocols on HIV and related conditions, including HCV. ACTG A5320 (V-HICS) is a 5-year prospective study where HCV/HIV and HCV participants enroll within 1 year of completion of DAA-based HCV treatment in clinical trials or in practice. HCV DAA-treated participants are enrolled into 1 of 4 groups based on HIV co-infection status and HCV treatment response (Group A: HCV/HIV, non-SVR; Group B: HCV, non-SVR; Group C: HCV/HIV, SVR; Group D: HCV, SVR). Additional enrollment limits specified that no more than 30% per group could have been treated with interferon plus a DAA, 10% per group could have been treated with telaprevir or boceprevir, and no more than 75% of any group could have received sofosbuvir as a component of their DAA regimen. Hepatitis B surface antigen–positive persons are excluded from enrollment. Version 1.0 of the study restricted enrollment to persons treated in an HCV clinical trial; version 2.0 of the study opened enrollment to any DAA-treated person.

Study visits were conducted every 6 months, with a planned follow-up of 5 years. Annual visits included clinical, alcohol, and behavioral risk assessments, a physical exam, and collection of basic laboratory parameters and imaging or fibrosis staging studies as well as phlebotomy for assessment of HCV RNA and genotype. Semi-annual visits are limited to an updated clinical assessment and phlebotomy for banked specimens.

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For the current analysis on interim data, participants in Groups C (HCV/HIV co-infected, n = 130) and D (HCV mono-infected, n = 125) who achieved SVR and had at least 1 year of follow-up in V-HICS were considered. SVR was defined as having achieved an HCV RNA of less than lower limit of quantification (LLOQ) at least 12 weeks after completion of DAA treatment with no known subsequent HCV RNA ≥LLOQ before V-HICS entry. HCV recurrence was defined as newly quantifiable HCV RNA after study entry and expressed as recurrence per 100 person-years (p-y) of follow-up with a 2-sided 95% Poisson confidence interval. HCV genotype determination (VERSANT HCV Genotype 2.0 assay [LiPA], Siemens) on stored plasma samples at the time of recurrence was compared with historical genotype obtained before DAA treatment. Additional stored samples were assayed (if available) to refine the timing of HCV recurrence.

RESULTS

VHICS enrollment began in March 2014; version 2.0 of the study, which allowed enrollment from clinical care and clinical trials, opened to enrollment in March of 2015. Accrual to the SVR groups closed in August of 2016 for Group C (HCV/HIV, n = 130) and in December 2016 for Group D (HCV, n = 125). A total of 205 participants from Groups C and D had ≥52 weeks of follow-up: 116 HCV/HIV and 89 HCV (Table 1). The HCV/HIV group was younger (53 vs 59 years), with a high proportion of participants identifying as black race in both groups. Both groups reported high rates of ever using recreational drugs (77% HCV/HIV and 85% HCV), with low rates of reported current use (<1%). The median time between treatment completion and V-HICS entry was 30 weeks, with the majority previously treated in clinical trials (72%).

Two HCV recurrences (1 Group C and 1 Group D) were detected over a combined 478.1 person-years of follow-up, resulting in similar HCV incidence rates between the 2 groups (Table 1). The HCV/HIV participant had recurrence detected 93 weeks (HCV RNA 354 000 IU/mL) after completion of 12 weeks of sofosbuvir/ledipasvir. HCV genotype was 1b before treatment and 3a at recurrence (on a unique sample), suggesting re-infection. The participant was a 48-year-old white female with a remote history of injection drug use. She did not report risk factors for re-infection such as injection drug use or high-risk sexual practices. At the time of data analysis, the participant had not undergone retreatment. The second recurrence occurred in a 50-year-old white male HCV participant with cirrhosis 37 weeks after completion of 12 weeks of sofosbuvir plus simeprevir. HCV RNA was 21 IU/mL at week 37, 160 IU/mL at week 43, and 12 373 IU/mL at week 50. Risk factors for re-infection included drug use at study entry (cocaine, route not specified but intravenous drug use not reported); genotype was 1a before treatment and at recurrence. The participant was subsequently re-treated with sofosbuvir/ledipasvir plus ribavirin for 12 weeks and attained SVR12 again.

DISCUSSION

We found similar low rates of HCV recurrence in HCV and HCV/HIV co-infected participants. Given a lack of pretreatment samples from which to conduct detailed phylogenetic analyses, we cannot determine whether both recurrences were re-infections. The HCV/HIV participant almost certainly experienced a re-infection given the genotype switch and late timing of recurrence. Although the participant did not self-report risk factors, appearance of genotype 3a may suggest injection drug use as this genotype is prevalent among PWID [10]. In contrast, the second recurrence occurred in an HCV mono-infected participant with cirrhosis who had been treated in a clinical trial with a shorter regimen than would currently be recommended, increasing the risk for viral relapse. Recurrence was with the

Table 1. Demographics and HCV Recurrence Rates

	HCV/HIV (n = 116)	HCV (n = 89)
Median age in years (min–max)	53 (19–69)	59 (25–74)
Male, %	78	75
Non-Hispanic white/black, %	37/45	46/39
HIV RNA <LLOQ, %	95 (n = 111)	N/A
Median CD4 (Q1, Q3), cells/mm^3	707 (492, 890) (n = 102)	N/A
Prior/current injection drug use, %	44/0	48/1
Any prior recreational drug use, %	77 (n = 106)	85 (n = 85)
Pre-DAA GT: 1a/1b, %	64/23	63/23 (n = 79)
FIB-4 >3.25, No. (%)	6 (n = 112)	7 (n = 85)
Treated in a clinical trial, %	87	53
Median weeks from completion of therapy to study entry (min–max)	30 (7–63)	32 (14–52)
Median weeks since completion of therapy (min–max)	122 (80–203)	101 (66–187)
Follow-up, p-y	287.5	190.6
HCV Recurrences, No.	1	1
Incidence rate (95% CI), p-y	0.35/100 (0.01–1.94)	0.52/100 (0.01–2.92)

Abbreviations: FIB-4, Fibrosis-4 Index; HCV, hepatitis C virus; LLOQ, lower limit of quantification; p-y, person-years.

same genotype, although genotype 1a is most prevalent in the Unietd States, and occurred relatively early after treatment. However, even if this last recurrence is considered a relapse, a single re-infection in the HCV/HIV group compared with none in the HCV group would not result in a significant difference in re-infection rates.

A number of factors may be contributing to the lower recurrence rates seen in HCV/HIV participants in our study compared with other studies. Compared with the recent study by Ingiliz et al., our population is older (53 vs 39 years) with a higher rate of HIV viral suppression (95% vs 82%), suggesting a demographically different HCV/HIV population that may be at lower risk for incident HCV infection [8]. In addition, studies and meta-analyses with a high rate of recurrence in those with HIV have reported on a primarily acutely HCV-infected HIV population—which by definition would be at high risk for re-infection [6–8]. The majority of participants in our cohort are predicted to have had chronic infection. Specifically, for HCV/HIV participants, 101 (87%) were enrolled after treatment in a clinical trial, and only 2/101 were in a trial for acute HCV infection.

Limitations to the generalizability of our data include a predominantly clinical trial–treated population and enrollment up to a year after the end of treatment, potentially excluding high-risk individuals with early re-infection. Finally, the current results are based on evolving interim data from an ongoing study.

In conclusion, we found low rates of HCV recurrence after DAA therapy in our cohort, predominantly treated for chronic infection, regardless of HIV co-infection status. We surmise that the low recurrence rate in HCV/HIV co-infected participants in our study is mainly due to inclusion of a fundamentally different population than other studies documenting high recurrence rates. Our data do not dissuade from the need for improved harm reduction strategies, particularly in HIV+ MSM with acute HCV infection. Rather, they inform the discussion of recurrence risk and highlight that not all HCV/HIV populations are likely to be at high risk for HCV re-infection.

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