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BRIEF REPORT

Optimal Frequency of Hepatitis C Virus (HCV) RNA Testing for Detection of Acute HCV Infection Among At-risk People With Human Immunodeficiency Virus: A Multicenter Study

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Using 3-stage pooled-plasma hepatitis C virus (HCV) RNA testing performed quarterly among at-risk people with human immunodeficiency virus (PWH), we found that if testing had been performed every 6 or 12 months, 58.6%–91.7% of PWH who recently acquired HCV would be delayed for diagnosis and might contribute to onward HCV transmission with longer durations.

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Hepatitis C virus (HCV) infection has emerged as a sexually transmitted infection (STI) among people with human immunodeficiency virus (PWH) in the past 2 decades worldwide [1]. Although highly effective direct-acting antiviral agents (DAAs) against HCV have successfully decreased the incidence and prevalence of HCV viremia among PWH [2, 3], HCV reinfections continue to pose challenges to HCV microelimination [2, 4, 5]. PWH who are men who have sex with men (MSM) or have recently acquired HCV infection are at the highest risk of HCV reinfection following treatment [5]. To mitigate the risk of onward transmission, timely identification of individuals with acute HCV infections or HCV reinfections and initiation of effective treatment are crucial. Regular and frequent HCV testing, rather than testing performed based on clinical symptoms or abnormal laboratory data, is the recommended approach to timely diagnosing individuals with newly developed HCV viremia [4].

Currently, the World Health Organization (WHO) recommends 3- to 6-monthly testing for HCV viremia for people at ongoing risk and having had a history of treatment-induced or spontaneous clearance of HCV infection [6]. We recently developed a cost-effective, 3-stage pooled-plasma HCV RNA testing to detect HCV viremia every 3 months among PWH at high risk for HCV transmission and have successfully identified PWH with HCV viremia who were linked to prompt DAA treatment [7]. The present study aimed to evaluate the impact of testing frequency on the delay of diagnosing newly acquired HCV viremia among at-risk PWH.

METHODS

Study Population and Setting

HCV testing, including anti-HCV antibody or HCV RNA testing, is recommended for PWH once annually according to the national HIV treatment guidelines in Taiwan; more frequent HCV testing could be conducted as dictated by the clinical presentations of STIs and elevations of transaminases. In Taiwan, DAAs were reimbursed once by the National Health Insurance after 2017; starting in 2021 a second course of reimbursed DAA treatment could be administered for any individuals with HCV reinfections or relapses. Hepatologists and primary HIV care physicians are authorized to provide HCV treatments for eligible PWH.

This multicenter, prospective study recruited PWH receiving HIV care at 10 designated hospitals around Taiwan. The populations at high risk for HCV infection included PWH

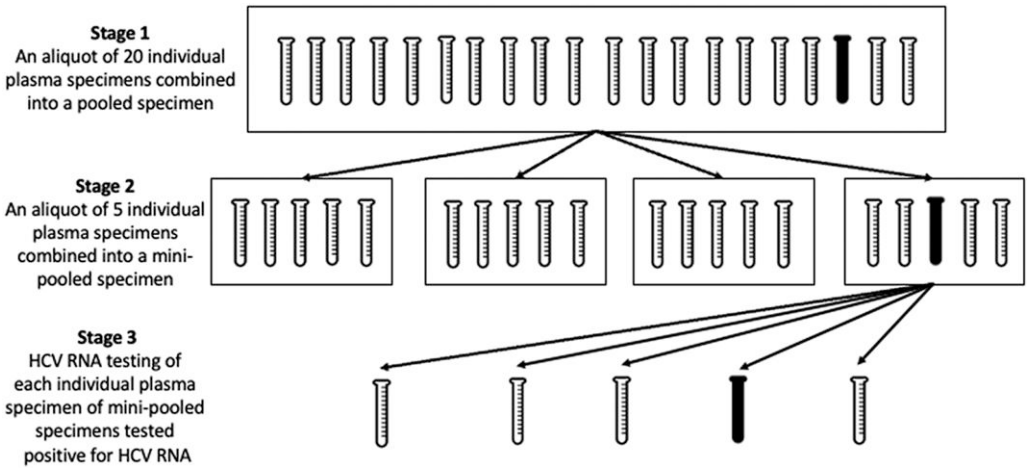

Figure 1. Procedure of the 3-stage pooled-plasma hepatitis C virus (HCV) RNA testing. The black test tube denotes the specimen with positive HCV RNA.

with STIs or elevated aminotransferases within the past 6 months of enrollment, spontaneous HCV clearance, or achievement of sustained virological response (SVR) by antivirals. Individuals with untreated HCV viremia were excluded.

The study participants underwent 3-stage, pooled-plasma HCV RNA testing every 12 weeks or as clinically indicated. The methods have been previously described [7]. In brief, 20 individual specimens were combined into a pool in stage 1; if the pool tested positive for HCV RNA in stage 1, 5 individual specimens were combined into a mini-pool in stage 2. The individual specimens of the mini-pool that tested positive for HCV RNA in stage 2 were tested for HCV RNA in stage 3 (Figure 1). Participants were followed until the detection of HCV RNA, loss to follow-up, death, or completion of 48-week follow-up. Participants with newly identified HCV viremia by this strategy were advised to return to the clinic to undergo further blood testing, including HCV RNA load and HCV genotyping, for assessment of the eligibility for the National Health Insurance–reimbursed DAAs. To calculate the incident rate, acute HCV infection was defined as occurrence of HCV viremia within the past 3 months. The estimated date of acute HCV infection was defined as the first date of HCV RNA detected after enrollment.

Patient Consent Statement

The study was approved by the institutional review board or research ethics committee of the participating hospitals. Patients' written consent was obtained.

RESULTS

From June 2019 to January 2023, a total of 2114 PWH were enrolled and 98.6% were MSM (Table 1). The majority of the participants were enrolled due to STIs (75.8%), achievement of SVR by antivirals (25.1%), and elevated aminotransferases (15.1%). At enrollment, all participants were receiving antiretroviral therapy, 96.8% had CD4 count >200 cells/μL, and 91.7% had achieved undetectable plasma HIV RNA levels (<50 copies/mL).

As of 31 January 2023, 126 cases of HCV viremia were identified. With the exclusion of 68 (54.0%) cases that were detected at enrollment, 58 (46.0%) with a mean plasma HCV RNA of 5.47 (range, 1.30–7.83) $\log_{10}$ IU/mL were identified during a total of 1403.5 person-years of follow-up (PYFU), leading to an incidence rate of acute HCV viremia of 41.32 cases per 1000 PYFU. Of them, 69.0% were enrolled due to STIs, 27.6% had been treated with anti-HCV agents, 42.1% had positive anti-HCV at enrollment, and 27.6% had negative anti-HCV on detection of HCV viremia. Except for 1 patient who did not return for HCV RNA testing, 3 (2.4%) had spontaneous HCV clearance and only 13 (10.4%) had a >2-log decline in plasma HCV RNA levels after a median follow-up interval of 22 days (interquartile range, 12–45 days).

If the serum HCV RNA testing had been performed every 6 or 12 months, the incidence rate of HCV viremia would decrease to 41.05 and 40.48 cases per 1000 PYFU, respectively. Of note, the diagnosis of acute HCV viremia would have been delayed in 34 of 58 (58.6%) cases at month 6 (mean HCV RNA, 6.01 [range, 2.48–7.77] $\log_{10}$ IU/mL) and 53 of 58 (91.4%) cases at month 12 (mean plasma HCV RNA, 5.52 [range, 1.30–7.82] $\log_{10}$ IU/mL), respectively, which might potentially contribute to 3462 and 10 501 infectious days, respectively.

DISCUSSION

Our study showed that diagnosis of HCV viremia would have been delayed in a significant proportion (58.6%–91.4%) of

Table 1. Characteristics of the Participants at Risk for Hepatitis C Virus Infection

Characteristics	No. (%)
Age, y, mean ± SD	37.3 ± 8.4
Male sex	2112 (99.9)
Risk group of HIV transmission	
MSM	2085 (98.6)
Heterosexuals	11 (0.5)
Injecting drug users	18 (0.9)
Criteria of enrollment	
Sexually transmitted infections	1602 (75.8)
SVR 12 wk off-therapy	531 (25.1)
Spontaneous HCV clearance	76 (3.6)
Elevated aminotransferases	320 (15.1)
Percentage of positive anti-HCV at enrollment	585/2085 (28.1)
Status of HIV infection at enrollment	
CD4 count >200 cells/μL	2026/2093 (96.8)
Plasma HIV RNA load <50 copies/mL	1934/2108 (91.7)
Use of antiretroviral therapy	2114 (100)
Follow-up duration	
Total duration, person-years	1403.5
Duration/case, person-years, mean ± SD	277.7 ± 94.6
Time point of the last follow-up as of 31 January 2023	
Day 1	497 (25.2)
Unscheduled date	1 (0.1)
Month 3	170 (8.6)
Month 6	204 (10.3)
Month 9	169 (8.6)
Month 12	931 (47.2)
Identified HCV viremia after enrollment	
Total No.	126 (100)
Cases with negative anti-HCV at HCV viremia	30/126 (23.8)
The time point when HCV viremia was identified	
Day 1	68 (54.0)
Unscheduled date	1 (0.8)
Month 3	18 (14.3)
Month 6	19 (15.1)
Month 9	15 (11.9)
Month 12	5 (4.0)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; MSM, men who have sex with men; SD, standard deviation; SVR, sustained virological response.

the at-risk population and potentially contributed to a remarkably high number of infectious days (3462–10 501) if plasma HCV RNA testing were conducted every 6 or 12 months, instead of every 3 months, suggesting that "the more you look, the more you find" [8]. Furthermore, 27.6% of PWH with newly developed HCV viremia were HCV seronegative in this study, indicating they had acute HCV infection. In the InC^3 study, among the 160 participants with well-characterized acute HCV infection (defined as infection being diagnosed within 3 months after HCV infection with the peak and subsequent HCV RNA levels <120 days), their median peak plasma HCV RNA during the first 3 months following infection ranged from 5.3 to 6.5 $\log_{10}$ IU/mL, no matter if viral plateau with persistence (41%), partial viral control with persistence (27%), or spontaneous clearance (32%) developed subsequently [9]. Likewise, our 58 PWH who developed new HCV viremia during follow-up also had a high plasma HCV RNA load of 5.47 (range, 1.30–7.83) $\log_{10}$ IU/mL. For PWH, the rate of spontaneous HCV clearance is lower than that in people without HIV infection [10]. Thus, without timely diagnosis and intervention, those with viral persistence may contribute to onward HCV transmission through sexual contacts or sharing of injection equipment. Furthermore, since the basic reproduction number of HCV infection was estimated to range from 1.21 to 2.93 [11] and the double time (defined as the time for an infected population to double in size) was 10-fold shorter in MSM than non-MSM hosts (0.44 vs 4.4 years) with the analysis of viral sequencing by phylodynamic methods [12], more frequent testing (every 3 vs 6–12 months) with subsequent linkage to effective DAAs is the most feasible way to halt onward transmission of HCV.

HIV-positive MSM are at significantly increased risk of HCV infection and reinfection after successful treatment [1, 5]. In the PARTNER study, about 24%–27% had STIs; 32%–37% had condomless sex, and the numbers of condomless sex acts were 41.3–43.4 per year [13]. The total number of condomless sex acts was 76 088 during eligible couple-years of follow-up, and 21%, 28%, and 15% reported 3–4, 5–8, and >8 times of condomless sex per month, respectively. Similarly, among our participants with newly developed HCV viremia, 69.0% were enrolled due to STIs. Given the finding that acute HCV infection (HCV seronegative, but viremic) may increase the risk of transmission by 28-fold [14], it is biologically plausible that these undiagnosed HCV infections with long delays before diagnosis could spread widely, if they have not been diagnosed and treated timely.

This study has several limitations. First, while the rate (11.9%) of spontaneous HCV clearance in MSM who are PWH is higher than that of our observation [10], the total duration of potentially infectious days for our participants with newly diagnosed HCV viremia in the real-world setting might be overestimated because of lack of information on sexual history. Nevertheless, it is known that plasma HCV RNA levels during the first 3 months following acute infection remain as high as 5.3–6.5 $\log_{10}$ IU/mL, regardless of subsequent spontaneous recovery [9], and that such high HCV RNA levels can contribute to HCV transmission significantly. Second, only 2.4% of the participants developed spontaneous HCV clearance in our study, but the median follow-up duration was short (22 days) because we aimed to expedite the linkage to DAA treatments. Third, only PWH meeting our predefined eligibility criteria were enrolled, so we might miss those who did not have these risks but developed HCV viremia. However, in our previous follow-up study, no cases with HCV viremia were identified in those without these risk factors [7]. Finally, whether a higher testing frequency is better

than testing every 3 months warrants further studies to identify the optimal frequency in different settings by balancing the costs and benefits; however, the feasibility of implementing such a strategy would be limited.

To achieve the ambitious goal of WHO to eliminate HCV infection by 2030, regular and frequent testing for HCV infection by HCV RNA in high-risk populations is imperative in addition to DAA scale-up. Our findings support the testing frequency of every 3 months to avoid delayed diagnosis of HCV infections and halt HCV onward transmission in these high-risk populations.

Notes

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