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Underserved Does Not Mean Undeserved: Unfurling the HCV Care in the Safety Net

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Abstract

The availability of the new generation of direct-acting antiviral (DAA) therapies for the treatment of chronic hepatitis C virus (HCV) infection has completely transformed the HCV therapeutic landscape. Current regimens provide pan-genotypic coverage that are of short duration, safer, and are highly effective than prior generations of HCV therapeutics. While data from clinical trials and real-world experience continue to demonstrate similar and high sustained virologic response (SVR) rates, the successful implementation of the HCV cascade-of-care including screening, confirmation of active infection, treatment initiation and successful completion of therapy among more challenging populations, such as the underserved populations who are also disproportionately affected by HCV, remains vital to HCV eradication efforts.

In this issue of *Digestive Diseases and Sciences*, we discuss three studies^{1–3} that highlight the uncertainties in estimation of true SVR rates of patients cared for in real-world clinical practice (e.g. other than in clinical trials) and the importance of patient follow-up post HCV therapy, in order to address this knowledge gap. Moreover, differences in practice setting (e.g. specialty care, primary care, academic center, or community practice) further increase the complexity of comparing treatment success and addressing barriers to achieving optimal treatment efficacy in HCV. Though real-world studies to date continue to report high SVR rates^{4,5}, even for underserved populations (e.g. patients lacking access to healthcare due to lack of insurance, low socioeconomic status, homelessness, substance abuse, mental illness, or other factors)⁶, Marshall, et al. raised concern that true SVR rates may be much lower when factoring in inconsistencies in treatment completion or posttreatment testing needed to calculate the SVR¹. In their study of 261 HCV genotype 1 patients, 22% were lost to follow-up (7% did not complete therapy and 15% did not return for SVR testing after completion of therapy). These observations are even more concerning given that their study population included academic center-based patients, all of whom received individualized education that emphasized the importance of compliance with treatment completion and laboratory monitoring. Similar observations were reported by Tran, et al. who evaluated the effectiveness of an on-site intensive specialty pharmacy program to improve SVR rates in an underserved population receiving care at a safety-net hospital² (e.g. a hospital that provides care regardless of health insurance). Though per-protocol SVR rates were 95% among patients who completed therapy, the intention-to-treat SVR was much lower at 71% due to

incomplete post-treatment follow up. Among their cohort of 219 patients, 25.1% (n=55) did not complete all follow-up visits, including 37 patients who did not complete SVR testing. This high rate of incomplete follow-up persisted despite the program's pre-treatment education efforts along with services such as prescription refill monitoring, direct communication with medical providers to discuss medication issues or concerns, and the choice of patients picking up medications in the clinic or home delivery². Stewart, et al evaluated an urban public hospital cohort of 435 HCV patients to assess real-world SVR rates in an underserved safety-net setting³. In this study, the investigators utilized multiple imputation statistical methods to account for the 28% missing SVR values and reported an overall SVR rate of 89%, which is comparable to that reported in other safety-net settings^{6,7}. While using multiple imputation technique enhances validity of findings, the assumption that the missing data are from random subjects may be erroneous⁸. Importantly, although it may be assumed that HCV cure rates will be high among those without laboratory confirmation given the effectiveness of the current regimens, it is possible that lack of adherence to follow-up signals unmeasured factors that also contribute to lower SVR rates. Importantly, loss to follow-up after therapy also results in missed opportunities for monitoring liver disease progression and hepatocellular carcinoma (HCC) screening in those with advanced fibrosis. Current post-SVR HCC surveillance recommendations are based on persistent, albeit lower, risk of *de novo* HCC in this group⁹. Better understanding of factors associated with lack of adherence to treatment and follow-up post therapy are important to implementation of interventions in addressing optimal HCV care. Nevertheless, as more data emerge that report high rates of treatment success in the underserved population comparable to other settings, targeting efforts to prioritize HCV testing and treatment uptake are essential to reducing HCV health disparities in this at-risk population.

There are likely multiple contributors to the lack of optimal HCV care delivery that spans all patient, provider, and system level challenges. These challenges are amplified in safety-net settings exposed to unique factors such as low health literacy and socioeconomic status, high prevalence of mental health and substance use disorders, unstable housing, language barriers, transportation issues, and compromised medication access despite expanded access to public insurance. The three studies in this issue highlight different approaches in enhancing treatment success: 1) an on-site specialty pharmacy program that systematically streamlines the process of initiating and monitoring HCV therapy along with patient education²; 2) an individualized patient education and counseling on the importance of adherence to treatment completion and monitoring during a pre-treatment nurse visit²; and 3) advanced practice provider-based on-treatment monitoring of compliance, adverse events, and treatment response³. In these studies and in others^{7,10-13}, it is clear that structured and integrated multidisciplinary models, patient navigation services, and access to patient assistance programs, particularly among safety-net populations, do improve all aspects of the HCV care cascade. Furthermore, utilization of multiple strategies, including enhanced integration of already existing safety-net health care services, tailored patient and interprofessional care team education, and broad dissemination of HCV guidelines may enhance adherence to post-treatment monitoring and HCC surveillance. In a recent study of 192 HCV patients with documented SVR at a safety-net hospital, Kim et al. evaluated the rates and predictors of post-SVR monitoring and HCC surveillance during a median follow-

up period of 22 months¹⁴. Among patients with advanced fibrosis (n=79), 25.3% had no primary care visit, 22.8% had no liver clinic visit, and 6.3% had no clinic visits at all. Importantly, 20.3% had no liver imaging and 3 cases of new HCC were identified during the relatively short post-SVR follow-up¹⁴. Thus, consistent post-treatment engagement into care is especially important for underserved patients with advanced fibrosis or cirrhosis in order to ensure that essential disease monitoring such as HCC surveillance and variceal screening occur.

Addressing challenges in treatment completion and post-SVR follow-up among safety-net populations is only the 'tip of the iceberg'. Continued efforts should be made to increase the rates of HCV screening in underserved populations followed by enrollment into comprehensive treatment and surveillance programs for those newly diagnosed with HCV. We retrospectively evaluated 34,810 birth cohort underserved patients engaged in primary care within the San Francisco's safety-net healthcare system from October 1, 2014 to October 31, 2016¹⁵. In this cohort, 99.7% had evidence of HCV screening and 13.8% were HCV antibody positive. Despite this high screening rate and expanded access to HCV therapy both within liver specialty and primary care settings in this system, only 20.8% of those with documented viremia initiated HCV treatment. Although overall 90.6% achieved SVR, younger age and absence of HIV coinfection were associated with lack of SVR testing that occurred in 8% of those who completed treatment¹⁵. Wong et al evaluated 29,544 patients chronically infected with HCV across four health systems including two safety-net institutions in the U.S. from January 1, 2011 to February 28, 2017¹⁶. Overall cumulative HCV treatment rate was 16.9%, with significantly lower rates of treatment reported in Hispanics and patients with Medicaid or other indigent care insurance.

Several initiatives have been studied in an attempt to improve the HCV cascade-of-care. Formal patient-centered education and counseling programs that emphasize the importance of follow-up care, monitoring, and surveillance are necessary for continued patient engagement¹⁰. Electronic health record (EHR) integrated quality improvement programs such as best practice alerts embedded into the EHR improves HCV testing rates¹⁷. Dedicated patient navigators are also effective in improving diagnosis, linkage, retention, and re-engagement of HCV patients into care¹³. More recently, novel endoscopy unit-based HCV screening followed by patient navigator support among an underserved safety-net health system improved HCV screening from 30.9% to 73.4%, with 100% linkage to care of patients with confirmed viremia¹⁸. While challenging, it is clear the structured programs that are systematically embedded into routine clinical practice can significantly reduce the gaps in the HCV care cascade that continue to persist in safety-net settings.

The advent of highly-effective HCV treatment regimens together with an increased awareness and implementation of screening programs has substantially improved the rate of HCV eradication. Nevertheless, with the initial wave of treatment successes, most of the 'low-hanging fruit' have been harvested. The medical community is now faced with caring for some of the most vulnerable underserved populations who not only have a high HCV burden, but also are subject to complex factors and multi-level barriers that limit effective diagnosis and access to treatment and cure. The demonstrated feasibility of treatment uptake in this population along with high rates of treatment success with adherence is very

encouraging in cultivating positive attitudes towards HCV care among both patients and the interprofessional teams caring for them. Yet, there is clearly a need for innovative and patient-centered programs that integrate already existing safety-net services tailored to uniquely meet the needs of each patient in order to create efficiencies in comprehensive and effective HCV care delivery throughout the entire cascade from diagnosis to linkage, curative treatment, and post-SVR monitoring.

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