



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

Mandana Khalili¹ · Robert J. Wong²

Published online: 11 October 2018
© Springer Science+Business Media, LLC, part of Springer Nature 2018

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 for 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. [1] raised concern that true SVR rates may be much lower when factoring in inconsistencies in treatment completion

or post-treatment testing needed to calculate the SVR. 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 hospital [2] (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 delivery [2]. Stewart et al. [3] evaluated an urban public hospital cohort of 435 HCV patients to assess real-world SVR rates in an underserved safety-net setting. 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 erroneous [8]. 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

✉ Mandana Khalili
Mandana.Khalili@ucsf.edu

¹ Division of Gastroenterology and Hepatology, University of California San Francisco, San Francisco, CA, USA

² Division of Gastroenterology and Hepatology, Alameda Health System, Highland Hospital, Oakland, CA, USA

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 group [9]. Better understanding of factors associated with lack of adherence to treatment and follow-up post-therapy is 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 education [2]; (2) an individualized patient education and counseling on the importance of adherence to treatment completion and monitoring during a pre-treatment nurse visit [1]; and (3) advanced practice provider-based on-treatment monitoring of compliance, adverse events, and treatment response [3]. 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 healthcare 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. [14] evaluated the rates and predictors of post-SVR monitoring and HCC surveillance during a median follow-up period of 22 months. 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 three cases of new HCC were identified during the relatively short post-SVR follow-up [14]. 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 occurs.

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, 2016 [15]. 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 treatment [15]. Wong et al. [16] evaluated 29,544 patients chronically infected with HCV across four health systems including two safety-net institutions in the USA from January 1, 2011 to February 28, 2017. 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 engagement [10]. Electronic health record (EHR)-integrated quality improvement programs such as best practice alerts embedded into the EHR improve HCV testing rates [17]. Dedicated patient navigators are also effective in improving diagnosis, linkage, retention, and re-engagement of HCV patients into care [13]. 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 viremia [18]. 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 toward 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.

References

1. Marshall MC, Herrera JL. Lack of patient compliance in real-world practice reduces sustained viral response rates to direct acting antiviral therapy for hepatitis C. *Dig Dis Sci*. (Epub ahead of print). <https://doi.org/10.1007/s10620-018-5247-5>.
2. Tran AN, Sachdev R, Fricker ZP, et al. Intensive pharmacy care improves outcomes of hepatitis C treatment in a vulnerable patient population at a safety-net hospital. *Dig Dis Sci*. (Epub ahead of print). <https://doi.org/10.1007/s10620-018-5231-0>.
3. Stewart RA, MacDonald BR, Chu TC, Moore JD, Fasanmi EO, Ojha RP. Ledipasvir/sofosbuvir effectively treats hepatitis C virus infections in an underserved population. *Dig Dis Sci*. (Epub ahead of print). <https://doi.org/10.1007/s10620-018-5205-2>.
4. Flamm SL, Bacon B, Curry MP, et al. Real-world use of elbasvir-grazoprevir in patients with chronic hepatitis C: retrospective analyses from the TRIO network. *Aliment Pharmacol Ther*. 2018;47:1511–1522.
5. Terrault NA, Zeuzem S, Di Bisceglie AM, et al. Effectiveness of Ledipasvir–Sofosbuvir combination in patients with hepatitis C virus infection and factors associated with sustained virologic response. *Gastroenterology*. 2016;151:1131–40 e5.
6. Beck KR, Kim N, Khalili M. Sofosbuvir-containing regimens for chronic hepatitis C are successful in the safety-net population: a real-world experience. *Dig Dis Sci*. 2016;61:3602–3608.
7. DeBose-Scarlett A, Balise R, Kwon D, et al. Obstacles to successful treatment of hepatitis C in uninsured patients from a minority population. *J Transl Med*. 2018;16:178.
8. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338:b2393.
9. Monitoring patients who are starting HCV treatment, are on treatment, or have completed therapy. Updated May 24, 2018. <https://www.hcvguidelines.org/evaluate/monitoring>. Accessed August 18, 2018.
10. Lubega S, Agbim U, Surjadi M, Mahoney M, Khalili M. Formal hepatitis C education enhances HCV care coordination, expedites HCV treatment and improves antiviral response. *Liver Int*. 2013;33:999–1007.
11. Beck KR, Kim NJ, Khalili M. Direct acting antivirals improve HCV treatment initiation and adherence among underserved african americans. *Ann Hepatol*. 2018;17:413–418.
12. Vu TM, Toribio W, Riazi F, et al. Increasing access to hepatitis C virus medications: a program model using patient navigators and specialty pharmacy to obtain prior authorization approval. *J Manag Care Spec Pharm*. 2018;24:329–333.
13. Trooskin SB, Poceta J, Towey CM, et al. Results from a geographically focused, community-based HCV screening, linkage-to-care and patient navigation program. *J Gen Intern Med*. 2015;30:950–957.
14. Kim NJ, Magee C, Cummings C, Park H, Khalili M. Liver disease monitoring practices after hepatitis C cure in the underserved population. *Hepatol Commun*. 2018;2:1274–1283. <https://doi.org/10.1002/hep4.1246>.
15. Kim NJ, Locke CJ, Park H, Magee C, Bacchetti P, Khalili M. Race and hepatitis C care continuum in an underserved birth cohort. *J Gen Intern Med*. 2018. <https://doi.org/10.1007/s11606-018-4649-6>.
16. Wong RJ, Jain MK, Therapondos G, et al. Race/ethnicity and insurance status disparities in access to direct acting antivirals for hepatitis C virus treatment. *Am J Gastroenterol*. 2018;113:1329–1338.
17. Konerman MA, Thomson M, Gray K, et al. Impact of an electronic health record alert in primary care on increasing hepatitis c screening and curative treatment for baby boomers. *Hepatology*. 2017;66:1805–1813.
18. Campbell B, Liu B, Bhuket T, Wong RJ. Pilot study of screening patients for hepatitis C virus infection during outpatient endoscopy. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc*. 2018;16:778–780.