

EDITORIAL AND COMMENT

The HCV Treatment Cascade: Race Is a Factor to Consider

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Chronic hepatitis C is the most common blood-borne viral infection in the USA and a leading cause of chronic liver disease, liver failure, and hepatocellular carcinoma (HCC). The complications of HCV infection are preventable. Antiviral treatment with sustained virological response (SVR) is associated with a 71–76% reduction in HCC risk¹ and a 74% reduction in risk of death compared to ongoing active infection.²

Following decades of struggle with ineffective and poorly tolerated therapies, the approval of all oral direct-acting antiviral (DAA) therapies in 2014 was a major breakthrough in HCV care. The high efficacy of DAAs coupled with their excellent safety profile has created the opportunity to consider treatment for nearly *all* HCV-infected persons, an attribute that has a potential for broad public health impact. Availability of DAA has added further impetus for several professional societies to advocate for broad screening of HCV among high-risk populations with the goal of universal HCV eradication by 2030. The birth cohort, meaning people born between 1945 and 1965, account for 75% of HCV burden in the USA and thus constitute a major priority group for screening and treatment by public health agencies in the USA, including the Centers for Disease Control and the U.S. Preventive Services Task Force.

The challenge now is to screen and identify individuals with HCV infection at the population-level and to ensure their successful progression through a care continuum termed the HCV treatment cascade. The treatment cascade—a concept originally developed in the context of caring for human immunodeficiency virus-infected persons—entails a series of necessary and inter-linked steps including the following: HCV screening by antibody testing, HCV confirmation with HCV RNA testing, linkage to HCV care, retention in care, prescription of HCV therapy, adherence to treatment, and finally achievement of SVR.

HCV-infected people are susceptible to falling off at any step along the cascade due to complexities in coordinating screening, diagnosis, and linkage to care. And extremely high rates of drop-offs do occur. This was starkly illustrated in a

2014 pooled analysis showing that only 50% of HCV-infected people were aware of their diagnosis, 27% of those with known status received confirmatory HCV testing, 16% were prescribed HCV treatment, and a mere 9% finally achieved SVR.³ Of note, these findings reflected care cascade in the “pre-DAA” HCV era, and one would expect increased uptake of screening, diagnosis, and treatment in this new post-DAA period. However, cumulating evidence how minimal improvements in the progression along the treatment cascade. For example, a retrospective analysis among birth cohort patients seen across three academic medical centers in the post-DAA era demonstrated that 56% of people with confirmed HCV infection were linked to care and only 16% ultimately completed treatment successfully,⁴ demonstrating the ongoing challenges with screening and linkage.

In this context, the study by Kim et al. in this issue of the journal is timely.⁵ Kim et al. evaluated the HCV care cascade among “birth cohort” patients seen in primary care clinics within a safety-net healthcare system between 2014 and 2016. The study population included a combination of medically insured and uninsured patients; HCV treatment was delivered in primary care, infectious disease, or hepatology clinics. The overall birth cohort ($n = 34,810$) had a median age of 59 years and 58% was male. Asian/Pacific Islanders (APIs) constituted the largest proportion of the cohort (33%) followed by Whites (26%), Blacks (21%), and Latinos (17%); 56% of the population was primarily English speaking. In total, 4% were HBV and 3.5% were HIV co-infected.

A remarkable 99% of the birth cohort underwent HCV screening ($n = 34,697$) in this study—to our knowledge, this is one of the highest rates of screening reported in any healthcare setting in the USA. This is particularly notable given the 11 to 13% screening rates reported across the general US population over the same time period.⁶ This proportion is also much higher than the 11 to 47% screening rates estimated by other cross-sectional analyses conducted among baby boomers.^{1–3} Among those found to be HCV antibody positive, 77% received HCV RNA confirmatory testing, of whom 62% ($n = 2827$) were confirmed to have HCV infection. The overall HCV infection rate in the studied population was 11% ($n = 3673$). However, only 21% ($n = 762$) of those with confirmed HCV infection initiated treatment and 17% ($n = 634$) achieved SVR. Thus, despite the near-universal HCV screening, few

patients benefited from antiviral treatment: 79% of patients with confirmed infection remained untreated during the study period.

There are public health benefits associated with screening and identification of infections alone. Knowledge of infection may reduce high-risk behaviors and lower transmission. In this regard, the 99% screening rate is a remarkable success, though the reasons for this unusually high screening rate are unclear from Kim et al.'s report. Without successful linkage to antiviral treatment, however, the full potential benefit of HCV screening is limited. Indeed, early cost-effectiveness analyses on birth cohort screening assumed at least 41% treatment initiation rate across the birth cohort.⁷ However, HCV treatment uptake remains much lower in most studies^{4, 8}—underscoring the importance of efforts tailored towards improving successful dissemination of treatment.

For such efforts to be successful, we need to understand the main reasons that result in the “breaks” in the HCV treatment care cascade. This paper adds to our understanding of these reasons. Kim et al. found that race/ethnicity may be an important factor in how HCV-infected individuals' progress through the HCV treatment cascade. It is useful to reflect on the significance of race at each milestone of the treatment cascade. Although screening rates were nearly universal, there were subtle differences by race. HCV infection rates were highest among Blacks and Whites (28% and 23% respectively) and lowest among Latinos and APIs (9% and 2% respectively), yet HCV screening rates were highest among APIs and Latinos (99% and 97% respectively) and lowest among Blacks and Whites (92% and 93%). While other studies have also reported racial differences in likelihood of HCV screening among baby boomers, the findings have varied. Some have noted greater screening likelihood in Blacks versus Asians⁹ and others in Hispanics and Blacks versus White and Asians.¹⁰ What we can take away from these findings is this is that racial variations in screening do occur, but the direction and trend may differ based on healthcare setting studied.

HCV confirmatory testing represented the first major drop off in the studied population, where 23% of HCV antibody positive patients did not undergo further evaluation with RNA testing. Similarly, high drop off rates at the point of confirmatory testing have been reported by many other studies conducted among diverse populations—Veterans Hospital, urban safety net, and general patient populations.^{4, 6} Whether race was a factor at this breakpoint is unclear from Kim et al.'s report, but does deserve greater scrutiny given the pervasive nature of this problem.

The effect of race was most evident in the HCV treatment step. In total, 35% of the APIs but only 19% of Blacks with chronic infection initiated antiviral treatment. During multivariate analysis, API race (OR 1.20, 95% CI 1.08–1.33) and HIV coinfection (OR 1.58, 95% CI = 1.07–2.34) were associated with higher odds of HCV treatment initiation while

primary English speaking (OR 0.54, CI 0.36–0.79) along with doubling of ALT (OR 0.39, CI 0.35–0.60) and HCV viral load (OR 0.83, CI 0.81–0.87) were each associated with a lower likelihood of treatment. The study also noted racial variation in rate of SVR following treatment; Hispanics had the highest rate of SVR failure (19%); Hispanics constituted the largest proportion (55%) of those who did not achieve SVR among the cohort. This is alarming as the observed SVR failure rate in Hispanics was much higher than an expected 8% DAA failure rate estimated using the Hepatitis C Disease Burden Simulation model.¹¹ Further, Hispanics have several factors predisposing them to poor liver disease outcomes including a higher risk of non-alcoholic fatty liver disease, progression to cirrhosis, and HCC.^{12, 13} Whether the lower SVR rates are related to healthcare adherence behaviors, the presence of more advanced liver disease versus yet undefined genetic factors among Hispanics is unknown but important to tease out in future studies.

Although the data presented in the paper by Kim et al. identify certain high-risk groups based on race and ethnicity—groups that should be targeted in future quality improvement efforts—the reasons underlying these race/ethnicity effects remain unclear. Furthermore, the identified factors likely explain a small proportion of the difference between observed and ideal treatment rates. Other factors, such as healthcare insurance, affordability of and access to antiviral treatment, and complexity of care coordination are likely important factors. Equally important is an understanding of “best practices” that may promote successful movement through the cascade within healthcare settings. For example, it would be useful to learn from the studied cohort if there were specific campaigns targeting healthcare providers to ensure near-universal healthcare screening and whether there were culturally specific healthcare campaigns that led to higher screening rate in APIs than in Blacks, for example.

Several public health groups are moving towards recommending HCV eradication strategies that extend beyond birth cohort screening to include universal HCV screening in the USA. This strategy (universal screening) may be cost-effective¹⁴ but assumes that all those who are screened and diagnosed with HCV receive treatment with DAAs. Kim et al.'s study demonstrates that universal one-time screening of all patients may indeed be an attainable goal but we cannot ensure success unless the link between case identification and treatment is strong. We believe that a concerted focus on ways to minimize the precipitous dropouts that occur in the HCV treatment cascade is vital. Without this information, the HCV care cascade is unlikely to result in substantial health benefits for the millions of individuals infected with HCV.

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Compliance with Ethical Standards:

Conflict of Interest: The authors declare that they do not have a conflict of interest.

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