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BARRIERS AND LIMITATIONS IN ANTIVIRAL THERAPY FOR HEPATITIS C

Mohamed Mostafa
International students faculty,
Asia International University, Bukhara
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Abstract:

Over the past three decades, the management of hepatitis C virus (HCV) infection has undergone a remarkable transformation, progressing from interferon (IFN)-based regimens with limited efficacy to highly effective pan-genotypic direct-acting antivirals (DAAs). In the early 1990s, alpha-interferon monotherapy represented the standard of care; however, sustained virological response (SVR) rates were low, and treatment was frequently complicated by significant adverse effects, restricting its clinical utility. The subsequent introduction of pegylated interferon (peg-IFN) improved the pharmacokinetic profile of IFN, permitting less frequent dosing and modestly enhanced response rates. Combination therapy with ribavirin further increased SVR rates, particularly in non-genotype 1 infections, though it was associated with additional toxicities, including hemolytic anemia and neuropsychiatric disturbances.

The advent of first-generation DAAs, such as telaprevir and boceprevir, marked a pivotal advance. When administered in combination with peg-IFN and ribavirin, these protease inhibitors significantly improved outcomes in genotype 1 HCV infection. Nonetheless, their use was limited by high rates of adverse events and the emergence of drug resistance. The development of second-generation DAAs, exemplified by sofosbuvir and ledipasvir, enabled IFN-free regimens with superior efficacy and safety profiles. Most recently, pan-genotypic DAAs—including glecaprevir-pibrentasvir and sofosbuvir-velpatasvir—have revolutionized therapy by achieving consistently high SVR rates across all genotypes, offering shorter treatment durations, and demonstrating excellent tolerability. These regimens now constitute the cornerstone of HCV management, providing a globally accessible and highly effective therapeutic solution.

Keywords

pan-genotypic; direct-acting antivirals DAAs; HCV; HCV therapy; peg-IFN; sustained virological response; SVR

Introduction

The World Health Organization (WHO) estimates that approximately 50 million individuals worldwide are chronically infected with hepatitis C virus (HCV), with 1 million new infections occurring annually, corresponding to a global prevalence of nearly 1%. HCV remains a leading cause of chronic liver disease, including cirrhosis and hepatocellular carcinoma (HCC). Chronic infection is frequently asymptomatic, progressing insidiously over decades before clinical detection. Without therapeutic intervention, 20–30% of chronically infected patients develop cirrhosis, and up to 5% progress to HCC. This natural history underscores the critical need for effective antiviral therapy to mitigate long-term hepatic complications and reduce HCV-related mortality.

Achievement of sustained virological response (SVR) through antiviral therapy has been shown to markedly reduce the incidence of cirrhosis, hepatic decompensation, and HCC, effectively constituting a virological cure. The therapeutic landscape has evolved substantially over the past three decades. Early interferon-based regimens demonstrated only modest efficacy and were associated with significant adverse effects, limiting their widespread applicability. The subsequent development of direct-acting antivirals (DAAs) represented a paradigm shift, offering high SVR rates with improved tolerability. Most recently, the introduction of pan-

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genotypic DAAs has simplified treatment protocols, enabling effective therapy across all HCV genotypes with shorter durations and minimal toxicity. These regimens have transformed HCV management, rendering cure feasible on a global scale.

This review aims to provide a comprehensive overview of the evolution of antiviral therapy for HCV, tracing the progression from interferon-based regimens to the advent of pan-genotypic DAAs. By examining therapeutic efficacy, safety, and limitations across successive treatment eras, it highlights pivotal advances in HCV therapy and their implications for global health and elimination strategies. Importantly, given the high burden of HCV infection and liver disease in resource-limited settings, equitable access to DAAs at affordable costs remains essential to achieving worldwide eradication.

Chronic hepatitis C virus (HCV) infection affects approximately 2.7 million individuals in the United States, based on data from the National Health and Nutrition Examination Survey (NHANES). When high-risk populations such as incarcerated, homeless, institutionalized, hospitalized, or active military personnel are included, prevalence estimates suggest a peak of about 1.6% of the U.S. population. Although highly effective direct-acting antiviral (DAA) agents have the potential to eradicate HCV, new infections continue to rise, largely driven by injection drug use, and significant barriers to treatment remain. Previous reviews have identified multiple reasons why many individuals with HCV remain untreated, including deficiencies in population screening, limited patient and physician awareness, contraindications to therapy, and restricted access to care.

Barriers to therapy were extensively studied during the interferon (IFN) era, when adverse effects limited treatment eligibility. At that time, only about 30% of patients with chronic HCV initiated IFN-based therapy, with psychosocial factors representing a major barrier. Active alcohol or substance use and poorly controlled psychiatric disorders were common concerns, given risks of non-adherence and exacerbation of psychiatric illness. In some studies, psychosocial factors accounted for a greater proportion of treatment ineligibility than medical contraindications (44% versus 19%). Financial barriers also played a significant role. Individuals with HCV were more likely to be uninsured compared with those without infection, and only 36% of treatment-eligible patients initiated IFN therapy, largely determined by payer status.

The introduction of DAA regimens in 2014 revolutionized HCV therapy, yielding markedly improved sustained virological response (SVR) rates, shorter treatment durations, and minimal adverse effects, even among populations historically considered difficult to treat. Despite these advances, barriers to treatment initiation persist. Eligible patients often experience delays or deferrals in therapy, with some subsequently lost to follow-up.

The high cost of DAA therapy has introduced new challenges, particularly payer restrictions. Many state Medicaid programs limit DAA treatment to patients with advanced fibrosis (e.g., Metavir stage F3 or F4), and some commercial insurers have adopted similar policies. These restrictions pose serious obstacles to treating HCV in health systems serving low-income or uninsured populations. Against this backdrop, the present study was designed to identify barriers to treatment initiation with DAA-containing regimens in an urban academic practice.

Direct-acting antivirals (DAAs) exert their efficacy by targeting multiple stages of the viral life cycle, thereby suppressing replication and reducing viral load. These agents selectively inhibit key HCV proteins, including NS5A, NS5B polymerase, and the nonstructural protein 3/4A protease. Through these mechanisms, DAAs achieve high rates of sustained virological response (SVR), effectively curing infection and mitigating the long-term health consequences of chronic HCV. Despite these therapeutic advances, substantial challenges remain in achieving global eradication. More than 70 million individuals worldwide remain untreated, reflecting persistent barriers to access and delivery of care.

The burden of HCV is disproportionately concentrated in low- and middle-income countries (LMICs), where lower gross national income per capita is often accompanied by deficiencies in

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healthcare infrastructure, limited diagnostic capacity, and restricted access to treatment. According to the World Health Organization (WHO), two-thirds of the global HCV burden is concentrated in just fifteen countries, eight of which—India, Pakistan, Nigeria, Ukraine, Uzbekistan, Vietnam, Bangladesh, and Ethiopia—are classified as LMICs. In these regions, individuals face significant obstacles to receiving DAAs, and a large proportion of those infected remain undiagnosed.

To achieve the WHO's target of eliminating HCV as a public health threat by 2030, it is essential to address the systemic barriers that hinder effective treatment delivery in LMICs. This review aims to examine the common challenges encountered in these settings, including issues of healthcare infrastructure, affordability, and awareness, while highlighting potential interventions that have demonstrated success in expanding access to DAAs and mitigating disparities in care.

Discussion

In this retrospective cohort of patients with chronic hepatitis C virus (HCV) infection managed at an urban academic practice, only 27% of individuals evaluated over a three-year period were initiated on direct-acting antiviral (DAA) therapy, with 18% achieving sustained virological response at 12 weeks (SVR12). This relatively low success rate is striking given the high efficacy of DAAs and underscores the importance of identifying and addressing barriers to treatment initiation. Psychosocial factors represented the most common impediment, affecting 47% of patients. These included non-adherence to laboratory testing and clinic follow-up, as well as ongoing substance abuse. Such findings are reminiscent of earlier studies conducted during the interferon (IFN) era, in which psychosocial contraindications prevented treatment initiation in the majority of patients. Notably, in contrast to prior reports where substance abuse accounted for a quarter of untreated cases and adherence issues were relatively uncommon, the present study identified adherence-related challenges as a predominant barrier. Provider-related factors were the second most frequent obstacle, noted in 11% of untreated cases, followed by medical comorbidities (8%) and insurance-related restrictions (3%).

Despite the high prevalence of psychiatric illness among patients with chronic HCV, uncontrolled psychiatric disease was identified as a barrier to treatment initiation in less than 1% of cases. This low rate reflects the favorable psychiatric safety profile of DAAs compared with IFN-based regimens. Other psychosocial factors, including substance abuse and incarceration, contributed to treatment failure in a minority of patients. Interestingly, provider-related barriers emerged as the second most common category, primarily due to failure to address HCV status and errors in ordering laboratory tests required for insurance authorization. These findings highlight the need for targeted educational interventions to improve provider awareness of HCV management and to ensure adherence to submission criteria, particularly within state Medicaid programs.

Psychosocial barriers emerged as a major determinant of failure to initiate hepatitis C virus (HCV) therapy in this urban academic clinic, despite the establishment of a multidisciplinary treatment team. This study provides insight into the characteristics and outcomes of a real-world urban cohort of patients managed for HCV. Limitations include the retrospective design, which inherently lacks granular detail. Nevertheless, the barriers identified suggest that the incorporation of patient navigators and specialized expertise in insurance authorization processes within HCV treatment teams may improve initiation rates in at-risk populations and warrant further prospective evaluation. These findings also underscore the broader healthcare challenges encountered in delivering care to urban populations, highlighting the need for systemic interventions to reduce disparities in access to therapy.

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