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Determinants of Nonresponse to Direct-Acting Antivirals in Chronic Hepatitis C Infection: A Narrative Review

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ABSTRACT

Direct-acting antivirals (DAAs) have transformed the treatment landscape for chronic hepatitis C virus (HCV) infection, offering sustained virology response rates exceeding 95% across diverse patient populations. However, patients fail to respond to therapy, resulting in persistent infection and continued risk of liver-related morbidity and mortality. A comprehensive review of published literature was conducted to identify host, viral, and disease-related factors associated with treatment failure in the DAA era. Particular focus was given to studies examining cirrhosis, comorbid conditions, virological factors, prior treatment history, and socio-behavioral determinants. The most consistently reported predictors of nonresponse include advanced liver disease (especially decompensated cirrhosis), thrombocytopenia, hypoalbuminemia, high fibrosis scores, HCV genotype 3, prior treatment failure, HIV or HBV co-infection, diabetes mellitus, and poor adherence. Patients with multiple risk factors often require individualized treatment strategies and closer clinical monitoring. Thus, this review aims to explore and summarize the key predictors of nonresponse to DAA therapy in patients with chronic hepatitis C, based on current clinical and epidemiological evidence.

Keywords DAA therapy; hepatitis C virus; Risk factors; Cirrhosis

Introduction

Hepatitis C virus (HCV) infection remains a significant global health concern, with an estimated 58 million people living with chronic HCV and approximately 1.5 million new infections occurring annually, according to the World Health Organization (WHO). Chronic HCV is a major cause of liver-related morbidity and mortality, contributing to the development of cirrhosis, hepatocellular carcinoma (HCC), and liver failure. The introduction of direct-acting antivirals (DAAs) over the past decade has dramatically transformed the treatment landscape, offering the possibility of a sustained virological response (SVR) considered a functional curein the vast majority of patients **(1)**.

Identifying the factors that contribute to DAA treatment failure is essential for optimizing patient selection, guiding individualized treatment strategies, and improving overall outcomes. Several host-related, viral, and disease-specific factors have been proposed as potential predictors of nonresponse, including advanced liver disease, co-existing comorbidities, viral genotype, and prior treatment history **(2).**

However, despite these advances, treatment failure still occurs in a small but clinically important subset of patients. Nonresponse to DAAs, often defined as the failure to achieve SVR at 12 or 24 weeks after treatment (SVR12 or SVR24), may result from a variety of interrelated factors. These include viral characteristics such as genotype variability, baseline viral load, and resistance-associated substitutions (RAS) as well as host-related variables like liver disease severity, comorbidities (e.g., diabetes, HIV co-infection), and prior treatment history. Additionally, behavioral and socioeconomic determinants, including poor adherence, reinfection, and limited access to care, play crucial roles in real-world treatment outcomes **(3,4).**

Understanding the multifactorial nature of nonresponse to DAAs is essential for clinicians to appropriately assess risk, tailor treatment regimens, and implement monitoring strategies. This is particularly important in resource-limited settings, where retreatment options may be scarce, and in vulnerable populations with high barriers to care. Moreover, as retreatment strategies become more standardized, identifying predictors of initial treatment failure will be vital in reducing the need for second-line therapies and minimizing the risk of liver disease progression **(5).**

This review aims to provide a comprehensive overview of the current evidence regarding predictors of nonresponse to DAA therapy in patients with chronic HCV infection. By understanding these factors, clinicians can better stratify risk, tailor treatment approaches, and ultimately move closer to the global goal of HCV elimination.

Chronic Hepatitis C Infection

Hepatitis C virus (HCV) enters the liver through the hepatic artery and the portal vein, which are the two blood vessels that transport blood into the liver. Acute HCV infection lasts from 0 to 24 weeks and often remains undetected. Approximately 70% of HCV-infected individuals develop chronic hepatitis C (CHC). Most patients do not develop substantial liver fibrosis or clinically relevant liver disease. However, in 15–25% of the cases, cirrhosis develops over 10–40 years. Decompensated cirrhosis and hepatocellular carcinoma are the most important causes of mortality in end-stage CHC **(2)**.

The natural history of the disease does not differ between genotypes, with the exception of HCV genotype 3, which induces liver steatosis more often than the other genotypes **(Figure 1)**.. However, individuals with different genotypes can vary in their response to treatment with recombinant IFNα or direct-acting antiviral drugs **(6)**.

A meta-analysis revealed that patients with decompensated cirrhosis had significantly lower SVR rates (e.g., 88–92%) compared to non-cirrhotic patients (>95%), especially when suboptimal regimens were used or treatment was interrupted due to adverse effects **(3)**.

Cirrhosis is also an indirect marker of longstanding infection, implying a more complex viral-host interplay, possibly involving immune exhaustion and fibrotic tissue that is less responsive to immune-mediated viral clearance **(1)**.

While direct-acting antivirals (DAAs) have largely overcome many host-related barriers that limited interferon-based therapies, several patient-specific factors still significantly influence the likelihood of achieving sustained virologic response (SVR). These include the severity of liver disease, comorbidities, coinfections, demographic characteristics, and immunological status **(6)**.

Therefore, host-related determinants, especially the severity of liver disease and metabolic comorbidities, remain critical predictors of DAA nonresponse. While DAAs have largely mitigated the negative impact of demographic variables such as age and gender, patients with decompensated cirrhosis, thrombocytopenia, or diabetes mellitus continue to require close monitoring and tailored regimens. Recognizing these host factors prior to treatment initiation is essential for risk stratification and optimization of therapy **(2)**.

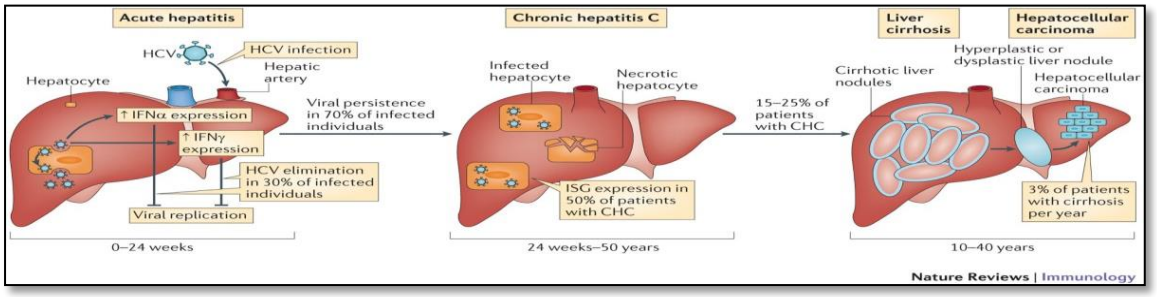

Fig. (1): Natural history of developing chronic hepatitis C (CHC) (2).

Virological Factors Contributing to Nonresponse

Virological determinants play a significant role in the failure of DAA therapy. These include viral genotypes and subtypes, baseline viral load, and, most notably, the presence of resistance-associated substitutions (RAS). Understanding these factors is essential for predicting treatment outcomes and tailoring antiviral regimens, particularly in populations at higher risk of failure **(7).**

1. HCV Genotype and Subtype

HCV exhibits considerable genetic diversity, classified into at least seven major genotypes (GT1–GT7) and over 60 subtypes. While pan-genotypic DAA regimens are increasingly used, certain genotypes and subtypes still demonstrate variable responses to specific DAA combinations **(8).**

Genotype 3 has consistently been associated with slightly lower SVR rates compared to genotypes 1 and 2, especially in patients with cirrhosis or prior treatment experience. Several studies have demonstrated that patients with GT3 are more likely to experience virological relapse, particularly when treated with shorter or suboptimal regimens (e.g., sofosbuvir + daclatasvir without ribavirin) **(9).**

Less common subtypes such as GT1l, 4r, and others, predominantly found in sub-Saharan Africa and parts of Asia, have been associated with intrinsic resistance to some NS5A inhibitors, posing challenges to standard treatment protocols **(7-9).**

The presence of these subtypes may go unrecognized in standard commercial genotyping assays, which can limit the effectiveness of selected regimens and lead to unexpected treatment failure.

2. Baseline Viral Load

Although DAAs are highly potent across a wide range of viral loads, some studies suggest that high baseline HCV RNA levels may be modestly associated with a lower likelihood of achieving SVR, particularly in the presence of other risk factors like cirrhosis or suboptimal adherence **(10)**.

In certain real-world cohorts, patients with viral loads exceeding 6 –7 million IU/mL had marginally higher relapse rates, although the overall impact of viral load appears less significant with modern, potent pan-genotypic regimens **(11)**.

Baseline viral load may still play a role in guiding treatment duration and the need for adjunctive agents (e.g., ribavirin) in select patient groups **(10)**.

3. Resistance-Associated Substitutions (RAS)

One of the most important virological determinants of DAA failure is the presence of resistance-associated substitutionsmutations in the HCV genome that confer reduced susceptibility to DAAs. NS5A RAS are particularly relevant due to the low genetic barrier to resistance of this drug class and the prolonged persistence of RAS after treatment failure (up to years in some patients) **(12)**.

RAS may be pre-existing (baseline) or emerge during treatment. The prevalence of baseline RAS varies by region and genotype. For example: **(12,13)**.

- NS5A RAS are found in up to 10–15% of treatment-naive GT1a patients.
- In treatment-experienced patients, especially those with prior NS5A exposure, the prevalence and impact of RAS are significantly higher.

Clinical implications of RAS include the potential need for resistance testing prior to treatment initiation in high-risk patients (e.g., prior DAA failure). Use of intensified regimens or retreatment protocols that include different classes of DAAs or extended treatment duration in those with known RAS. Consideration of next-generation agents (e.g., voxilaprevir, velpatasvir) that retain activity against common RAS **(14)**.

4. Viral Relapse vs Reinfection

Failure to achieve SVR can also result from reinfection, particularly in populations with ongoing risk behaviors such as people who inject drugs (PWID) or those with high-risk sexual practices **(15)**.

Differentiating virological relapse from reinfection is essential for both clinical management and epidemiological surveillance. This requires viral sequencing and genotyping pre- and post-treatment **(16)**.

In some cases, patients may achieve undetectable viral loads at the end of treatment, only to test positive weeks later due to a new infection, which can be mistakenly categorized as relapse **(14,16)**.

Thus, the DAAs have transformed the therapeutic landscape of chronic hepatitis C, offering cure rates exceeding 95% in many populations. However, treatment failure although uncommonstill affects a clinically significant minority of patients. Understanding the multifaceted determinants of nonresponse is essential for optimizing treatment outcomes, individualizing therapy, and informing retreatment strategies **(10,14)**.

Gaps and areas for further research

- More data are needed in low- and middle-income countries, especially regarding RAS prevalence, real-world adherence and outcomes.
- Better characterisation of the impact of minor viral subtypes and rare genotypes on DAA efficacy is needed.
- Further research on optimal retreatment strategies for those with failure, especially in context of RAS.
- Studies addressing how to improve adherence and access in vulnerable populations.
- Long-term outcomes of those who fail DAAs: how many fail due to relapse vs reinfection, what are their risks of complications, how to monitor and manage them.

Conclusion:

Although nonresponse to DAAs is uncommon, it remains clinically significant. Early identification of high-risk patients through assessment of predictive factors can improve treatment outcomes and guide therapeutic decisions.

Virological factors, particularly the presence of resistance-associated substitutions (RAS), certain genotypes and subtypes (notably genotype 3), and high baseline viral loads, remain central contributors to treatment failure. These are compounded by host-related factors such as advanced liver disease (especially decompensated cirrhosis), thrombocytopenia, diabetes mellitus, and HIV or HBV coinfections, all of which can alter drug pharmacokinetics, impair immune responses, or increase treatment complexity.

Continued research is needed to refine predictive models and address gaps in care, particularly in underserved and high-risk populations.

Recommendation

- Routine risk stratification: Clinicians should perform comprehensive baseline assessments to identify patients at higher risk of nonresponse, including evaluation of liver fibrosis stage, platelet count, serum albumin, comorbidities (e.g., diabetes, HIV), and prior treatment history.
- Tailored treatment approaches: Patients with predictors of poor response, such as decompensated cirrhosis or genotype 3 infection, may benefit from extended treatment durations, adjunctive use of ribavirin, or close virologic monitoring during and after therapy.
- Enhancing adherence and support: Addressing barriers to adherence—such as substance use, psychiatric illness, or unstable social situations—through multidisciplinary care teams can significantly improve treatment outcomes, especially in vulnerable populations.

- Post-treatment monitoring: Even after DAA completion, high-risk patients should undergo long-term surveillance for hepatocellular carcinoma and liver function deterioration, particularly those with cirrhosis or previous treatment failure.
- Targeted research and policy efforts: More studies are needed to validate predictive models in diverse populations, including those with chronic kidney disease, transplant recipients, and those in low-resource settings. Policymakers should support equitable access to retreatment options and integrate predictive risk assessment into national HCV treatment guidelines

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