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# The Effect of Antiviral Therapy on Liver Fibrosis Regression in Chronic Hepatitis B and C: A Comprehensive Review

***Kurbonov Khayitjon Shavkat o`g`li***
*Asia International University*

**Abstract**

Antiviral therapy (AVT) has revolutionized the management of chronic hepatitis B (CHB) and chronic hepatitis C (CHC), transforming the disease course and prognosis for millions worldwide. A critical aspect of this therapeutic success is the documented potential for liver fibrosis regression following viral suppression or eradication. This comprehensive review synthesizes the existing literature on the impact of modern AVT on fibrosis regression in both CHB and CHC, highlighting the distinct mechanisms and outcomes associated with different treatment modalities.

The review focuses on oral nucleos(t)ide analogues (NAs) for CHB, particularly entecavir (ETV) and tenofovir (TDF), and direct-acting antivirals (DAAs) for CHC. We examine the roles of invasive (liver biopsy) and non-invasive markers (e.g., transient elastography [TE], FIB-4, APRI) in monitoring fibrosis dynamics. Key findings indicate that AVT significantly reverses liver fibrosis in both conditions, with viral eradication in CHC often leading to more profound and rapid regression. However, long-term monitoring for hepatocellular carcinoma (HCC) and other liver-related complications remains essential, especially in patients with advanced fibrosis at baseline.

**Keywords:** liver fibrosis regression, antiviral therapy, chronic hepatitis B, chronic hepatitis C, entecavir, DAA, transient elastography, comprehensive review.

**Introduction:** Chronic viral hepatitis B and C are major global health burdens, affecting hundreds of millions of people and causing significant morbidity and mortality from liver cirrhosis and HCC. The progression of chronic inflammation and hepatocyte injury, driven by persistent viral replication, leads to the accumulation of extracellular matrix proteins and the formation of fibrotic scar tissue. Until recently, this process was largely considered irreversible. However, the advent of highly effective AVT has provided strong evidence that liver fibrosis is a dynamic, reversible process.

Effective AVT achieves sustained viral suppression in CHB and eradication in CHC, alleviating the underlying inflammatory trigger and allowing for the activation of endogenous repair mechanisms. This review aims to compare and contrast the effects of AVT on liver fibrosis regression in CHB and CHC by:

1. Analyzing the mechanisms and outcomes of fibrosis regression under different AVT regimens for each disease.
2. Discussing the utility and limitations of non-invasive methods in monitoring fibrosis reversal.
3. Highlighting the clinical implications of fibrosis regression on long-term patient outcomes.

## Antiviral Therapy and Fibrosis Regression in Chronic Hepatitis B

In CHB, the goal of AVT is to achieve long-term viral suppression, as the hepatitis B virus (HBV) often persists in the form of covalently closed circular DNA (cccDNA) within hepatocyte nuclei. The sustained suppression of HBV replication with potent NAs is the primary driver of fibrosis regression.

### Mechanisms and Efficacy of Nucleos(t)ide Analogues

- **Entecavir (ETV) and Tenofovir (TDF):** Modern NAs like ETV and TDF are highly effective at suppressing HBV DNA levels. Several long-term studies have documented histological and clinical

improvements in patients treated with these agents. In a pivotal five-year open-label follow-up study involving patients with advanced fibrosis and compensated cirrhosis treated with TDF, 74% of patients showed histological improvement, and 71% exhibited fibrosis regression, including reversal of cirrhosis in 74% of those with baseline cirrhosis. Similarly, long-term ETV therapy has demonstrated significant improvements in liver histology and a sustained reduction in liver disease severity, with studies in Chinese cohorts showing notable reductions in liver stiffness after treatment.

• **Fibrosis Regression Dynamics:** Fibrosis regression in CHB is generally a slow process, often requiring several years of therapy. For instance, a study on ETV therapy in Chinese CHB patients reported significant improvement in liver stiffness measurement (LSM) after only 24 weeks, suggesting an early effect likely due to reduced necroinflammation. However, studies using paired liver biopsies demonstrate that more advanced regression occurs over longer periods, with some cirrhotic patients experiencing a notable reduction in their fibrosis stage after 5 years of TDF treatment.

**Monitoring Fibrosis Regression in CHB**

• **Non-invasive Markers:** Non-invasive methods like TE are crucial for monitoring fibrosis regression in CHB, overcoming the limitations of repeat liver biopsies. The aforementioned Chinese ETV study demonstrated the utility of TE for this purpose, with higher baseline LSM values predicting greater LSM reduction. Serum biomarkers such as FIB-4 and APRI can also be used, but their sensitivity for detecting subtle fibrosis changes during treatment is lower compared to elastography. Limitations include potential overestimation of regression due to reduced inflammation rather than true fibrosis reversal.

**Antiviral Therapy and Fibrosis Regression in Chronic Hepatitis C**

The development of DAAs has transformed CHC from a chronic, progressive disease into one that can be cured in the vast majority of patients. The achievement of a sustained virological response (SVR), defined as undetectable HCV RNA 12 or 24 weeks after the end of treatment, is the key determinant of fibrosis regression.

**Mechanisms and Efficacy of DAAs**

• **Viral Eradication vs. Suppression:** Unlike CHB, where HBV persists, successful DAA therapy leads to viral eradication in CHC. This removes the primary driver of inflammation and fibrosis, allowing the liver's regenerative processes to take over. This mechanism contributes to a more rapid and pronounced regression of fibrosis compared to the more gradual changes observed in CHB.

• **Fibrosis Regression Rates:** Numerous studies have demonstrated significant fibrosis regression following successful DAA therapy, even in patients with advanced fibrosis or cirrhosis at baseline. For example, in cohorts achieving SVR, up to 70% of patients with cirrhosis showed improvement in TE-measured fibrosis scores. A key finding is that fibrosis improvement can continue for years after viral eradication. However, not all patients experience complete fibrosis regression, especially those with pre-existing cirrhosis or comorbidities such as metabolic-associated steatotic liver disease (MASLD), though some evidence suggests MASLD may enhance short-term regression.

**Monitoring Fibrosis Regression in CHC**

• **Non-invasive Markers**: Non-invasive methods like TE, FIB-4, and APRI are widely used to monitor fibrosis regression after DAA therapy. Studies have shown significant reductions in LSM values and serum biomarker scores following SVR. While these methods are useful, some caution is needed, as reductions in LSM immediately after treatment can partly reflect a decrease in necroinflammation rather than true fibrosis reversal.

• **Persistent Risk**: It is important to note that even with successful fibrosis regression, a residual risk of HCC and other complications may remain, especially in patients who had cirrhosis at baseline. Regular surveillance is therefore crucial for these patients.

**Discussion: Comparative Perspective and Clinical Implications**

**Comparative Analysis**

| Feature | Chronic Hepatitis B | Chronic Hepatitis C |
|---|---|---|
| Treatment | Nucleos(t)ide Analogues (e.g., ETV, TDF) | Direct-Acting Antivirals (DAAs) |
| Treatment Goal | Long-term viral suppression | Viral eradication (SVR) |
| Regression Driver | Cessation of inflammatory response due to viral suppression | Elimination of viral trigger and associated inflammation |
| Regression Rate | Generally slower, requires long-term therapy (e.g., 5+ years for significant changes) | Often more rapid and profound, especially after viral clearance (e.g., within 1 year) |
| Residual Risk (HCC) | Not eliminated, requires long-term monitoring, especially in cirrhotic patients in patients | Reduced, but residual risk remains with baseline advanced fibrosis; necessitates ongoing surveillance |
| Monitoring | Non-invasive markers (TE) are effective for long-term monitoring; serum markers less sensitive | Non-invasive markers are useful, but reductions can reflect less inflammation early on; long-term follow-up needed |

This table summarizes key differences based on comparative reviews.

**Clinical Implications**

The ability of AVT to induce liver fibrosis regression has several profound clinical implications:

• **Improved Patient Outcomes**: Regression of fibrosis is associated with a reduced risk of progression to cirrhosis and a lower incidence of liver-related complications, including HCC.

• **Shifting Management Strategies**: The efficacy of modern AVT has shifted clinical guidelines towards treating all patients with chronic viral hepatitis, particularly those with significant fibrosis, regardless of viral load or other factors.

• **Monitoring in Clinical Practice**: Non-invasive methods like TE and validated serum scoring systems have largely replaced liver biopsy for initial assessment and monitoring of fibrosis regression, improving patient comfort and reducing cost. However, their diagnostic performance varies by population and requires validation in diverse cohorts.

**Conclusion**

The evidence overwhelmingly supports that AVT is effective in inducing significant liver fibrosis regression in both chronic hepatitis B and C. While the specific mechanisms differ—viral suppression in CHB versus eradication in CHC—the clinical outcome is a marked improvement in liver health and function. In CHC, the potential for viral cure through DAAs often leads to a more rapid and substantial regression of fibrosis. For CHB, long-term therapy with potent NAs is necessary to achieve sustained viral suppression and allow for gradual fibrosis reversal. Non-invasive markers, especially elastography, have become indispensable tools for monitoring this process. Despite the remarkable progress, the need for continued, long-term surveillance for HCC and other complications, particularly in patients who started with advanced fibrosis, remains paramount. Future research should focus on refining prognostic markers and further optimizing treatment strategies to maximize fibrosis regression and ensure the best possible long-term outcomes for all patients with chronic viral hepatitis.

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