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# Chronic hepatitis C genotype 1 virus: Who should wait for treatment?

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## Abstract

Elucidation of the natural history of chronic hepatitis C (CHC) and the identification of risk factors for its progression to advanced liver disease have allowed many physicians to recommend deferral treatment (triple therapy) in favour of waiting for new drug availability for patients who are at low risk of progression to significant liver disease. Newer generation drugs are currently under development, and are expected to feature improved efficacy and safety profiles, as well as less complex and shorter duration delivery regimens, compared to the current standards of care. In addition, patients with cirrhosis and prior null responders have a low rate (around 15%) of achieving sustained virological response (SVR) with triple therapy, and physicians must also consider the decision to wait for new treatments in the future for these patients as well. Naïve patients are the most likely to achieve a close to 100% SVR rate; therefore, it may be advisable to recommend that patients with mild to moderate CHC should wait for the newer therapy options. In contrast, patients with advanced fibrosis and cirrhosis will be those with the greatest need for expedited therapeutic intervention. There remains a need, however, for establishing definitive clinical management guidelines to maximize the benefit of waiting for new drugs and minimize risk of side effects and non-response to the current triple therapy.



**Key words:** Hepatitis C virus; Chronic hepatitis C; Treatment of hepatitis C; Cirrhosis; Protease inhibitors

**Core tip:** Identification of risk factors for progression of chronic hepatitis C has allowed physicians to recommend treatment deferral (triple therapy) to wait for anticipated new drugs with better efficacy and safety profiles for patients with mild to moderate disease. Patients with cirrhosis and prior null responders rarely obtain sustained virological response with triple therapy and the decision to wait for new treatments must be considered. For each patient population, definitive clinical management guidelines are needed to maximize the benefit of waiting for new drugs and minimize risk of side effects and non-response to the current triple therapy.

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## INTRODUCTION

More than 170 million people worldwide suffer from chronic infection with the hepatitis C virus (HCV)[1]. In

Brazil, a nationwide population-based survey conducted in all macro-regions to estimate the seroprevalence of HCV antibodies in the urban population showed an overall prevalence of 1.38% (95%CI: 1.12%-1.64%)[2].

Chronic hepatitis C (CHC) is a leading cause of end-stage liver disease and hepatocellular carcinoma (HCC)[3,4], as well as the most common indicator for orthotopic liver transplantation in the Western world[1,5]. Following the development of HCV-related cirrhosis, the annual risks of clinical decompensation, death or transplantation, and HCC are 6% (range, 4%-8%), 3% (range, 2%-6%), and 3% (range, 2%-6%), respectively[6-10]. A recent study estimated that the 5-year cumulative incidences of mortality, hepatic decompensation, and HCC were significantly higher (9%, 31%, and 17%, respectively) in HCV-related compensated cirrhotic patients with esophageal varices than in those without esophageal varices (2%, 7%, and 9%, respectively)[9].

The aim of therapeutic intervention for CHC patients is to halt disease evolution to cirrhosis, or if already established, to prevent its complications[11]; these effects will facilitate regression of fibrosis and help to avoid reinfection of allograft in patients who underwent liver transplantation[12].

## CLASSICAL MANAGEMENT

Interferon (IFN) has been the keystone of HCV therapy for more than 20 years. In the early 1990s, only 5%-10% of patients achieved sustained virological response (SVR) after 24 wk of therapy with IFN[13], and extending the treatment period to 48 wk only increased the rate of SVR to nearly 20%. A considerable and clinically meaningful increase in the rate of SVR (38%-43%) achieved with IFN was finally obtained by the co-administration of ribavirin (RBV), but this combination therapy was limited by additional side effects[14,15].

Modification of the standard IFN molecule to couple with a polyethylene glycol (PEG) further improved the success rates of achieving SVR (54%-56%); unfortunately, the overall safety profile of IFN-based HCV targeted therapy was not correspondingly improved, and the modification might have further increased side effects[16,17]. Nonetheless, the combination treatment with PEG-IFN and RBV has been the standard-of-care (SOC) therapy for CHC since 2003, despite that fact that the related rate of response is suboptimal particularly for genotype 1 HCV (HCV-1), with a less than 46% cure rate[16,17].

## PEG-IFN AND RBV IN "REAL LIFE" CONTEXT

There remains a lack of independent studies on PEG-IFN and RBV therapies that have been carried out in a "real life" context (*i.e.*, outside the context of clinical assays). Aiming to fill this gap, we performed an intention-to-treat (ITT) analysis to evaluate the SVR rates in CHC HCV-1 patients who had participated in a public therapeutic intervention program in southern Brazil. In the cohort of 323 individuals treated with PEG-IFN and RBV for 48 wk, SVR was achieved in 114 (35.3%) of the patients. Thus, the SVR rate in patients with CHC HCV-1 achieved by PEG-IFN and RBV combination treatment in a public health system did not reproduce the results reported from the major clinical trials[18].

The effectiveness of PEG-IFN and RBV combination treatment of hepatitis C has also been evaluated in urban ethnic minority patients[19]. Specifically, ITT analysis of 255 patients with a mean age of 50 years (60% male; 68% genotype 1; 29% with cirrhosis) showed that SVR was achieved in 14% of the genotype 1 patients and 37% of the genotype 2/3 patients ($P < 0.001$). Thus, the dual treatment was less effective in this population than in that reported from controlled trials, suggesting that new strategies are needed to care for such patients.

One explanation for the differences between these two effectiveness studies may be the fact that the Feuerstadt *et al*[19] study lost 26% of the patients to follow-up, whereas the study conducted by de Almeida *et al*[18] did not have such a problem. It is important to remember that losses of more than 20% in cohort studies may reduce the reliability of their results[20].

Nonetheless, in a recent "real life" multicentric study evaluating more than 7000 patients, Marcellin *et al*[21] observed SVR in only 41.8% of HCV-1 patients.

## PREDICTORS OF RESPONSE TO PEG-IFN AND RBV THERAPY

The ability to identify which individuals will respond to HCV treatment remains limited. Pre-treatment predictors of response have became crucial to selecting therapy candidates, and include HCV genotype (2/3 best response), ethnicity (Asians responding best and African Americans worst, with Caucasians and Hispanics in-between), low HCV baseline viral load, younger age, histology (low fibrosis and little or no steatosis), metabolic syndrome, and interleukin 28B (*IL28B*) genotype[22,23].

Genetic variants in the region of the *IL28B* gene were recently shown to have a strong association with the outcome of PEG-IFN and RBV therapy[24,25]. In the cohort from the Individualized Dosing Efficacy *vs* Flat Dosing to Assess Optimal Pegylated Interferon Therapy (IDEAL) study, carriage of the favourable IL28B genotype was associated with SVR rates of 70%-80% in Caucasian patients treated with 48 wk of PEG-IFN and RBV, compared to 30%-40% in patients carrying one of the unfavourable genotypes. *IL28B* genotyping was recommended and immediately proved useful for pre-treatment counselling for HCV-1 patients[26].

The rapid virological response (RVR) and early virological response (EVR) parameters are used as the on-treatment predictors of response. Clinical studies have identified RVR as a valuable early predictor of SVR in patients with CHC[27]. RVR is defined as undetectable serum HCV-RNA level at week 4 of treatment, and is

considered an important milestone in the treatment of patients with CHC. Patients who reach RVR have a 90% chance of attaining SVR, regardless of genotype. RVR assessment is also being used to individualize treatment duration, and represents a key opportunity to individualize a patient's therapy according to treatment-related viral kinetics[27].

The other response predictor, EVR, is observed as a viral load decline at week 12 and is capable of sufficiently distinguishing non-responders from potential responders[28]; as such, EVR is used to modify treatment according to the negative predictive value. In an assessment of HCV-1 patients treated with PEG-IFN and RBV, we observed that the worst results were obtained in patients with partial EVR, age > 40 years, high viral load, and pronounced fibrosis (F4 stage); the expected probability of SVR was only 3.8% for these patients. Thus, presence of these conditions also represents a low chance of achieving SVR, especially if the patient did not show negative PCR results in treatment week 12; it was recommended that treatment discontinuation be considered for such patients[29].

## FIRST DIRECTLY ACTING ANTIVIRALS

Elucidation of the natural history of CHC and the identification of risk factors for its progression to advanced liver disease have allowed many physicians to recommend deferral of treatment (triple therapy) in favour of waiting for new drug availability for patients who are at low risk of progression to significant liver disease. Nearly a decade passed after the licensing of PEG-IFN before a new and more effective therapy was developed. Studies published in 2011 introduced the directly acting antivirals (DAAs), providing a promising new therapeutic approach for treating HCV-1 patients in particular[30-34].

Telaprevir and boceprevir are non-structural serine (NS3/4) protease inhibitors and the first DAAs approved for use in the United States and in the European Union, although many others are in the research and development pipeline[35]. Release of these drugs for clinical use marked a new era in HCV therapy. For many patients with HCV-1, DAA-based therapy has offered a significant improvement from the previous SOC[30,31]. Triple therapy consisting of the immunomodulator PEG-IFN, RBV and DAA agents rapidly became the gold standard for this patient population.

Both telaprevir and boceprevir stop HCV replication by inhibiting the NS3/4 protease, which is required for processing the HCV polyprotein[36]. Although protease inhibitors are potent antiviral agents, they must be given in combination with PEG-IFN and RBV to prevent the rapid selection of resistant variants[37,38]. Thus, optimizing the rates of SVR by this approach will require strategies that promote appropriate use and avoid misuse of these drugs.

Five distinct phase-Ⅲ trials have been performed with boceprevir and telaprevir to date[30-34]. For outcomes of treatment in naïve patients, the SPRINT-2[30] trial examined the effects of PEG-IFN-α-2b in association with RBV and boceprevir, whereas the ADVANCE[31] and ILLUMINATE[34] studies investigated the effects of PEG-IFN-α-2a associated with RBV and telaprevir. These studies observed SVR rates ranging between 63% and 75%. Treatment-experienced patients were included in the re-treatment groups with boceprevir and PEG-IFNα2b plus RBV for the RESPOND-2 study[32] and with telaprevir and PEG-IFN-α-2a plus RBV in the REALIZE study[33]. The SVR rates were between 69% and 88% for the prior relapsers, between 40% and 59% for the prior partial responders, and between 29% and 33% for the prior null responders.

The phase-Ⅲ trials for boceprevir and telaprevir have provided several important insights into the opportunities and limitations of triple therapy for diverse populations; many patients given boceprevir and telaprevir were able to receive a reduced duration of treatment without compromising efficacy. Among the treatment-experienced patients, prior relapsers showed the best responses, whereas less than one-third of the prior null responders attained SVR. For some other patient populations, such as those with advanced fibrosis or cirrhosis, lower rates of SVR were obtained even when the triple therapy approach was applied. The many adverse effects related to telaprevir and boceprevir have limited their preferred status among patients and health professionals alike.

Approximately 60% of patients who initiate the triple therapy regimen achieve an extended RVR[39,40], giving them at higher chance of achieving SVR. For patients who do not achieve an RVR, a delayed virological response (undetectable HCV-RNA before week 24 of treatment) is still beneficial, as it is associated with SVR rates between 64% and 75% if these patients retain the HCV-RNA undetectable status throughout the 48-wk treatment period[30-34]. Such a delayed virological response has been estimated to occur in 15%-20% of HCV patients[41].

The good rates of SVR achieved with triple therapy have led to this therapeutic intervention strategy being recommended as the SOC by the guidelines from the various national Associations for the Study of Liver Disease, including the United States of America (AASLD)[39], Europe (EASL)[42], Latin-America (ALEH)[43], Canada[44], the United Kingdom[45], and France[46]. As with most previous improvements in therapy for HCV, both of the currently licensed DAAs, boceprevir and telaprevir, significantly increase the rate and severity of adverse events. Thus, the higher efficacy that they provide is gained at the cost of additional and potentially severe adverse effects (SAE), mainly in patients with advanced fibrosis[47]. Furthermore, it is important to emphasize that the DAAs can interact with other drugs, as well as induce the emergence of HCV resistant variants[48]; the clinical significance of these potentially complicating features are not yet definitely established.

The most significant "real life" study of triple therapy treatment of cirrhotic patients was recently published by

**Table 1 New drugs for treating chronic hepatitis C**

| Class | Drug | Phase of study |
|---|---|---|
| NS3/4A protease inhibitors | Telaprevir | Approved |
| | Boceprevir | Approved |
| | Simeprevir | Ⅲ |
| | Faldaprevir | Ⅲ |
| | Danoprevir | Ⅱ |
| | Vaniprevir | Ⅱ |
| | Narlaprevir | Ⅱ |
| | Asunaprevir | Ⅱ |
| | GS-9256 | Ⅱ |
| | GW-9451 | Ⅱ |
| | ABT-450/r | Ⅱ |
| | ACH-1625 | Ⅱ |
| | ACH-2684 | Ⅰb |
| | MK-5172 | Ⅱ |
| Nucleoside/nucleotide analogue inhibitors of HCV-RNA dependent RNA polymerase | Sofosbuvir | Ⅲ |
| | Mericitabine | Ⅱ |
| | IDX184 | Ⅱ |
| | PSI-938 | Ⅱ |
| | INX-189 | Ⅰb |
| Non-nucleoside inhibitors of HCV-RNA dependent RNA polymerase | Tegobuvir | Ⅱ |
| | Filibuvir | Ⅱ |
| | Setrobuvir | Ⅱ |
| | BI207127 | Ⅱ |
| | ABT-333 | Ⅱ |
| | VX-222 | Ⅱ |
| | TMC-647055 | Ⅰb |
| NS5A inhibitors of HCV-RNA dependent RNA polymerase | Daclatasvir | Ⅱ |
| | PPI-461 | Ⅰb |
| | GS-5885 | Ⅰb |
| | GSK2336805 | Ⅰb |
| Cyclophilin inhibitors | Alisporivir | Ⅲ |
| | SCY-465 | Ⅱ |

Adapted from Pawlotsky *et al*[50]. HCV: Hepatitis C virus.

the Compassionate Use of Protease Inhibitors in Viral C Cirrhosis (CUPIC) study group. CUPIC is an early-access French program consisting of cirrhotic prior non-responders. The study's results indicated that the telaprevir and boceprevir-based treatments produced a smaller virological response and had a general poor tolerability[47]. Specifically, a 16-wk analysis of 292 patients receiving telaprevir and 205 patients receiving boceprevir showed a significantly higher number of patients with SAE compared to published clinical trials (32.7%-45.2% SAE in CUPIC *vs* 9%-14% in the clinical trials). In addition, death or severe complications were shown to be related to platelet count of $\leqslant 100000/mm^3$ and albumin of $< 3.5$ g/dL, with a risk of 44.1% being estimated for patients with both factors.

Future "real life" studies assessing patients with different fibrosis grade are expected to show lower SVR rates (adherence to treatment will be an important factor in this regard) and higher adverse effects than clinical trials.

It is interesting to consider that even in the United States of America - the first country to approve the new DAAs - a retrospective cross-sectional study[49] found that boceprevir and telaprevir triple therapies were administered to only 18.7% of patients with HCV-1 infection in the 12 mo after the Food and Drug Administration approval was given. This low percentage might reflect concerns about the related side effects and/or anticipation for more effective medications becoming available in the near future.

## NEW DRUGS

On-going clinical trials hold considerable promises for advances in HCV therapy. A newer generation of NS3/4A protease inhibitors are currently under development to deliver more effective, safe, less complex and shorter duration therapy than the current SOC. These new drugs include the NS5A polymerase inhibitors, NS5B polymerase inhibitors, lambda interferon, and cyclophilin inhibitors (Table 1). It is believed that agents featuring increased potency that allow for simultaneous targeting of various aspects of HCV replication using multiple agents will result in IFN-free therapy[50-61].

Amongst the many new drugs that were introduced in mid-2013, two deserve distinction: sofosbuvir and simeprevir. Both of these drugs have concluded the phase-Ⅲ trials and been submitted to the appropriate regulatory agencies. The results thus far have shown that besides favouring a high SVR, both of these drugs present excellent safety profiles (Table 2). Sofosbuvir is a nucleotide analogue HCV NS5B polymerase inhibitor with similar *in vitro* activities against all HCV genotypes (in phase-Ⅱ studies). SVR rates of 87%-90% were obtained in previously untreated patients with HCV-1 infection[62]. Moreover, no virologic breakthrough has been observed during therapy with sofosbuvir in clinical trials, which is consistent with the drug's mechanism of action and high genetic barrier to resistance. The phase-Ⅲ studies have mainly evaluated patients with HCV-1 infection who had not received previous treatment and the SVR rate is estimated to be 90% at 12 wk, supporting the use of sofosbuvir as an effective drug to treat CHC[63].

The new protease inhibitors simeprevir and faldaprevir are currently completing phase-Ⅲ clinical trials as well. Similar to the currently available protease inhibitors, these agents will be applied as triple therapy with PEG-IFN and RBV combination treatment. In the phase-Ⅱ clinical trials of both of these protease inhibitors, the overall SVR rates in the treatment-naive population were between 70% and 85%[51,60], for patients with a prior partial response to PEG-IFN and RBV the SVR rates were between 40% and 70%, and for prior non-responders the SVR rates were between 30% and 50%. These results are similar to those observed with the current SOC[54,59]. The advantages of these two new protease inhibitors are a reduced pill burden and a more favourable adverse event profile when compared with telaprevir and boceprevir[67].

When determining which patients should receive therapy, some authors[68] have suggested considering treating a broader population of patients who might have had treatment delayed in the past. However, concerns about adverse events from PEG-IFN-based regimens remain an obstacle. Additionally, patients with the CC poly-

**Table 2 New directly acting antivirals submitted to regulatory agencies**

| Ref | Phase | Drug | Gen | *n* | Status | PEG-IFN | RBV | SVR |
|---|---|---|---|---|---|---|---|---|
| Kowdley *et al*[62] (ATOMIC) | Ⅱ | Sofosbuvir | 1 | 316 | Naïve | Y | Y | 87%-89% |
| Lawitz *et al*[63] | Ⅱ | Sofosbuvir | 1 | 122 | Naïve | Y | Y | 90% |
| | | | 2, 3 | 25 | | | | 92% |
| Gane *et al*[56] (ELECTRON) | Ⅱa | Sofosbuvir | 2, 3 | 40 | Naïve | Y/N | Y/N | 60%-100% |
| | | | 1 | 35 | Naïve/experienced | N | Y | 10%-84% |
| Lawitz *et al*[64] (NEUTRINO/FISSION) | Ⅲ | Sofosbuvir | 1, 4, 5, 6 | 327 | Naïve | Y | Y | 90% |
| | | | 2, 3 | 499 | Naïve | N | Y | 67% |
| Jacobson *et al*[65] (POSITRON/FUSION) | Ⅲ | Sofosbuvir | 2, 3 | 207 | Naïve | N | Y | 78% |
| | | | 2, 3 | 103 | Experienced | | | 50% |
| Fried *et al*[51] (PILLAR) | Ⅱb | Simeprevir | 1 | 388 | Naïve | Y | Y | 75%-86% |
| Zeuzem *et al*[54] (ASPIRE) | Ⅱb | Simeprevir | 1 | | Experienced | Y | Y | 70%-96% |
| Jacobson *et al*[66] (QUEST 1) | Ⅲ | Simeprevir | 1 | 394 | Naïve | Y | Y | 80% |
| Manns *et al*[67] (QUEST 2) | Ⅲ | Simeprevir | 1 | 391 | Naïve | Y | Y | 81% |

Gen: Genotype; RBV: Ribavirin; PEG-IFN: Polyethylene glycol-interferon; Y: Yes; N: No; SVR: Sustained virological response.

morphism of IL28B, which is associated with increased response to therapy, should be able to achieve SVR from dual therapy that is comparable to that anticipated for the triple therapy; no randomized clinical trials testing this assertion have been published though[24].

Boceprevir and telaprevir must not be administered as monotherapies and should only be given in combination with PEG-IFN and RBV in order to minimize and prevent development of viral resistance[39]. The importance of adherence to all drugs in the triple therapy regimen must be fully explained to each patient, and potential barriers to adherence should be addressed prior to initiation of the therapy regimen[68]. Regardless of the noteworthy increase in the chance of obtaining SVR with these protease inhibitors, the current treatment with DAAs is more complex; it also increases the chance of SAE, can promote viral resistance, and may not be effective in some sub-groups[69,70]. Patients with cirrhosis who are prior null responders have a particularly low chance of obtaining SVR with triple therapy (about 15%), and the decision to wait for new treatments in the future must be confronted with the consequences of not starting treatment immediately.

## WHO SHOULD WAIT FOR TREATMENT?

Correct selection of patients for therapy initiation or delay is also necessary to make treatment as cost-effective as possible. For the newly introduced DAA agents, professionals may be unable to initially treat all patients requesting therapy and will be forced to allocate scarce resources appropriately. Some authors have shown that both universal triple therapy and IL-28B-guided triple therapy are cost-effective when the least-expensive protease inhibitor is used for patients with advanced fibrosis[71].

With the expectation of highly effective and better-tolerated new therapies becoming available in the near future (including those that are IFN-free), the decision about whether or not to treat patients immediately may present a challenge to clinical management. This decision must take many factors into consideration, such as the probability of obtaining SVR, the urgency of treatment, contraindications, tolerability, motivation, and the actual perspective of access to the new drugs. Though treatment duration of the new drugs is still evolving, a close to 100% SVR rate is almost certain to become a reality within the next 3 years, at least for treatment-naïve patients; cirrhotic patients will likely remain more difficult to treat.

Thus, the major clinical question facing physicians caring for patients with CHC in 2013 is: Does the patient need treatment now or is there time to wait for the anticipated very promising newer treatments? In favour of immediate treatment, independently from other factors, one should consider that triple therapy enhances the chances of achieving SVR. Certainly, earlier initiation of therapy increases the chance of success; from a practical standpoint, if SVR is achieved, disease progression can be arrested. Furthermore, it is important to consider the present difficulties in predicting the stage or time of progression of a particular patient's disease. Uncertainties regarding the time of approval, dispensing, and cost of these anticipated future drugs and therapies can affect the decision as well[72].

The reasoning to defer therapy must consider the fact that the first generation DAAs are associated with SAE; if the therapy fails, it will affect future treatments. The progression of liver disease is generally slow, and future treatments will produce higher rates of SVR, including for special patient populations. In addition, it is anticipated that the regimen for these future drugs will be simple (greater adhesion), with less adverse events, and probably IFN-free, and that the future treatments will be effective in patients with non-genotype 1 HCV[72].

Shiffman and Benhamou[73] present a rather interesting position, suggesting to treat patients with F1/F2, as not treating them would favour the reduction of SVR in the population. Paradoxically, they consider postponing treatment in patients who are difficult to treat (non-white, high viral load, IL28 TT polymorphism carrier, advanced fibrosis, and null responder).

Given the scenarios presented herein, we deem that patients with mild to moderate disease should be advised to wait for the newer drugs and therapies to become available, as IFN-free treatments are likely to emerge with greater chance for SVR and fewer side effects than the current treatments. In contrast, patients with advanced fibrosis (F3), and more so those with cirrhosis (F4), will be those with the greatest need for more expedited treatment.

We are particularly intrigued by the United Kingdom's consensus guidelines for the use of the protease inhibitors boceprevir and telaprevir in HCV-1 patients[45] for cirrhotic patients who are also prior null responders. The decision to wait for novel therapies or to use a 4-wk lead-in with PEG-IFN and RBV to identify patients more likely to achieve SVR should be made following careful and balanced discussion with the patient. Patients with < 1 log decline during the lead-in phase have been shown to have low SVR (about 6%), indicating that there is a low chance of achieving SVR for those failing to reach the 1 log decline by week 4 in the lead-in period[32,74]. Therefore, it is important to determine whether and the extent of treatment that should be given to prior null responder cirrhotic patients, considering the high risk of SAE and low chance of SVR.

In conclusion, we propose that treatment-naïve patients with HCV-1 CHC be evaluated for IL28B genotype and fibrosis grade (by invasive or non-invasive methods). Those with a favourable IL28B genotype (CC) and with mild fibrosis can be treated with PEG-IFN and RBV. If the IL28B TC or TT polymorphisms are present, along with mild fibrosis (F1-F2), then treatment may be deferred. In patients with pronounced fibrosis (F3-F4), DAAs are indicated. On the other hand, for patients who are prior relapsers, DAAs are recommended; DAAs may be considered for prior partial responders, and prior null-responders should be evaluated for fibrosis grade (by invasive or non-invasive methods). If advanced fibrosis is present (F3), treatment may be indicated. With cirrhosis (F4), lead-in is recommended; in this case, if < 1 log decline occurs during the lead-in phase, then treatment could be deferred, and if > 1 log decline occurs, then DAAs may be indicated.

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