

# Addressing Adherence Prior to Initiating HCV Treatment

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Section 4: [Evaluation and Preparation for Hepatitis C Treatment](#)

Topic 4: [Addressing Adherence Prior to Initiating HCV Treatment](#)

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## Measurement of Adherence

### Definition of Adherence

Medication adherence refers to whether patients take their medications as prescribed.[1] Most medical providers now prefer using the term adherence as opposed to compliance, since the latter implies the patient passively follows orders to take medications.[1,2] Adherence has been further divided into the subcategories of initiation, implementation and persistence, and discontinuation.[1]

### Methods to Measure Adherence

Adherence to drug treatment is difficult to measure accurately. Several methods to quantify drug adherence exist, though all have limitations.[2,3,4,5]

- **Patient Self-Reports:** This measure has low cost and can help to determine reasons for nonadherence. A major limitation is that it tends to reflect primarily short-term adherence and appears to be accurate only if poor adherence, not good adherence, is reported.
- **Pill Counts:** This measure, based on the return of excess pills, provides tangible evidence of nonadherence and can aid in understanding the dynamics surrounding missed medication. Limitations include the requirement for patients to return medication packaging and the potential for “pill dumping” to appear adherent, which may lead to overestimation of adherence.
- **Pharmacy Refills:** This adherence measure, sometimes referred to as medication possession ratio, compares actual versus expected refills. The percent adherence is typically calculated as the sum of the days’ supply of medication dispensed over a fixed time interval (e.g. 12 weeks) divided by the number of days between the first and final fills of that interval. Advantages include: (1) does not require patient recall, (2) reduces susceptibility to patient deception, and (3) allows for retrospective assessment from computerized pharmacy records. The potential disadvantage is the lack of information on adherence patterns within an interval.
- **Drug Levels:** This adherence measure determines drug concentrations. The assays are expensive, levels typically reflect only recent doses of medications, and the serum level may not accurately predict intracellular concentration of drugs.
- **Microelectronic Monitors:** Electronic systems can record medication bottle openings and closings, allowing reconstruction of patterns of adherence. These monitors, however, are costly and limited by the assumption that the correct dose is taken each time the bottle is opened, which may lead to inaccuracies if multiple doses (or no doses) are removed when the bottle is opened.



## Adherence to Treatment and Correlation with Response

### Adherence to Direct-Acting Antiviral Therapy and Virologic Response

Adherence with direct-acting antiviral (DAA) therapy is inherently much easier than with older interferon and peginterferon-based therapies due to markedly better medication side effect profile, easier dosing schedule, and overall shorter treatment duration. Less is known about the predictors or impact of adherence to these agents than to interferon-based therapies, largely due to the lack of population-based studies evaluating DAA adherence in clinical practice settings. Much of the adherence data to date with DAA therapy have derived from secondary analyses of clinical trials; these analyses should be interpreted with caution given the intensely monitored setting of such trials, which does not reflect what occurs in routine clinical practice. There are, however, several studies that provide some insight into DAA adherence:

- **Ledipasvir-Sofosbuvir with or without a Third DAA:** In this trial that enrolled primarily an inner-city patient population, investigators examined adherence via pill count and microelectronic monitors among study participants taking ledipasvir-sofosbuvir, with or without a third drug (GS-9451 or GS-9669).[\[6\]](#) Adherence rates overall were excellent (greater than 95% with all regimens) ([Figure 1](#)).[\[6\]](#) Adherence rates were slightly lower in 12-week regimens than in a 6-week regimen and with a pill burden of 3 pills per day (95%) versus 1 pill per day (98%). In the 12-week treatment arm, adherence to ledipasvir-sofosbuvir was significantly lower among participants who used drugs (including marijuana, cocaine, or heroin) or abused alcohol (more than 3 drinks per day or more than 5 drinks in a 2 to 4 hour period) within 6 months prior to starting DAA therapy.[\[6\]](#)
- **Sofosbuvir-Based Therapy:** In a study of veterans living with chronic HCV infection who were enrolled in the Electronically Retrieved Cohort of HCV-Infected Veterans (ERCHIVES) study, adherence to different sofosbuvir-based regimens (e.g. sofosbuvir plus simeprevir; ledipasvir-sofosbuvir; sofosbuvir plus ribavirin; and sofosbuvir plus peginterferon plus ribavirin) was assessed using pharmacy refill data.[\[7\]](#) The SVR rates for the all-oral regimens of ledipasvir-sofosbuvir and sofosbuvir plus simeprevir remained high even when the person received less than a full prescribed course of treatment.[\[7\]](#)
- **DAA Therapy Among People Who Inject Drugs:** In a clinical trial examining the impact of directly observed therapy (DOT) on adherence among adults with HCV genotype 1 who received DAA therapy within an opiate agonist program, 51 participants were randomized to DOT (received DAA doses from study nurses at the same time as receiving methadone or buprenorphine), 48 to group treatment (received DAA doses during attendance at weekly treatment groups), and 51 to individual treatment (self-administered DAA therapy).[\[8\]](#) Adherence to DAA therapy was determined via electronic blister packs and self-report. Mean DAA adherence by self-report over the entire HCV treatment course was high in all three arms (DOT = 94.8%; group = 95.5%; and individual = 94.2%).[\[8\]](#) The SVR 12 rate was higher in the DOT and group arms than in the individual arm (DOT: 98%; group: 93%; individual: 89%), but the differences were not statistically significant ( $P = 0.19$ ).[\[8\]](#) These results provide important evidence supporting administration of DAA-based HCV treatment to people who inject drugs.

## Changes in Antiviral Adherence over the HCV Treatment Course

### Changes in Antiviral Adherence over Time

Examining how antiviral adherence changes over the course of HCV therapy can identify time periods when antiviral adherence declines and when medical providers should emphasize the importance of adherence. At this time, most of these data are from studies of interferon-based therapy. In a cohort study among 5,706 patients with chronic HCV infection, mean adherence to peginterferon and ribavirin (determined by pharmacy refills over 12-week intervals) was high during the initial 12 weeks of treatment, but declined over the subsequent course of therapy ([Figure 2](#)).<sup>[9]</sup> Overall, there was a mean decline in ribavirin adherence of 6.6 percentage points per 12-week interval and in interferon adherence of 3.4 percentage points per 12-week interval.<sup>[9]</sup> Notably, during the final 12 weeks of HCV therapy for genotype 1 or 4 patients (i.e. weeks 36 to 48), mean adherence to peginterferon was 89% and mean adherence to ribavirin was 76%.<sup>[9]</sup> Similar results were observed in a separate cohort study of HCV treatment adherence among 333 persons with HIV and HCV coinfection.<sup>[10]</sup> In that study, there was a mean decline in interferon adherence of 2.5 percentage points and in ribavirin adherence of 4.1 percentage points per 12-week interval.<sup>[10]</sup> Thus, these data indicate that adherence to both peginterferon and ribavirin declines during treatment, particularly after week 12 of therapy. One study evaluated the change in adherence to DAA treatment over time: adherence to ledipasvir-sofosbuvir with or without a third DAA was high over the initial 4-weeks of treatment, but subsequently declined over weeks 4 to 8 and 8 to 12 ([Figure 3](#)).<sup>[6]</sup>

### Within-Person Differences in Adherence

In the initial two studies discussed above,<sup>[9,10]</sup> adherence to ribavirin was lower than adherence to peginterferon over each 12-week interval of HCV therapy. The authors suggested that the higher frequency of ribavirin administration (twice daily) may make it more burdensome to remember and more vulnerable to drop-offs in adherence over time. The authors also suggested that patients may select a day of the week on which they administer their peginterferon injection prior to the start of therapy, and this scheduling routine might facilitate higher levels of adherence for interferon than ribavirin. Studies of adherence to DAA-based HCV treatment regimens with more than one drug (e.g. sofosbuvir plus simeprevir; sofosbuvir plus ribavirin; paritaprevir-ritonavir-ombitasvir plus dasabuvir; daclatasvir plus ribavirin; elbasvir-grazoprevir plus ribavirin) have not examined within-person differences to the individual drugs within these regimens. However, the presence of coformulated DAA regimens and single-tablet regimens likely mitigates this issue.

## Barriers to Adherence with Hepatitis C Therapy

### Factors Associated with Adherence

The critical factors that can influence adherence to a drug regimen fall into four main groups:

1. **Patient Factors:** Age; use of injection or non-injection drugs; alcohol consumption; presence of comorbidities (e.g. psychiatric disease); use of other prescribed or over-the-counter medications that could potentiate drug interactions and side effects; literacy (medical and otherwise); physical impairment (e.g. vision problems, impaired dexterity); cognitive impairment; availability of social support
2. **Medication Regimen:** Dosing complexity; side effects; number of medications in a treatment regimen; coformulation of drugs in a regimen; food requirements
3. **Patient-Health Care Provider Relationship:** Closeness of relationship; trust; provider-patient communication skills
4. **System of Care:** Access to healthcare; continuity of care; medication costs

### Barriers to Adherence to Direct-Acting Antiviral-Based HCV Therapy

Some studies have evaluated the factors associated with nonadherence to DAAs to treat chronic HCV infection. One group evaluated patient-reported outcomes (determined by short-form-36 questionnaire, chronic liver disease questionnaire-hepatitis C version, and functional assessment of chronic illness therapy-fatigue) from 4,825 patients who received either DAA-based or peginterferon-containing HCV treatment regimens via validated questionnaires to assess functional status.[\[11\]](#) Among patients prescribed ledipasvir-sofosbuvir, with or without a third medication, longer treatment duration, higher pill burden, and recent substance use were associated with lower adherence.[\[6\]](#) Notably, patient characteristics, such as symptoms of depression or psychiatric disease, were not associated with lower adherence.[\[6\]](#) In the study of the veterans living with chronic HCV infection who underwent sofosbuvir-based therapy within the ERCHIVES, SVR rates were not significantly lower among patients who received less than the full prescribed course of treatment, and no consistent factor was associated with lower prescription rates.[\[7\]](#) In another study of 74 patients in a community-based HCV clinic, adherence patterns were measured via self-administered weekly adherence questionnaires.[\[12\]](#) History of lifetime depression and substance use were highly prevalent in this cohort. While 41% of participants had at least one missed dose, the mean number of missed doses in weeks with a missed dose was only 1.7 days. Overall, only 11% of all treatment weeks (combined amongst all 74 patients) had a recorded missed dose.[\[12\]](#) In univariable analysis, depression and drug use in the past 30 days was associated with missing doses. However in multivariable analysis, the only factor independently associated with missing doses was moderate to heavy alcohol use.[\[12\]](#)

## Addressing Adherence Problems Prior to HCV Treatment

### Strategies to Maximize Adherence

Given that adherence to HCV therapy has been shown to decrease over the HCV treatment course and since a higher level of adherence to HCV therapy is associated with an increased likelihood of SVR, adherence to the HCV treatment regimen should be a focus of clinical care teams prior to and throughout HCV therapy to help achieve SVR. Although interventions to increase adherence to HCV therapy have not been tested,<sup>[13]</sup> medical providers could consider a number of strategies to help patients increase adherence or maintain high levels of antiviral adherence during their treatment course ([Figure 4](#)).

### Evaluating Adherence

At visits prior to and during treatment, providers should educate their patients on the importance of adherence to their regimen. Medical providers should probe for potential barriers to adherence and discuss ways tailored to each patient's needs that will help overcome these barriers. Medication diaries, weekly pill sorting in medication boxes, and reminder alarms may be helpful to establish medication-taking routines. In addition, patients should be educated on the common toxicities associated with each medication and be provided with plans for how to address these adverse effects. Addressing HCV treatment-related toxicities soon after they occur may help to minimize the likelihood of declines in medication adherence. Further, medical providers should perform a careful medication reconciliation prior to initiating DAA therapy to ensure that potentially harmful drug interactions are avoided. Patients should be counseled to notify their HCV provider if additional medications are initiated during HCV treatment. Peer groups or a patient-designated ally can provide social support and encourage adherence among patients receiving HCV therapy. Finally, medical providers can determine the dates of antiviral fills to allow for calculation of antiviral adherence ( $\% \text{ adherence} = \text{days' supply of antiviral prescribed} / \text{days between antiviral fills}$ ), permitting real-time monitoring of adherence and feedback to patients.

## Summary Points

- Adherence to an HCV treatment regimen should be a focus of clinical care teams prior to and throughout HCV therapy to help achieve SVR.
- Adherence to DAA therapy has been reportedly high although much of the published data derives from secondary analyses of clinical trials. Small differences in adherence rates do not appear to impact rates of SVR in the DAA era.
- Adherence to both peginterferon-based and DAA-based HCV treatment has been shown to decline over the treatment course. Thus, clinicians should emphasize the importance of maintaining high levels of adherence to their regimen throughout treatment. Shorter treatment regimens may provide an advantage for adherence.
- Clinicians should not be reluctant to initiate HCV treatment in patients with a history of uncontrolled depression, bipolar disorder, post-traumatic stress disorder, or schizophrenia, particularly if these conditions have been controlled, since observational studies suggest that these conditions are not associated with lower antiviral adherence.
- Medical providers should implement strategies individualized to each patient's needs to help increase adherence or maintain high levels of antiviral adherence during HCV treatment.

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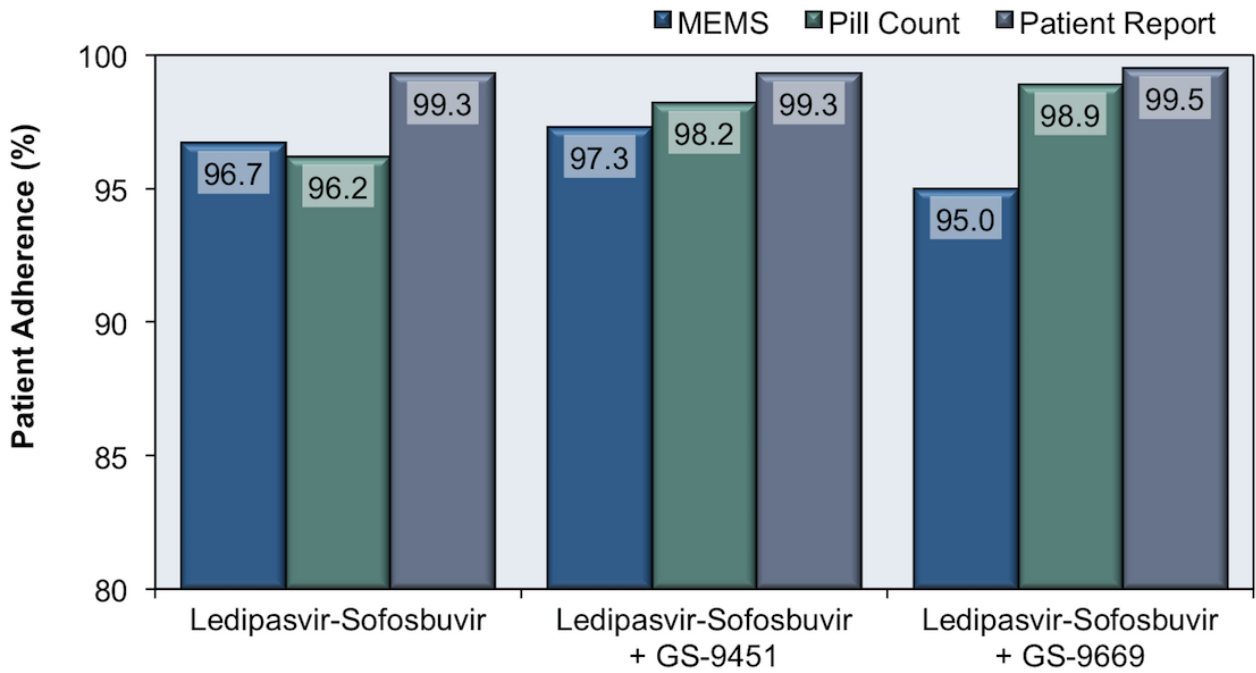
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## Figures

**Figure 1 Adherence with All-Oral Direct-Acting HCV Antiviral Regimens**

In this study, investigators measured adherence with microelectronic monitors (MEMS), pill count, and patient report. All measures and all regimens had greater than 95% adherence.

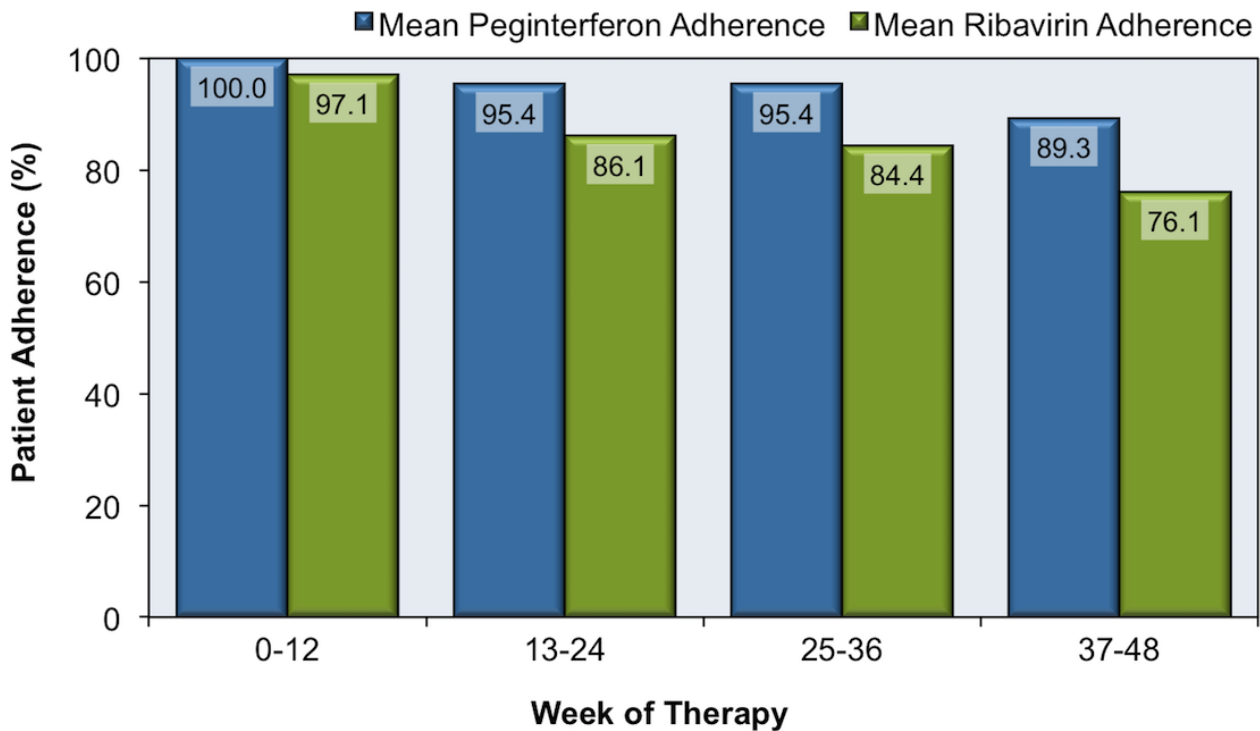
Source: Petersen T, Townsend K, Gordon LA, et al. High adherence to all-oral directly acting antiviral HCV therapy among an inner-city patient population in a phase 2a study. *Hepatology*. 2016;10:310-9.



**Figure 2 Adherence to Peginterferon and Ribavirin During 48 Weeks of HCV Therapy**

This study examined the mean adherence to peginterferon and ribavirin over 12-week intervals of treatment among 5,706 patients treated for chronic hepatitis C virus infection in the Veterans Health Administration between 2003 and 2006. Adherence to both antivirals was high over the initial 12 weeks of therapy but subsequently declined. For each interval, mean adherence to peginterferon was higher than for ribavirin.

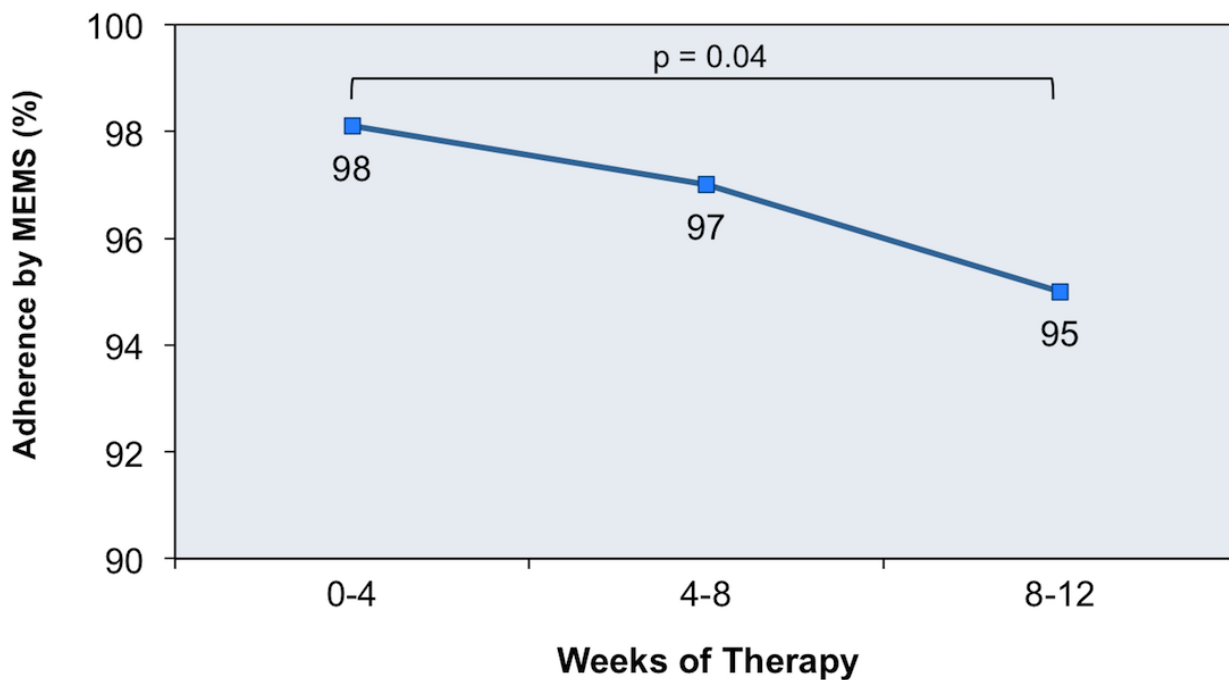
Source: Lo Re V, 3rd, Teal V, Localio AR, Amorosa VK, Kaplan DE, Gross R. Relationship between adherence to hepatitis C virus therapy and virologic outcomes: a cohort study. *Ann Intern Med.* 2011;155:353-60.



### Figure 3 Adherence to DAA Therapy over a 12-Week HCV Treatment Course

This graphic shows a decline in adherence over a 12-week treatment course with DAA therapy.

Source: Petersen T, Townsend K, Gordon LA, et al. High adherence to all-oral directly acting antiviral HCV therapy among an inner-city patient population in a phase 2a study. *Hepatol Int.* 2016;10:310-9.



**Figure 4 Potential Strategies to Maximize Adherence During Chronic HCV Treatment**

Strategy	Potential Advantages
Adherence education	<ul style="list-style-type: none"> <li>• Encourages patients to learn about medications</li> </ul>
Directly observed therapy	<ul style="list-style-type: none"> <li>• Might encourage adherence</li> <li>• Helps reporting of treatment-related adverse effects</li> </ul>
Discuss adherence barriers	<ul style="list-style-type: none"> <li>• Encourages identification of barriers to adherence and potential solutions to overcome them</li> </ul>
Encourage pill sorting	<ul style="list-style-type: none"> <li>• Helps establish routine</li> </ul>
Medication diary	<ul style="list-style-type: none"> <li>• Helps establish routine</li> <li>• Allows identification of patterns of missed doses</li> </ul>
Reminder alarms	<ul style="list-style-type: none"> <li>• Helps establish routine</li> </ul>
Support group	<ul style="list-style-type: none"> <li>• Provides social support to take medications as prescribed, report treatment-related adverse effects</li> </ul>