

Addressing Anticipated Adherence Problems Prior to Treatment

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

Lesson 5: [Addressing Anticipated Adherence Problems Prior to 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 non-adherence. A major limitation is that it reflects only 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 non-adherence 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 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 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

Peginterferon and Ribavirin Adherence and Virologic Response

Data with peginterferon-based treatment regimens used prior to the direct-acting antiviral (DAA) era have shown that adherence of 85% or more to peginterferon and ribavirin, as measured by pharmacy refills, has been associated with increased likelihood of early virologic response, or HCV suppression after the initial 12 weeks of HCV therapy.[6] Two cohort studies using data from the Veterans Health Administration measured adherence to peginterferon and ribavirin during the HCV treatment course using pharmacy-refill measures over four 12-week intervals and evaluated the relationship between adherence and early virologic response and sustained virologic response (SVR) in patients with chronic HCV without HIV coinfection and in HIV/HCV coinfecting patients.[7,8] Both of these studies found that the proportion of patients with early virologic response increased with higher levels of adherence to both peginterferon and ribavirin. These data, although not directly applicable to current DAA-based therapy, provide evidence that higher levels of adherence to an HCV treatment regimen throughout the course of therapy are associated with increased HCV virologic response.

Adherence to Direct-Acting Antiviral Therapy and Virologic Response

Adherence with 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 course.

- **Boceprevir plus Peginterferon and Ribavirin:** To evaluate the relationship between adherence with boceprevir-based antiviral therapy and SVR, investigators analyzed data from two phase 3 clinical trials (SPRINT-2 and RESPOND-2).[9] Patients with HCV genotype 1 patients to received peginterferon and ribavirin, plus either boceprevir or placebo. Adherence was assessed by patients' self-reported dosing diaries and by the amount of study drug dispensed and returned (pill counts). Note that boceprevir (and placebo) dosing required taking four capsules three times daily. Among 1,500 patients enrolled in the two trials, 63 to 68% of previously untreated patients and 68 to 71% of those who failed prior therapy adhered to 80% or more of their assigned treatment duration. Patients who adhered to 80% or more of their assigned treatment duration had higher SVR rates than those who adhered to less than 80% of their treatment duration.
- **Ledipasvir-Sofosbuvir with or without a Third DAA:** In a trial that enrolled primarily an inner-city patient population and evaluated SVR rates with the regimen ledipasvir-sofosbuvir, with or without a third drug (GS-9451 or GS 9669), adherence rates overall were excellent (greater than 95% with all regimens) (Figure 1).[10] 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%).
- **Sofosbuvir-Based Therapy:** In a study of chronic HCV-infected veterans within the Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES) study, the 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.[11] The SVR rates remained high regardless of the type of sofosbuvir-based therapy, even when only 50% of a full medication treatment course was prescribed.
- **DAA Therapy Among People Who Inject Drugs:** In a recent presentation of results from a clinical trial examining adherence among HCV genotype 1 adults who received DAA therapy within an opiate agonist program, 51 participants were randomized to directly observed therapy (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).[12] Adherence with DAA therapy was determined by electronic blister packs and self-report.

Mean DAA adherence by self-report over the entire HCV treatment course was high in all three arms (directly observed therapy (DOT): 94.8%; group: 95.5%; individual 94.2%). However, overall adherence was higher in participants randomized to directly observed therapy compared to those in either group or individual HCV treatment (directly observed therapy 82.8%; group 77.5%; and individual 74.4%, $P=0.007$). The SVR was also higher in the directly observed therapy and group arms than in the individual arm, but the differences were not statistically significant. The results provide important evidence supporting the treatment of hepatitis C in 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, 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](#)).^[7] 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. 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%. Similar results were observed in a separate cohort study of HCV treatment adherence among 333 HIV/HCV-coinfected patients.^[8] 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. 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](#)).^[10]

Within-Person Differences in Adherence

In both of the above studies, 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 increasing presence of co-formulated DAA regimens and single-tablet regimens is likely to mitigate 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-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; co-formulation of drugs in a regimen; food requirements.
3. **Patient-Health Care Provider Relationship:** Closeness of relationship; 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 non-adherence 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.[\[13\]](#) 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.[\[10\]](#) Notably, patient characteristics, such as symptoms of depression or psychiatric disease, were not associated with lower adherence.[\[10\]](#) In the study of chronic HCV-infected veterans 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.[\[11\]](#)

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, 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 to ensure that potentially harmful drug interactions are avoided. Peer groups or a patient-designated ally can provide social support and encourage adherence among patients receiving antiviral 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 HCV treatment regimen should be a focus of clinical care teams prior to and throughout HCV therapy to help achieve SVR.
- Higher levels of adherence to peginterferon-based and DAA-based HCV treatment regimens are associated with higher rates of SVR.
- 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 and shorter treatment regimens may provide an advantage for adherence.
- Clinicians should not be reluctant to initiate treatment in patients with depression, bipolar disorder, post-traumatic stress disorder, and schizophrenia, particularly if these conditions have been controlled.
- 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.

Citations

1. Vrijens B, De Geest S, Hughes DA, et al. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol*. 2012;73:691-705.
[\[PubMed Abstract\]](#) -
2. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353:487-97.
[\[PubMed Abstract\]](#) -
3. Wagner JH, Justice AC, Chesney M, Sinclair G, Weissman S, Rodriguez-Barradas M. Patient- and provider-reported adherence: toward a clinically useful approach to measuring antiretroviral adherence. *J Clin Epidemiol*. 2001;54 Suppl 1:S91-8.
[\[PubMed Abstract\]](#) -
4. Alcoba M, Cuevas MJ, Perez-Simon MR, et al. Assessment of adherence to triple antiretroviral treatment including indinavir: role of the determination of plasma levels of indinavir. *J Acquir Immune Defic Syndr*. 2003;33:253-8.
[\[PubMed Abstract\]](#) -
5. Hansen RA, Dusetzina SB, Dominik RC, Gaynes BN. Prescription refill records as a screening tool to identify antidepressant non-adherence. *Pharmacoepidemiol Drug Saf*. 2010;19:33-7.
[\[PubMed Abstract\]](#) -
6. Lo Re V, 3rd, Amorosa VK, Localio AR, et al. Adherence to hepatitis C virus therapy and early virologic outcomes. *Clin Infect Dis*. 2009;48:186-93.
[\[PubMed Abstract\]](#) -
7. 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.
[\[PubMed Abstract\]](#) -
8. Lo Re V, 3rd, Teal V, Localio AR, Amorosa VK, Kaplan DE, Gross R. Adherence to hepatitis C virus therapy in HIV/hepatitis C-coinfected patients. *AIDS Behav*. 2013;17:94-103.
[\[PubMed Abstract\]](#) -
9. Gordon SC, Yoshida EM, Lawitz EJ, et al. Adherence to assigned dosing regimen and sustained virological response among chronic hepatitis C genotype 1 patients treated with boceprevir plus peginterferon alfa-2b/ribavirin. *Aliment Pharmacol Ther*. 2013;38:16-27.
[\[PubMed Abstract\]](#) -
10. 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.
[\[PubMed Abstract\]](#) -
11. Butt AA, Yan P, Shaikh OS, Chung RT, Sherman KE. Treatment adherence and virological response rates in hepatitis C virus infected persons treated with sofosbuvir-based regimens: results from ERCHIVES. *Liver Int*. 2016;36:1275-83.
[\[PubMed Abstract\]](#) -
12. Litwin AH, Agyemang L, Akiyama M, Norton B, Ning Y, Heo M, Umanski G, Arnsten JH. The PREVAIL Study: Intensive models of HCV care for people who inject drugs. *J Hepatol* 2017; 66 [Supplement]:S72.
[\[Journal of Hepatology\]](#) -

13. Younossi ZM, Stepanova M, Henry L, Nader F, Younossi Y, Hunt S. Adherence to treatment of chronic hepatitis C: from interferon containing regimens to interferon and ribavirin free regimens. *Medicine (Baltimore)*. 2016;95:e4151.
[\[PubMed Abstract\]](#) -

References

- Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, Wong PK. Medication compliance and persistence: terminology and definitions. *Value Health*. 2008;11:44-7.
[\[PubMed Abstract\]](#) -
- Evon DM, Esserman DA, Bonner JE, Rao T, Fried MW, Golin CE. Adherence to PEG/ribavirin treatment for chronic hepatitis C: prevalence, patterns, and predictors of missed doses and nonpersistence. *J Viral Hepat*. 2013;20:536-49.
[\[PubMed Abstract\]](#) -
- Gross R, Zhang Y, Grossberg R. Medication refill logistics and refill adherence in HIV. *Pharmacoepidemiol Drug Saf*. 2005;14:789-93.
[\[PubMed Abstract\]](#) -
- Grossberg R, Gross R. Use of pharmacy refill data as a measure of antiretroviral adherence. *Curr HIV/AIDS Rep*. 2007;4:187-91.
[\[PubMed Abstract\]](#) -
- Lo Re V, 3rd, Amorosa VK, Localio AR, et al. Adherence to hepatitis C virus therapy and early virologic outcomes. *Clin Infect Dis*. 2009;48:186-93.
[\[PubMed Abstract\]](#) -
- Lo Re V, 3rd, Teal V, Localio AR, Amorosa VK, Kaplan DE, Gross R. Adherence to hepatitis C virus therapy in HIV/hepatitis C-coinfected patients. *AIDS Behav*. 2013;17:94-103.
[\[PubMed Abstract\]](#) -
- 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.
[\[PubMed Abstract\]](#) -
- Mason K, Dodd Z, Guyton M, et al. Understanding real-world adherence in the directly acting antiviral era: A prospective evaluation of adherence among people with a history of drug use at a community-based program in Toronto, Canada. *Int J Drug Policy*. 2017 Jun 12. [Epub ahead of print]
[\[PubMed Abstract\]](#) -
- Mathes T, Antoine SL, Pieper D. Factors influencing adherence in Hepatitis-C infected patients: a systematic review. *BMC Infect Dis*. 2014;14:203.
[\[PubMed Abstract\]](#) -
- McHutchison JG, Manns M, Patel K, et al. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. *Gastroenterology*. 2002;123:1061-9.
[\[PubMed Abstract\]](#) -
- Miller LG, Hays RD. Measuring adherence to antiretroviral medications in clinical trials. *HIV Clin Trials*. 2000;1:36-46.

[\[PubMed Abstract\]](#) -

- Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med.* 2005;353:487-97.
[\[PubMed Abstract\]](#) -
- Raptopoulou M, Tsantoulas D, Vafiadi I, et al. The effect of adherence to therapy on sustained response in daily or three times a week interferon alpha-2b plus ribavirin treatment of naive and nonresponder chronic hepatitis C patients. *J Viral Hepat.* 2005;12:91-5.
[\[PubMed Abstract\]](#) -
- Reddy KR, Shiffman ML, Morgan TR, et al. Impact of ribavirin dose reductions in hepatitis C virus genotype 1 patients completing peginterferon alfa-2a/ribavirin treatment. *Clin Gastroenterol Hepatol.* 2007;5:124-9.
[\[PubMed Abstract\]](#) -
- Shiffman ML, Di Bisceglie AM, Lindsay KL, et al. Peginterferon alfa-2a and ribavirin in patients with chronic hepatitis C who have failed prior treatment. *Gastroenterology.* 2004;126:1015-23.
[\[PubMed Abstract\]](#) -
- Steiner JF, Koepsell TD, Fihn SD, Inui TS. A general method of compliance assessment using centralized pharmacy records. Description and validation. *Med Care.* 1988;26:814-23.
[\[PubMed Abstract\]](#) -
- Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol.* 1997;50:105-16.
[\[PubMed Abstract\]](#) -
- Weiss JJ, Brau N, Stivala A, Swan T, Fishbein D. Review article: adherence to medication for chronic hepatitis C - building on the model of human immunodeficiency virus antiretroviral adherence research. *Aliment Pharmacol Ther.* 2009;30:14-27.
[\[PubMed Abstract\]](#) -
- Wendel CS, Mohler MJ, Kroesen K, Ampel NM, Gifford AL, Coons SJ. Barriers to use of electronic adherence monitoring in an HIV clinic. *Ann Pharmacother.* 2001;35:1010-5.
[\[PubMed Abstract\]](#) -

Figures

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

In this study, investigators measured adherence with 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.

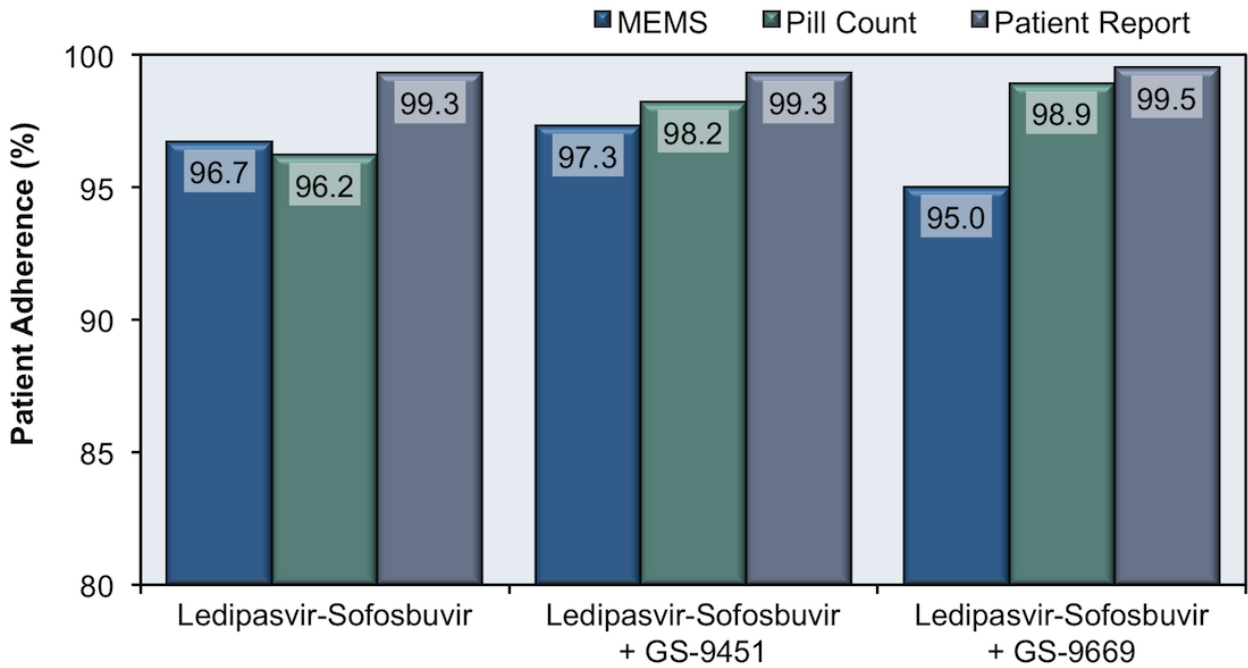


Figure 2 Adherence to Peginterferon and Ribavirin During 48 Weeks of Therapy

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.

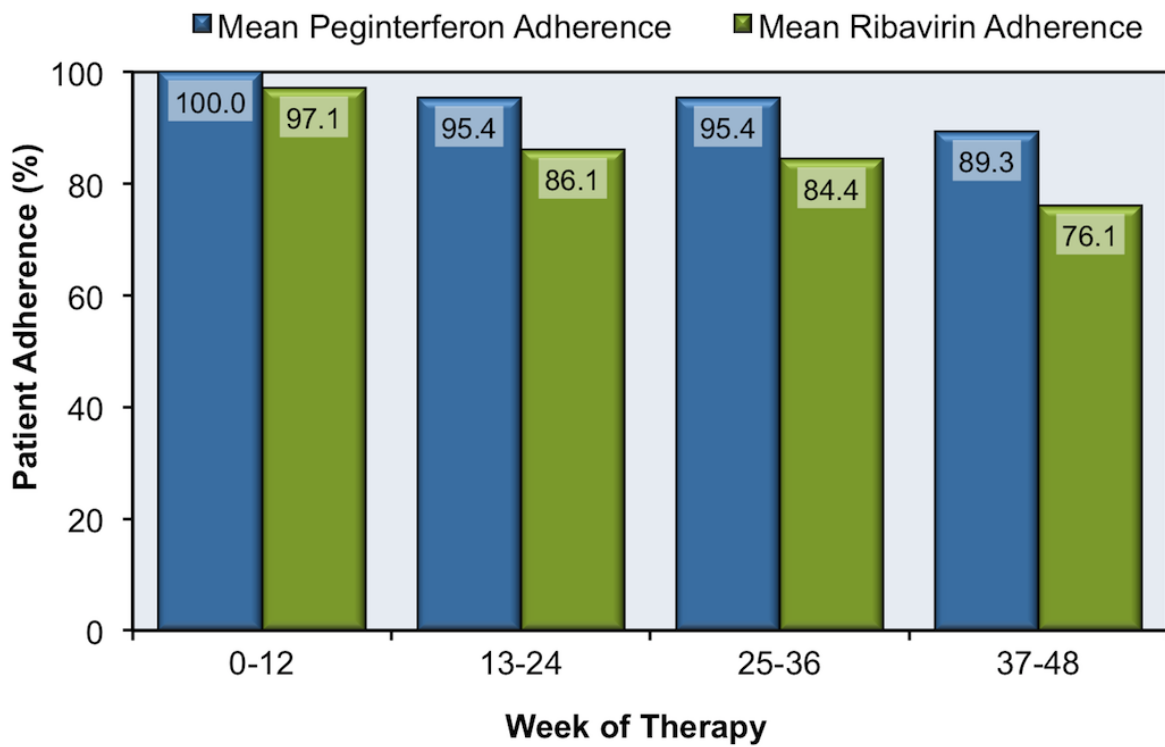


Figure 3 Adherence to DAA Therapy Over 12 Week Treatment Course

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. *Hepatology*. 2016;10:310-9.

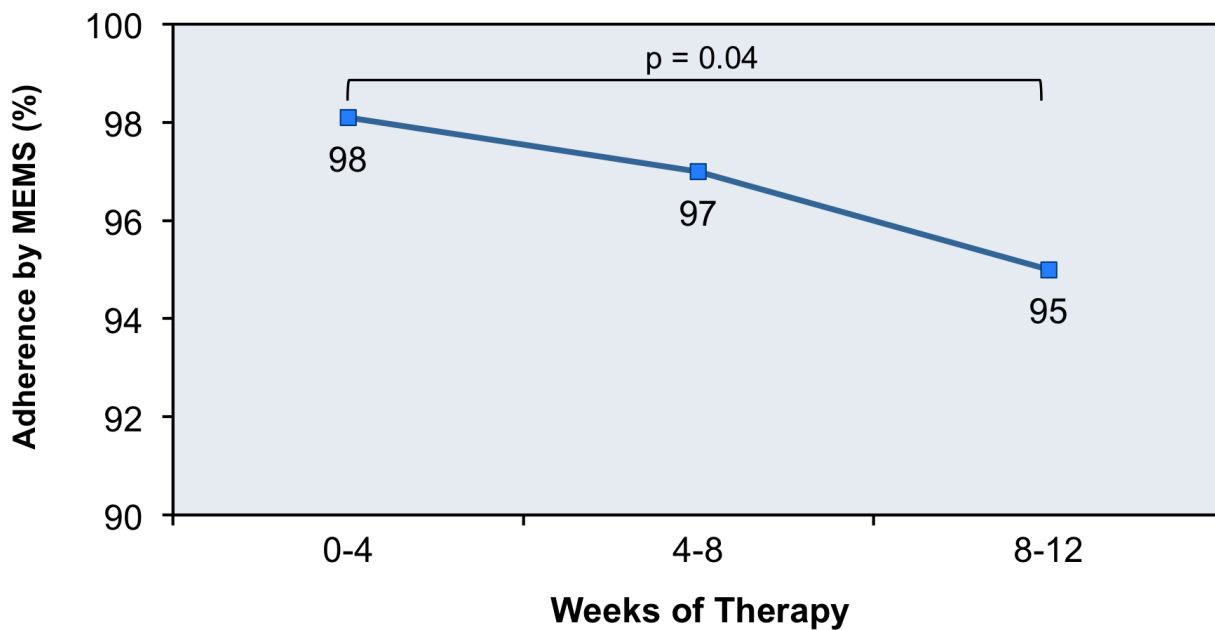


Figure 4 Potential Strategies to Maximize Adherence During Chronic Hepatitis C Treatment

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