

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. 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.

Methods to Measure Adherence

Adherence to drug treatment is difficult to measure accurately. Several methods to quantify drug adherence exist, though all have limitations.

- **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:** Although 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.

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. 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 1](#)). 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. 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.

Within-Person Differences in Adherence to Interferon and Ribavirin

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.

Barriers to Adherence with Hepatitis C Therapy

Factors Associated With Adherence

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

1. **Patient factors:** Age; drug use; alcohol use; presence of comorbidities; literacy; 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; 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

No studies have yet evaluated factors associated with non-adherence to direct-acting antiviral agents used to treat hepatitis C. The addition of these drugs to the existing pegylated interferon and ribavirin regimen has increased the complexity of HCV therapy because these new medications are dosed more frequently (telaprevir and boceprevir require dosing every 8 hours), increase the pill burden of the HCV treatment regimen (telaprevir: 2 tablets every 8 hours; boceprevir: 4 capsules every 8 hours), may require dietary modifications to ensure absorption (telaprevir requires 20 grams of fat with every dose), and have additional toxicities (telaprevir: rash, anorectal discomfort; boceprevir: anemia, dysgeusia) that further challenge adherence. Future all-oral direct-acting antiviral regimens, which are anticipated to have shorter treatment durations, may also be encumbered by these characteristics that could adversely affect adherence. Further, non-adherence to these regimens could lead to antiviral resistance that could compromise the ability to use future therapies. As a result, identifying and addressing the barriers to adherence to these new direct-acting antivirals will remain critically important for future HCV therapies.

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 2](#)).

Evaluating Adherence

At visits prior to and during treatment, providers should educate their patients on the importance of adherence to each antiviral medication within their regimen. 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 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. Weekly visits during HCV therapy for administration of pegylated interferon, preparing a week's supply of oral antivirals into a medication box, and assessment for any adverse effects can facilitate maintaining high levels of antiviral adherence. Peer groups can provide social support and encourage adherence among patients receiving antiviral therapy. Determining the dates of antiviral fills could allow for calculation of antiviral adherence ($\% \text{ adherence} = \text{days' supply of antiviral prescribed} / \text{days between antiviral fills}$), allowing for real-time monitoring of adherence and feedback.

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.
- Sustained virological response increases with higher levels of adherence to pegylated interferon and ribavirin.
- Adherence to pegylated interferon and ribavirin declines over time, but more so for ribavirin.
- Achievement of an SVR among users of boceprevir-based antiviral therapy may be more dependent on adherence to the assigned duration of treatment than adherence to the three times a day dosing with boceprevir.
- 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.
- Providers should implement strategies individualized to each patient's needs to help increase adherence or maintain high levels of antiviral adherence during HCV treatment.

References

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

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

Figures

Figure 1 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.

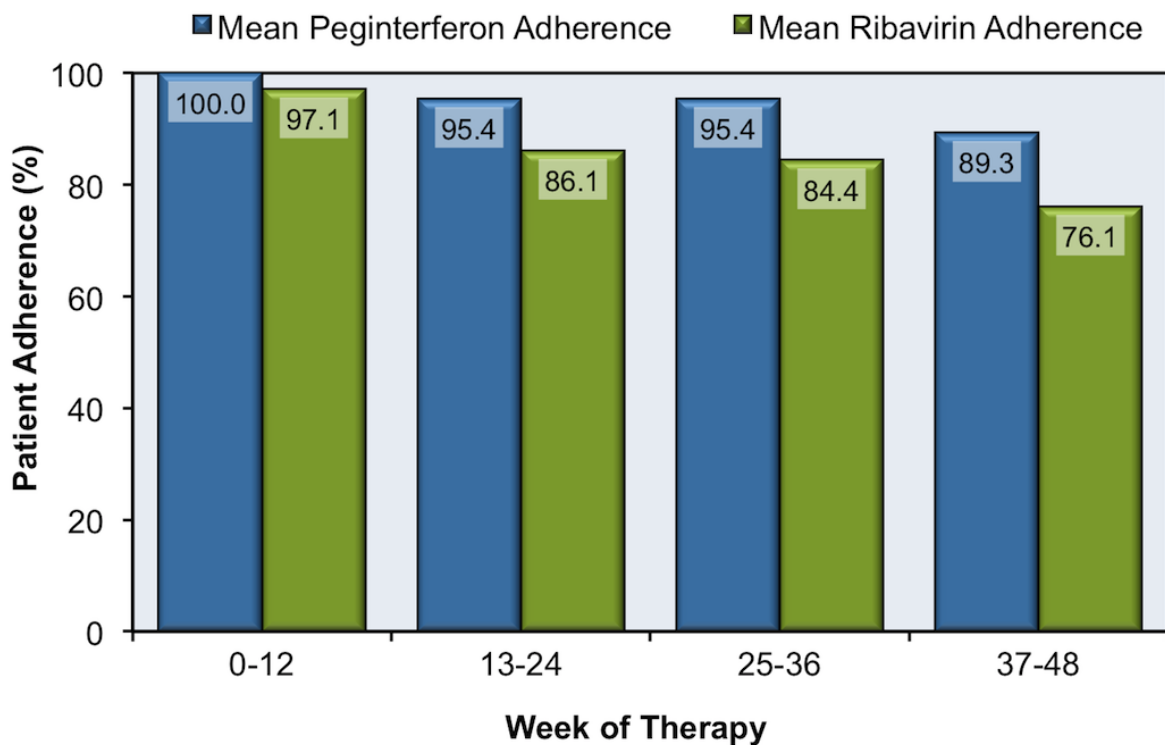


Figure 2 Potential Strategies to Maximize Adherence During Chronic Hepatitis C Treatment

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