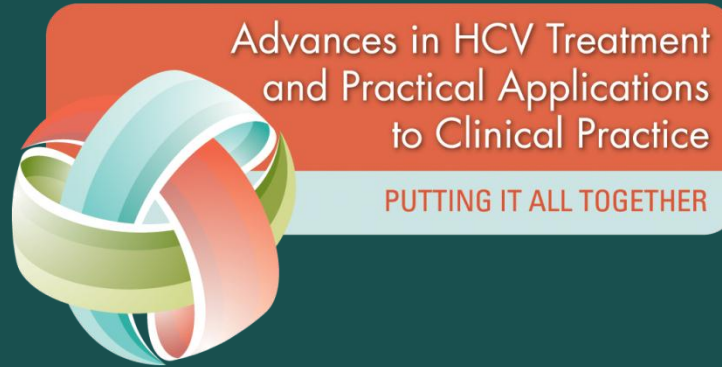


Advances in HCV Treatment and Practical Applications to Clinical Practice

PUTTING IT ALL TOGETHER



CME jointly sponsored by the Institute for Healthcare Education,
the Liver Institute for Education and Research, and Enabled, LLC



CASE:

How to Help Manage Adherence



44-Year-Old White Man with HCV Genotype 1a

- IV drug user for 20 years, stopped 2 years ago
- Stable on methadone maintenance 75 mg daily
- Chronic fatigue
- Depression; takes citalopram 20 mg daily
- HCV diagnosed 5 years ago at methadone clinic
- Genotype 1a; viral load 760,000 IU/L
- *IL28b* genotype CC
- Serum ALT 72 mg/dL; AST 34 mg/dL
- Hemoglobin 15.2 g/dL; platelet count 262,000/ μ L
- Ultrasound normal, refuses liver biopsy

ALT = alanine aminotransferase; AST = aspartate aminotransferase.



44-Year-Old White Man with HCV Genotype 1a

- Works part-time in loading dock of warehouse
- Lives alone but has a sister involved in his care
- Divorced, 2 children
- Alcohol: Heavy use for few years but none for 15 years
- IV drug use: Heroin for 20 years, many attempts to stop; now drug-free for longest period in past 20 years
- Depression for many years; stable
- Sees a counselor every 2 weeks for depression and addiction care



44-Year-Old White Man with HCV Genotype 1a

- Patient eager for treatment but very anxious about side effects
- *IL28b* genotype CC
- HepaScore 0.33 (F1)
- Good candidate for RGT with 24–28 weeks of treatment

- What strategies are best employed in clinical practice to manage adherence in this patient?

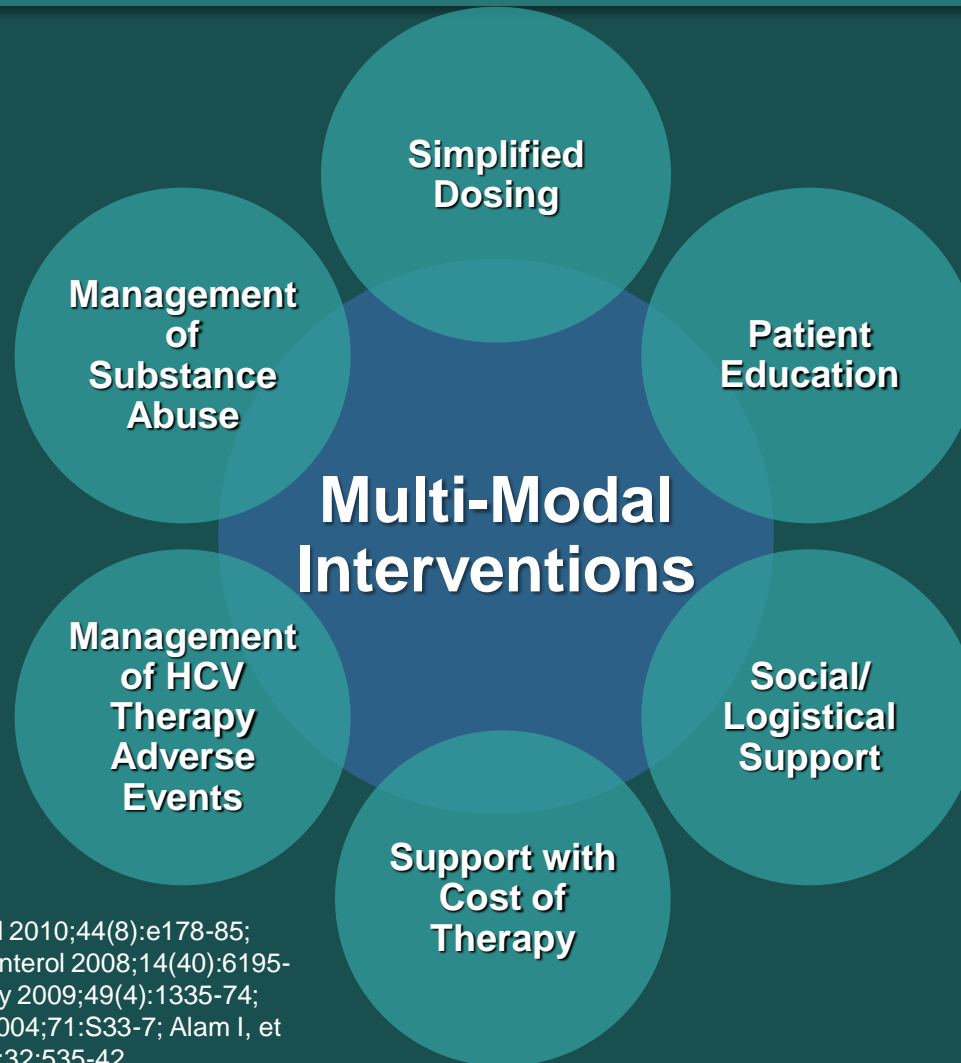
RGT = response-guided therapy.

Evidence Supports a Collaborative Care Approach to Medication Adherence in Chronic HCV



Yozviak JL, et al. International Conference on Viral Hepatitis, April 11-12, 2011, Abstract 70752, p. 27;
Gujral H, et al. Clev Clin J Med 2004;71:S33-7.

Evidence Supports a Multimodal Approach to Adherence Interventions in Chronic HCV



Liu SS, et al. J Clin Gastroenterol 2010;44(8):e178-85;
Cacoub P, et al. World J Gastroenterol 2008;14(40):6195-203;
Ghany MG, et al. Hepatology 2009;49(4):1335-74;
Gujral H, et al. Clev Clin J Med 2004;71:S33-7; Alam I, et al. Aliment Pharmacol Ther 2010;32:535-42.



Several Studies Have Shown Benefits of Collaborative or Integrated Care Models in Chronic HCV Management

- These collaborative care models involved integrating HCV management with:
 - Substance abuse management
 - Mental health services
 - Social support
 - Referral to other specialists as needed
- Collaborative care models have helped with chronic HCV medication adherence
- However, this approach is resource-intensive

Barriers to Chronic HCV Medication Adherence and Potential Interventions

Barrier	Potential Intervention
Depression	<ul style="list-style-type: none"> • Proactively screen for depression • Use of antidepressants as needed • Referral to psychiatrist if necessary
Active substance abuse	<ul style="list-style-type: none"> • Methadone maintenance programs • Recommendation of 12-step programs
Lack of belief in benefits of therapy	<ul style="list-style-type: none"> • Patient education about benefits of therapy • Suggest enrollment in HCV patient class and support group
Costs of therapy	<ul style="list-style-type: none"> • Copay programs; referral to reimbursement specialist
Logistical/social issues	<ul style="list-style-type: none"> • Referral to social worker to help with housing needs, transportation to clinic appointments, etc. • Counseling about modifying work schedule, household chores, if possible
Medication side effects	<ul style="list-style-type: none"> • Education about side effect management
Complex dosing regimens	<ul style="list-style-type: none"> • Simplified dosing regimens whenever possible


Liu SS, et al. J Clin Gastroenterol 2010;44(8):e178-85; Cacoub P, et al. World J Gastroenterol 2008;14(40):6195-203; Ghany MG, et al. Hepatology 2009;49(4):1335-74; Gujral H, et al. Clev Clin J Med 2004;71:S33-7; Alam I, et al. Aliment Pharmacol Ther 2010;32:535-42.



44-Year-Old White Man with HCV Genotype 1a

- Started on PEG-IFN 180 μ g SC weekly, RBV 600 mg PO twice a day, and telaprevir 750 mg PO three times a day with a fatty meal
- Week 2: mild anemia (hemoglobin 11.8 g/dL), increasing fatigue
- Week 4: HCV RNA undetectable
- Week 8: worsening depression, mild confusion, difficulty in remembering whether he has taken medications appropriately

*PEG-IFN = pegylated interferon; PO = by mouth;
RBV = ribavirin; SC = subcutaneous.*



Antidepressant Therapy in Patients with Chronic HCV and Depression

Pharmacy Benefits Management (PBM) Claims Database

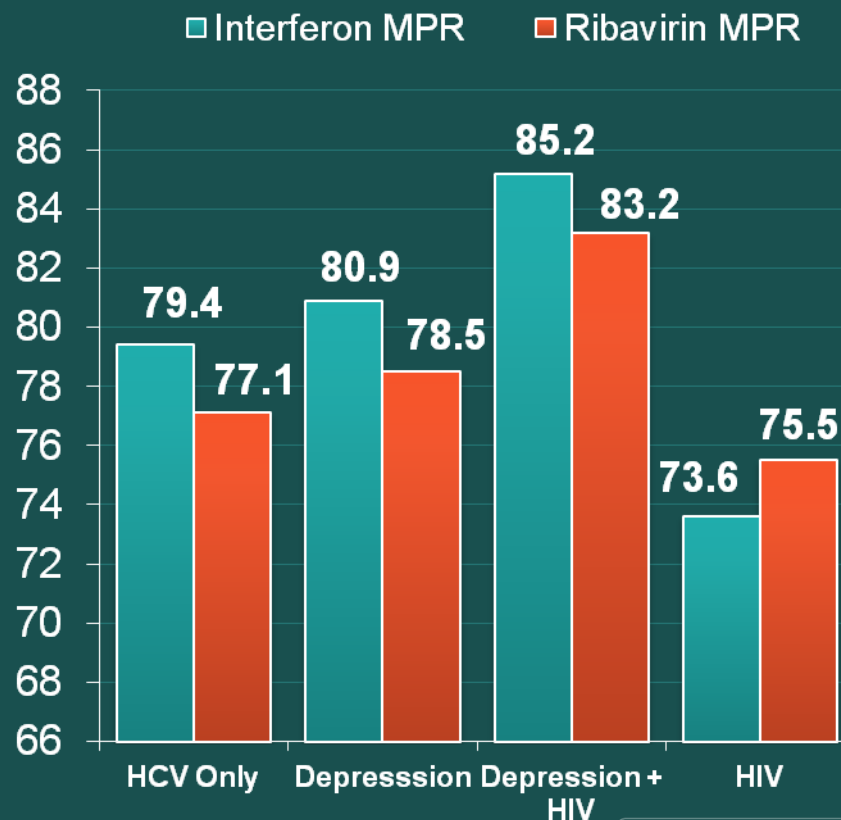
Study Design	<ul style="list-style-type: none">• Prospective, observational study• One-year follow-up
Patient Population	<ul style="list-style-type: none">• 3,607 HCV-infected patients; no previous chronic HCV therapy<ul style="list-style-type: none">– 1,657 (45.9%) treated for depression– 109 (3%) coinfectd with HIV– 66 HCV–HIV coinfectd patients also treated for depression
Adherence Assessment	<ul style="list-style-type: none">• Calculation of medication possession ratio (MPR)• Adherence to therapy defined as MPR \geq80%

Antidepressant Therapy Valuable in Patients with Chronic HCV and Depression

PBM Claims Database

- Overall, 60.4% of patients were adherent to therapy
- Patients treated concomitantly for depression showed slightly higher rates of adherence
- Patients treated concomitantly for depression and HIV coinfection showed the highest rates of adherence

Impact of Depression on MPR

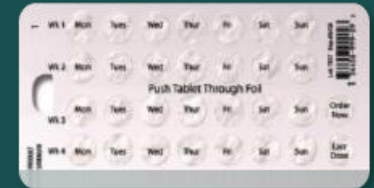


The Role of Simplified Dosing and Adherence

Systematic Review

Study design

- Systematic review of 10 randomized, controlled trials (RCTs) on adherence to medication in various chronic diseases
 - Two trials had insufficient data for evaluation
- Interventions analyzed
 - Calendar blister packaging
 - Calendar pill organizers
 - With or without other interventions (e.g., patient education)





2 of 3 RCTs Showed Improved Adherence with Calendar Blister Pack

Systematic Review

Study	Patient Population	Intervention	Results
Becker et al. 1986	Hypertension (N=86)	Calendar blister pack	No significant difference in adherence
Schneider et al. 2008	Hypertension (N=47)	Calendar blister pack	Significant difference in adherence in favor of calendar blister pack ($P=0.039$)
Valenstein et al. 2009	Severe mental illness (N=54)	Calendar blister pack plus reminder calls and mail, patient education	Significant difference in adherence in favor of blister pack, all but 1 other intervention ($P<0.01$)

4 of 5 RCTs Showed Improved Adherence with Calendar Pill Organizers

Systematic Review

Study	Patient Population	Intervention	Results
Peterson et al. 1984	Epilepsy (N=26)	Calendar pill organizer plus patient education	Significant difference in adherence in favor of calendar pill organizer ($P<0.01$)
Skaer et al. 1993	Hypertension (N=85)	Calendar pill organizer (pharmacy-filled)	Significant difference in adherence in favor of calendar pill organizer ($P<0.05$)
Skaer et al. 1993	Diabetes Type II (N=53)	Calendar pill organizer	Significant difference in adherence in favor of calendar pill organizer ($P<0.05$)
Azrin 1998	Severe mental illness (N=13)	Calendar pill organizer plus patient education	Significant difference in adherence in favor of calendar pill organizer ($P<0.01$)
Huang et al. 2000	Disease prevention (N=89)	Calendar pill organizer (patient-filled)	No significant difference in adherence

Potential Adherence Advantages with Blister Packaging

ADHERE Registry

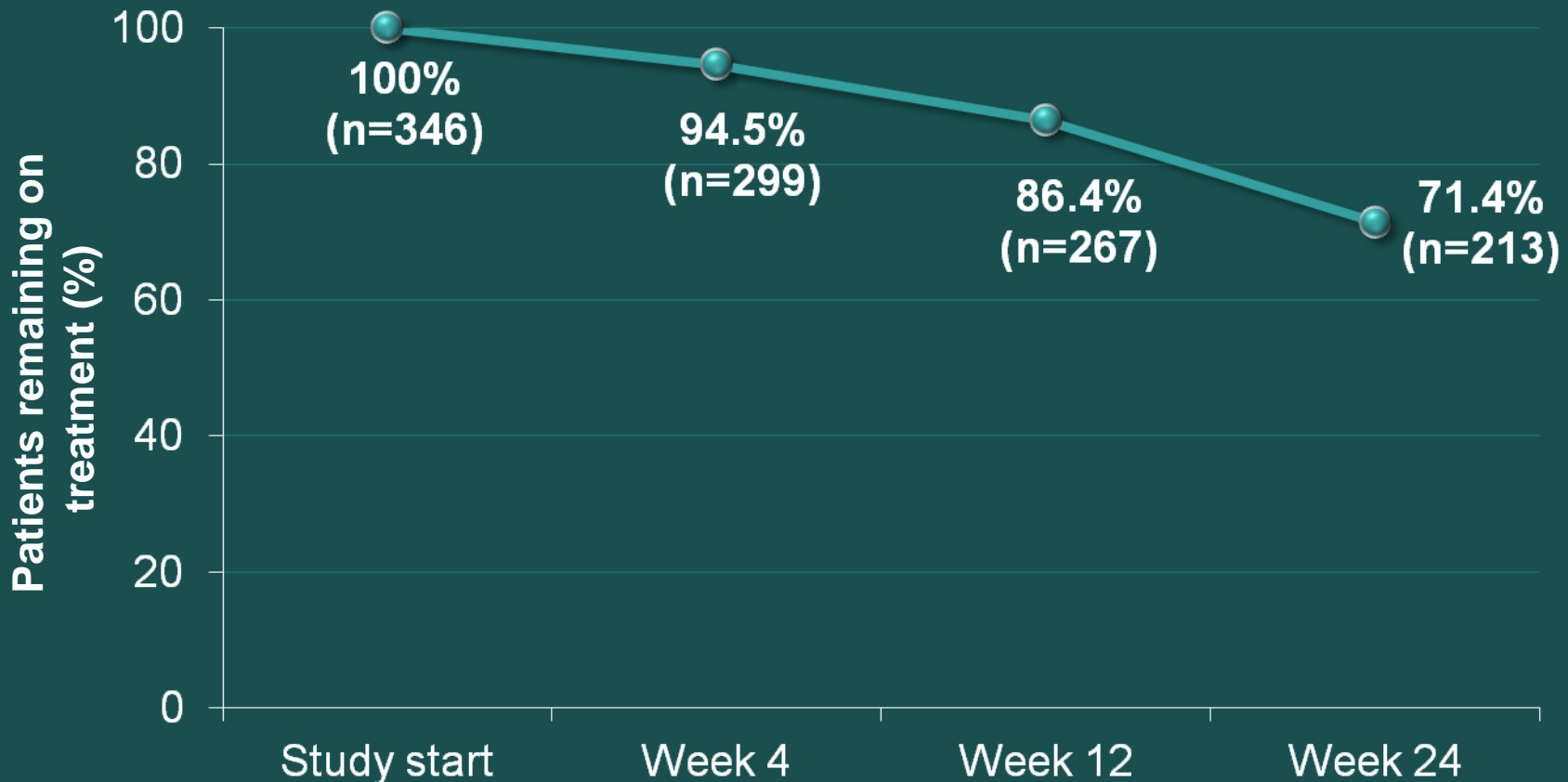
- Study design
 - Prospective, multicenter registry
- Primary objective:
 - Assess impact of RBV blister packaging on adherence
- Patients: Adults with chronic HCV taking PEG-IFN/ribavirin
 - 346 took ribavirin packaged in a blister pack
 - 157 took other ribavirin products
- Adherence definition: Taking $\geq 80\%$ of prescribed doses
- Adherence assessment
 - Pill count
 - Patient self-report



*ADHERE = Accurate Dosing in Hepatitis C:
Examining the RibaPak Experience*

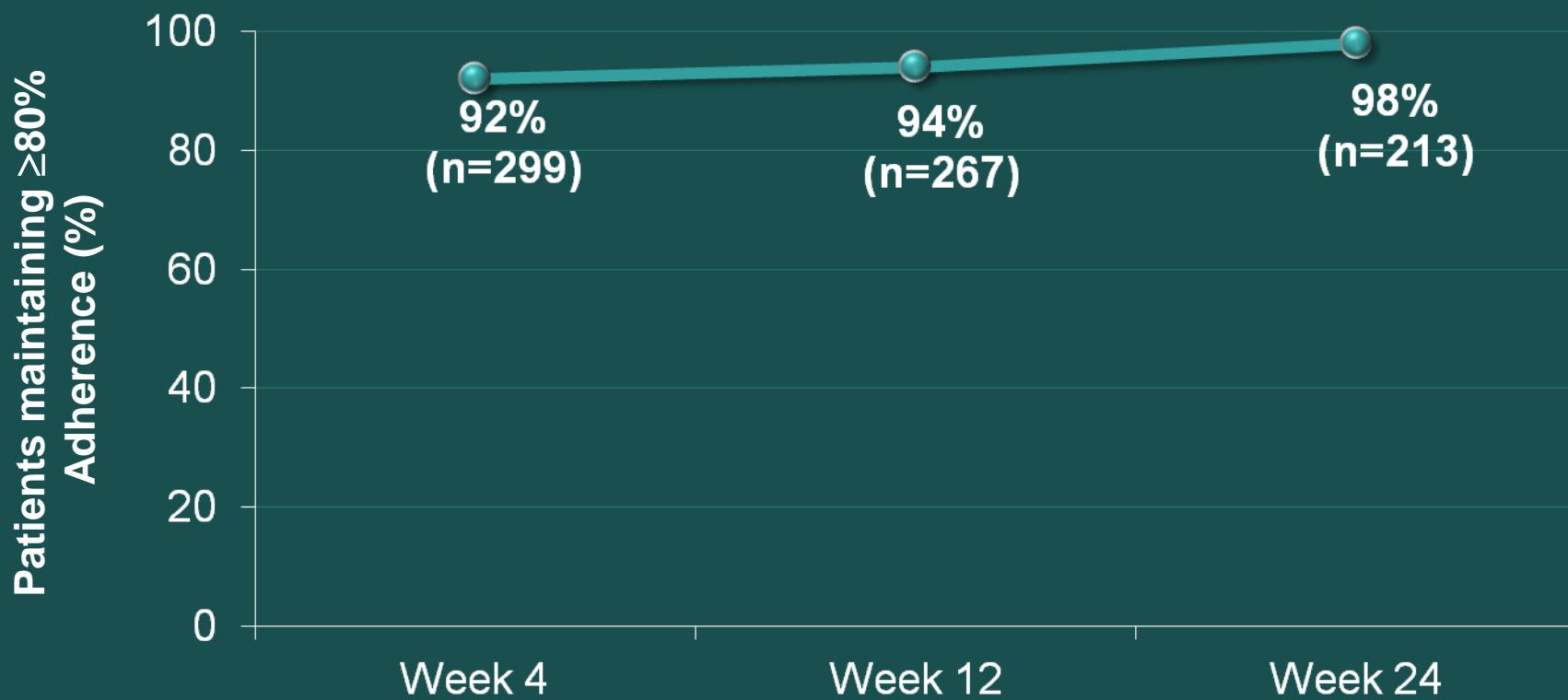
Patients Taking Ribavirin in a Blister Pack Remaining on Therapy at 24 Weeks

ADHERE Registry



Of Patients Who Remained on Treatment, Over 90% Maintained $\geq 80\%$ Adherence Throughout 24 Weeks

ADHERE Registry





44-Year-Old White Man with HCV Genotype 1a

- Week 12: Using calendar pill organizer; states he has been very adherent
 - HCV RNA undetectable; telaprevir stopped
 - Depression improved with higher dose of citalopram and seeing counselor more often
- Week 24: HCV RNA undetectable, treatment stopped



Summary

- Patients with chronic HCV infection often have issues that are barriers to medication adherence
- Multiple interventions usually are needed to address these issues
 - Management of depression, if present
 - Substance abuse counseling, if warranted
 - Patient education on benefits of therapy, in simple language
 - Patient education on management of side effects with chronic HCV medications
 - Simplified dosing, including use of blister packs
- Evidence also supports the use of a collaborative care model to promote chronic HCV medication adherence