Overcoming Psychiatric Barriers to Effective Hepatitis C Treatment

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Disclosures

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Overview

- *Patient-specific psychiatric barriers* to testing and treatment include knowledge deficits, treatment fears or indifference, perceived stigma, psychiatric illness, and co-morbid substance use.

- *Provider-specific psychiatric barriers* to testing and treatment include provider stigma, communication breakdowns, misperceptions of contraindications, and concerns over treating patients with comorbid psychiatric disorders and substance use disorders.

Objectives

- Describe the treatment impact surrounding stigma, which include social stigma, internalized stigma and provider stigma.
- Be able to compare and contrast psychiatric side effects of older and newer HCV treatments
- Describe the impact of psychiatric illness and co-occurring drug and alcohol use on hepatitis C treatments.
- Give three recommendations for overcoming psychiatric barriers to hepatitis C treatment

Knowledge Deficit as a Barrier

- Lack of awareness of being infected (largest barrier)
  - 66-75% unaware of infection [1]
- Lack of awareness of more broad testing measures
  - Age-based testing allows for inclusiveness
    - "all boomers need testing"
- Lack of awareness of treatment issues
  - 70% knew treatments existed, but only 22% knew it could cure HCV[2]
  - 32% didn't know if treatment was safe

1. Mitchell 2010 2. Mehta 2008

Primary Reasons for Deferring Treatment:

- *Fears of side effects*

  → Solution: Discuss lower side effect profile of newer treatments compared to interferon

- *Asymptomatic nature of infection*[1]

  →Solution: Discuss both short-term and long-term benefits

  - **Less fatigue**[2]
    - 53% fatigue at baseline → dropped to 33% at 24 weeks post Rx
    - Most severely fatigued patients: 2/3 less fatigue after treatment
  - **Improved cognition**[3]
  - **Improvements in sexual dysfunction**[4]

    (desire, performance, satisfaction)

1. Khokhar 2007, 2. Souvik 2012, 3. Bajaj 2013, 4. Herbert 2007

The Barrier of Stigma

- Stigma: 35% - 85% of patients with HCV report being stigmatized[1]
  - Social Stigma
  - Internalized Stigma
  - Perceived Provider Stigma
  - True Provider Stigma

1. Modabbernia 2013

Social Stigma as a Barrier

- More than half HCV patients perceive stigma from the community[1,2]
  - Feel community links HCV diagnosis to HIV, promiscuity, and substance abuse.
  - Impacts common socialization behaviors:
    - 47% less likely to share drinking glasses
    - 1/3 less likely to share a towel
    - 20% reduced frequency of kissing

1. Zacks 2006, 2. Zickmund 2003

Barrier: Internalized Stigma

- Perceived external stigma often associated with internalizing stigma and leads to…[1,2]
  - Shame and embarrassment
  - Reduced self-care behaviors
  - Higher anxiety and depression
  - Worse quality of life
  - Felt loss of control and difficulty coping
  - More problems in healthcare, work, and family life
- Some describe removing the fear and shame as a motivator for treatment[3]

1. Treloar 2013, 2. Zickmund 2003, 3. Sublette 2015

Perceived Provider Stigma

- Stigma: up to 85% of patients with HCV report being stigmatized and most commonly occurred in the healthcare setting.[1]

- Osilla: HCV/HIV co-infected patients, 60% agreed to treatment and, compared to those who declined treatment, were more likely to view their…[2]
  - Providers with more lenient views of depression and substance use as barriers of HCV treatment readiness
  - Provider was perceived as trustworthy
  - Provider had a nonjudgmental and accepting attitude

1. Modabbernia 2013 2. Osilla 2010

Barrier: Perceived Poor Doctor-Patient Communication

- Zickmund 2004[1]
  - 131/322 outpatients with HCV (41%) reported communication issues with their doctors
  - Poor communications skills (28%)
    - Felt misunderstood, rushed, not listened to, or treated unkindly.
  - Feeling misdiagnosed, misled, or abandoned (16%)
  - Feeling stigmatized (9%)

  - Nonresponse to treatment was correlated to perceived physician conflict related to *poor communication*

1. Zickmund 2004

Reducing Stigma via Integrating HCV treatment into Methadone Maintenance and Primary Care for People Who Inject Drugs

- Nonjudgmental culture of HCV treatment at a Methadone Clinic[1]
- On site: Peer Educators, HCV treatment, medical / mental health and optional HCV group treatment
- Over the course of treatment participants reported:
  - Reduced internalized stigma and shame
  - Increased willingness to disclose HCV-status
  - Reduced substance use
  - Increased self care
  - Desire to help others with HCV

1. Batchelder 2015

Overcoming Patient Stigma

- *Treat patients with respectful, nonjudgmental, and accepting attitude*[1]
  - "People Who Inject Drugs" better than "IV Drug Abuser"
- *Collaborate with patients to treat infection*
  - Use more "we" language, less "you" language
  - Stay involved after referral to specialist (57% fail to attend initial subspecialty evaluation)[2-4]
- *Treat comorbid depression*[5]
  - Depression independently linked to <u>perceiving</u> more barriers to care
- *Access to Group Treatment Settings or Peer Educator Support*

1. Ossilla 2011, 2. Butt 2005, 3. Cawthorne 2002, 4. Groom 2008, 5. Evon 2010

Barrier: Provider Stigma

- Review of 21 articles (1995-2006) on stigmatization by healthcare practitioners on HCV patients[1]
  - 1. Stigma arises out of practitioner's negative views of injection drug use
  - 2. Stigma arises out of practitioner's negative attitude towards HCV patients due to a lack of knowledge about the disease

- High rates of deferral of treatment for both psychiatric illness and substance abuse.[2]

1. Paterson 2007, 2. Sublette 2015

Co-Morbid Psychiatric Disorders

- CDC in 1997 excluded "unstable" mental disorders from HCV treatment, but in 2002 CDC changed stance to *encouraging* treatment in prisoners and patients with mental disorders.
- High prevalence of psychiatric disorders in HCV patients[1]
  - 86% VA population had at least one past or present psychiatric illness, 60% had both substance use disorder AND mental disorder
- Depression rates in HCV vary from 30-58%
  - Two thirds often require antidepressants
  - One quarter are suicidal[2]
  - HCV may be directly causing depression as HCV genetic sequences found in post mortem brain tissue.[3]

1. El-Serag 2002, 2. Dieperink 2004, 3. Forton 2003

IFN Treatment in HCV Patients with Co-morbid Psychiatric Disorders

- When "high-risk psychiatric" HCV patients were treated with multidisciplinary monitoring: similar adherence, compliance, and SVR and <u>not at increased risk for depression</u> compared to controls (IFN study)[1]

- 2012 comparison of IFN-based treatment in Bipolar patients, Major Depression patients, and those without psychiatric illness[2]
  - *Psychiatric complications* in 69% of Bipolars and 55% of Depressed patients, compared to 37% of those without a psychiatric history
  - Discontinuation rates, completion rates, and SVR were similar for all three groups

1. Sostre 2013, 2. Kelly 2012

Minimizing Psychiatric Side Effects to Interferon HCV Treatments

- Interferon-induced depression: 3-57%
  - Pre-treatment with antidepressants can reduce depression rates from 44% to 11%[1]
  - If present, treat depression before starting treatment as mood symptoms immediately prior to treatment predict treatment-emergent depression[2]
- Interferon rarely can trigger agitated mania or psychosis[3]
  - Treat by removal of antidepressant and atypical neuroleptic

1. Musselman 2001, 2. Miyaoka 1999, 3. Onyike 2004

Less Psychiatric Side Effects of New HCV Treatments Reduces Barriers

- Simeprevir
  - No psychiatric side effects (without Ribavirin (RBV))[1-2]

- Sofosbuvir +/- Ledipasvir [3-7]
  - Irritability ≤ 8% -RBV, ≤ 13% +RBV
  - Anxiety 0% -RBV, ≤ 22% +RBV
  - Depression 0% -RBV, ≤ 22% +RBV

1. NCT00812331, 2. Lawitz 2014. 3. Zeurem 2014,
4. Sulkowski 2014, 5. Kowdley 2014, 6. Afdahal 2014, 7. Gane 2014

Less Psychiatric Side Effects of New HCV Treatments reduces Barriers

- Ombitasvir/Dasabuvir/Paritaprevir/Ritonavir [1-4]
  - Irritability 6.3% -RBV, ≤ 12% +RBV
  - Anxiety 3.8% -RBV, ≤ 8.1% +RBV
  - Depression 1.3% -RBV, ≤ 7% +RBV

- Daclatasvir (- RBV)[5]
  - Irritability 4%
  - Anxiety 6-7% (17% with RBV)
  - Depression 3-11%

1. Feld 2014, 2. NCT01464827, 3. Poordad 2014, 4. Zeurem 4/2014, 5. Sulkowski 2014

Reduced Psychiatric Side Effects of Newer HCV Treatments Opens Door for More Treatment in Comorbid Psychiatric Disorders

- Newer HCV treatments have far less psychiatric side effects
  - Anxiety, Depression, and Irritability can occur but much less than from IFN-based treatments
- Assess psychiatric stability before treatment; address unstable psychiatric conditions first
- In patients with premorbid psychiatric disorders, selecting a regiment without Ribavirin may be advisable if there are comparable alternative regiments available.
  - 4 suicide attempts reported during newer treatments, but all in regiments with ribavirin

Co-morbid Substance Use Disorder

- 2011 Survey of HCV Specialists in Canada, only 20% would consider treatment for active drug users[1]
- High prevalence of psychiatric illness and comorbid alcohol abuse among PWID[2-3]
- Concerns regarding poor HCV Rx adherence[4]
  - 6.8% PWID noncompliant vs 4.9% without drug use
- Concerns for reinfection after clearing virus
  - Reinfection rate of those reporting ongoing IV use after SVR = 5.3 per 100 person-years (modest risk)

1. Myles 2011, 2. Golub 2004, 3. Davis 2001, 4. Hconline 2015

Importance of treating PWID to reduce future spread[1]

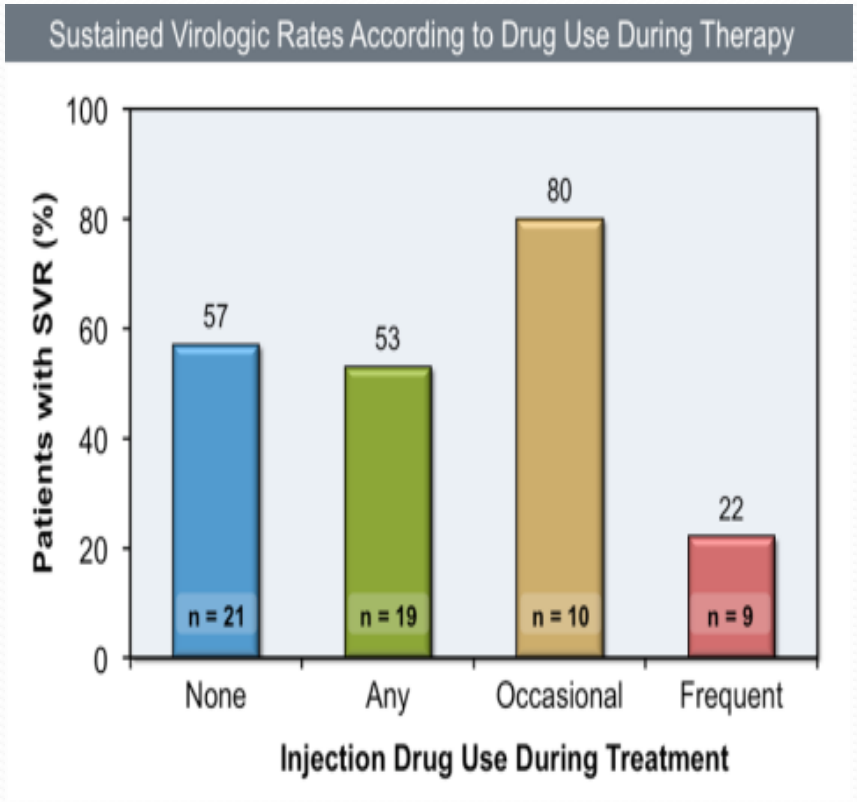
- Treatment (IFN) annually of 25 per 1000 PWID reduces prevalence of HCV…
  - 50% at 30 years

- Newer treatments are estimated to reduce an *additional*
  - 23% at 15 years
  - 38% at 30 years

1. Hellard 2009

Treatment outcomes for HCV Treatment in PWID

- 4/5 studies found similar rates of completion similar to non-PWID [1]
- Another study found <u>frequent</u> drug use during IFN treatment was associated with lower SVR compared to abstinence or occasional drug use during treatment.[2]



1. Hconline 2015, Hellard 2009

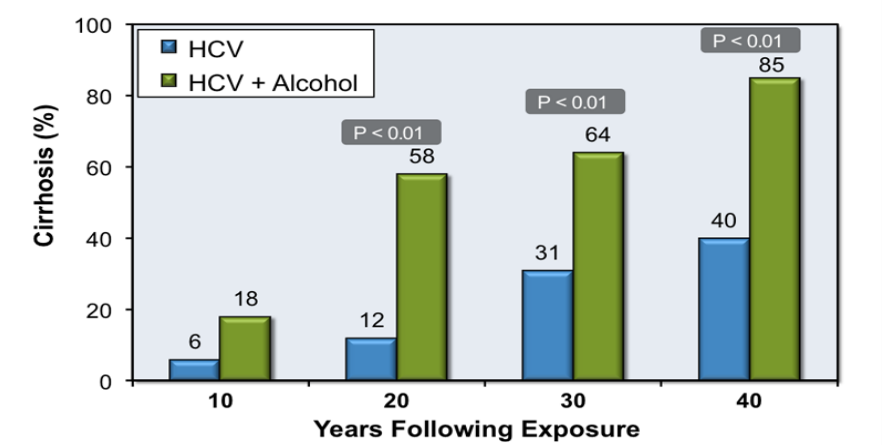
Recommendations for HCV treatment in PWID[1]

- Consider treatment on an individual basis
- Evaluate degree of support system
- Assess for comorbid psychiatric illness
- Assess for comorbid alcohol use
- Consider referral for agonist therapy program

1. Hconline 2015

Comorbid Alcohol Abuse

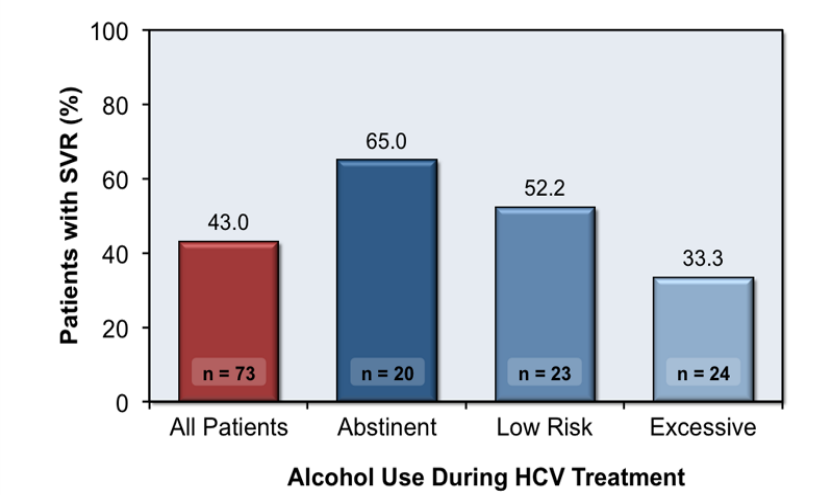
- Heavy alcohol use accelerates HCV-related hepatic fibrosis[1]



*Excessive alcohol defined as > 40 g/day for women and > 60 g/day for men

- Alcohol use impairs HCV-treatment response[1]
  - Excessive: male ≥ 5 drinks
  - Excessive female ≥ 3.5 drinks

Sustained Virologic Rates According to Alcohol Consumption During Therapy



1. Hconline 2015

Comorbid Alcohol Abuse

- Regardless if SVR is achieved or not, progression of liver disease continues among heavy alcohol users[1]
- Guidelines (2009)
  - Address heavy alcohol abuse and dependence before HCV treatment
  - Treatment is NOT contraindicated in a past history of alcoholism or an occasional drink.
  - Recommended to avoid alcohol during HCV treatment
  - Refer for CD treatment and consider cessation medications (naltrexone, acamprosate)

1. Hconline 2015

Cannabis Use

- Daily cannabis use significantly associated with *moderate to severe fibrosis*[1]
  - Odds ratio of 3.21 and 6.78
- Cannabis use should be discouraged in patients with chronic Hepatitis C infection.[2]
- One study found a positive correlation between cannabis use and adherence to HCV treatment.[3]
- During treatment, patients are <u>advised to abstain</u> from regular cannabis use, although ongoing use is not considered a contraindication for treatment.

1. Ishida 2008, 2. Hezode 2008, 3. Sylvestre 2006

Summary: Solutions to Overcoming Psychiatric Barriers to HCV Treatment[1]

- Maintain a respectful, accepting and collaborative relationship
- Maintain connectedness to patients after referral and during treatment
- Assess psychiatric stability and treatment needs in patients with psychiatric illness
- Individually address readiness of patients with substance and alcohol use disorders
- When available utilize Navigators to assist with authorization/appointments/transportation , Peer Educators, and Group Treatments

1. Sublette 2015

References [1]

- Mitchell, AE. Institute of Medicine Recommendations for the prevention and control of hepatitis B and C. Hepatology. Mar. 2010 51(3):729-733.
- Sublette V. The Hepatitis C treatment experience: Patients' perceptions of the facilitators of and barriers to uptake, adherence and completion. Psychology & Health 2015; 30(8): 987-1004.
- Butt AA, Wagener M, Shakil AO, Ahmad J. Reasons for non-treatment of hepatitis C in veterans in care. J Viral Hepat. Jan; 2005 12(1):81–85.
- Cawthorne CH, Rudat KR, Burton MS, et al. Limited success of HCV antiviral therapy in United States veterans. The American journal of gastroenterology. Jan; 2002 97(1):149–155.
- Groom H, Dieperink E, Nelson DB, et al. Outcomes of a Hepatitis C screening program at a large urban VA medical center. J Clin Gastroenterol. Jan; 2008 42(1):97–106.
- Khokhar OS et al. Reasons why patients infected with chronic hepatitis C virus choose to defer treatment: do they alter their decision with time? Dig Dis Sci. May; 2007 52(5):1168-1176.
- Musselman DL. Paroxetine for the prevention of depression induced by high-dose interferon alfa. N Engl. J Med 2001 Mar 29; 344(13): 961-6.
- Evon DM et al. Barriers to accessing care in patients with chronic hepatitis C: impact of depression. Alement Pharmacol Ther. Nov; 2010 32(9): 1163-1173.
- Miyaoka H. Depression from Interferon therapy in patients with hepatitis C. American J Psychiatry. 1999 Jul; 156(7):1120.

References [2]

- Zacks S et al. Social stigmatization and hepatitis C virus infection. J Clin Gastroenterol. Mar; 2006 40(3): 220-224.
- Paterson BL. The Depiction of stigmatization in research about hepatitis C. Int J Drug Policy 2007 Oct; 18(5): 364-73.
- Zickmund S et al. "They treated me like a leper." Stigmatization and the quality of life of patients with hepatitis C. J Gen Intern Med. Oct. 2003 18(10): 835-844.
- Zickmund S et al. Hepatitis C virus-infected patients report communication problems to physicians. Hepatology. Apr; 2004 39(4): 999-1007.
- Treloar, C. Understanding barriers to hepatitis C virus care and stigmatization from a social perspective. 2013. Clin. Infect. Dis. 57 (Suppl. 2), S51-S55.
- Batchelder A. "Hepatitis C treatment turned me around:" Psychological and behavioral transformation related to hepatitis C treatment. Drug and Alcohol Dependence 153(2015) 66-71.
- Souvik S. Fatigue Before, During, and After Antiviral Therapy of Chronic Hepatitis C: Results from the Virahep-C Study. J Hepatol 2012 Nov; 57(5): 946-52.
- Bajaj J. Cognitive Improvement after HCV Eradication: Extending the Benefits. Hepatology Vol 58 (2) 2013: 480-482.
- Herbert L. SVR improved quality of life and sexual function in patients with advanced fibrosis in HALT-C Study. Journal of Hepatology. March 2007.

References [3]

- El-Serag HB et al. Psychiatric disorders among veterans with hepatitis C infection. Gastroenterology. 2002; 123(2): 476-482.
- Dieperink E. Suicidal ideation during interferon and ribavirin treatment of patients with chronic hepatitis C. General Hosp Psychiatry May-June 2004. 26(3): 237-240.
- Feld, J. Treatment of HCV with ABT-450/r Ombitasvir, and Dasabuvir with Ribavirin. N.EJM 370: 37 April 24, 2014.
- Unpublished trial NCT01464827 www.clinicaltrials.gov
- Poordad, F. ABT-450/r-ombitasvir and Dasaburvir with Ribavirin for Hepatitis C with Cirrhosis. NEJM 370: 21. May 22, 2014.
- Zeuzem, S. Retreatment of HCV with ABT-450/r-Ombitasvir and Dasabuvir with Ribavirin. N Eng J Med (April 2014) 370:17.
- Zeurem, S. Sofosbuvir and Ribavirin in HCV Genotypes 2 and 3. 2014 NEJM 370 (21): 1993-2001.
- Sulkowski, M. Sofosbuvir and Ribavirin for HCV in pts with HIV coinfection. JAMA 2014; 312 (4) 353-361.
- Kowdley K. Ledipasivir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. 2014 NEJM 370 (20) pg 1879-1888.
- Afdahal, Nezam Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. NEJM 370 (16) April 17 , 2014. Pg 1483-1493.
- Gane, E. Efficacy of Nucleotide Polymerase inhibitor Sofosbuvir plus ledipasvir or GS9669 against HCV genotype 1. 2014

References[4]

- Unpublished Trial NCT00812331 (2008) www.clinicaltrials.gov
- Lawitz, Simeprevir + sofosbuvir +/- RBV to treat chronic infection.Lancet Vol 384 (Nov 2014)
- Sulkowski, M. Daclatasvir plus Sofosbuvir for Previously Treated or Untreated Chronic HCV Infection. NEJM Jan 2014, 370: 211-21.
- Forton DM. Cerebral dysfunction in chronic hepatitis C infection. J Viral Hepat. 2003 Mar; 10(2): 81-6.
- Hellard ME et al. Modelling antiviral treatment to prevent hepatitis C infection among people who inject drugs in Victoria, Australia. Med J Aust. 2012 Jun 4; 196(10): 638-41.
- Golub ET et al. Screening for depressive symptoms among HCV-infected injection drug users: examination of the utility of the CES-D and the BDI. J Urban Health. Jun; 2004 81(2): 278-290.
- Davis GL et al. Treatment of chronic hepatitis C in active drug users. N England J Med 2001; 345: 215-7.
- Mehta SH et al. Limited uptake of hepatitis C treatment among injection drug users. J Community Health. Jun; 2008 33(3):126-133.
- Hellard, M et al. Hepatitis C Treatment for Injection Drug Users: A Review of the Available Evidence. Clin Infect Dis (2009) 49 (4): 561-573.
- Hepatitis C online course modules: “Evaluation and Preparation for Hepatitis C Treatment” 2015 from http://www.hepatitisc.uw.edu/

References[5]

- Ishida JH et al. Influence of cannabis use on severity of hepatitis C disease. Clin Gastroenterol Hepatol. 2008 Jan; 6(1): 69-75.
- Hezode C et al. Daily cannabis use: a novel risk factor of steatosis severity in patients with chronic hepatitis C. Gastroenerol 2008 Feb; 134 (2): 432-9.
- Osilla K. Patient and Provider Characteristics Associated with Decision of HIV Co-infected Patients to start Hepatitis C Treatment. 2011 AIDS Patient Care STDS Sep 25(9): 533-8.
- Onyike C. Mania During Treatment of Chronic Hepatitis C with Pegylated Interferon and Ribavirin. Am J Psychiatry 161:3, March 2004, 429-435.
- Modabbernia A. Neuropsychiatric and Psychosocial Issues of Patients With Hepatitis C Infection: A Selective Literature Review. Hepat Mon. 2013; 13(1): e8340.
- Kelly EM. Bipolar patients can safely and successfully receive interferon-based hepatitis C antiviral treatment. Eur J Gastroenterol Hepatol. 2012; 24(7):811-6.
- Myles A. Physicians' attitudes and practice toward treating injection drug users with hepatitis C: results from a national specialist survey in Canada. Can J Gastroenterol 2011; 25:135-9.
- Sostre S. Strategies for treating depression in patients with hepatitis C. April 2013. Current Psychiatry. 12 (4).
- Sylvestre DL. Cannabis use improves retention and virological outcomes in patients treated for hepatitis C. Eur J Gastroenterol Hepatol. 2006 Oct; 18(10): 1057-63.