Hepatitis C Virus Infection in Injection Drug Users

Judith Tsui, MD MPH

May 4, 2012

Topics to Cover

- HCV epidemiology (focus on IDU)
- HCV natural history
- HCV screening and treatment (focus on IDU)
- Barriers to HCV care in IDU
- Models of care delivery that integrate HCV and substance use treatment
- Directions for future research

Historical Background: Hepatitis C Virus (HCV)

- RNA virus, 6 major genotypes
- “non-A, non-B hepatitis”
- First identified 1988
- Screening in blood products 1992
- No vaccine currently available

Prevalence of HCV in the US

- Based on population based survey (NHANES), anti-HCV prevalence in the U.S. is 1.6%
  - 4.1 million (CI, 3.4 million to 4.9 million) anti-HCV–positive persons nationwide
- Prevalence with chronic infection (viral load +) is 1.3%
  - 3.2 million (CI, 2.7 million to 3.9 million) with chronic HCV
- ***Strongest risk factor for HCV is injection drug use***
  - OR for IDU=149 (95% CI: 45-494) v. transfusion prior to 1992 OR=2.6 (95% CI: 0.9-7.3)
  - 48.4% of anti-HCV–positive persons reported a history of IDU
  - Among those reporting IDU, 83.3% had not used injection drugs for at least 1 year before the survey.

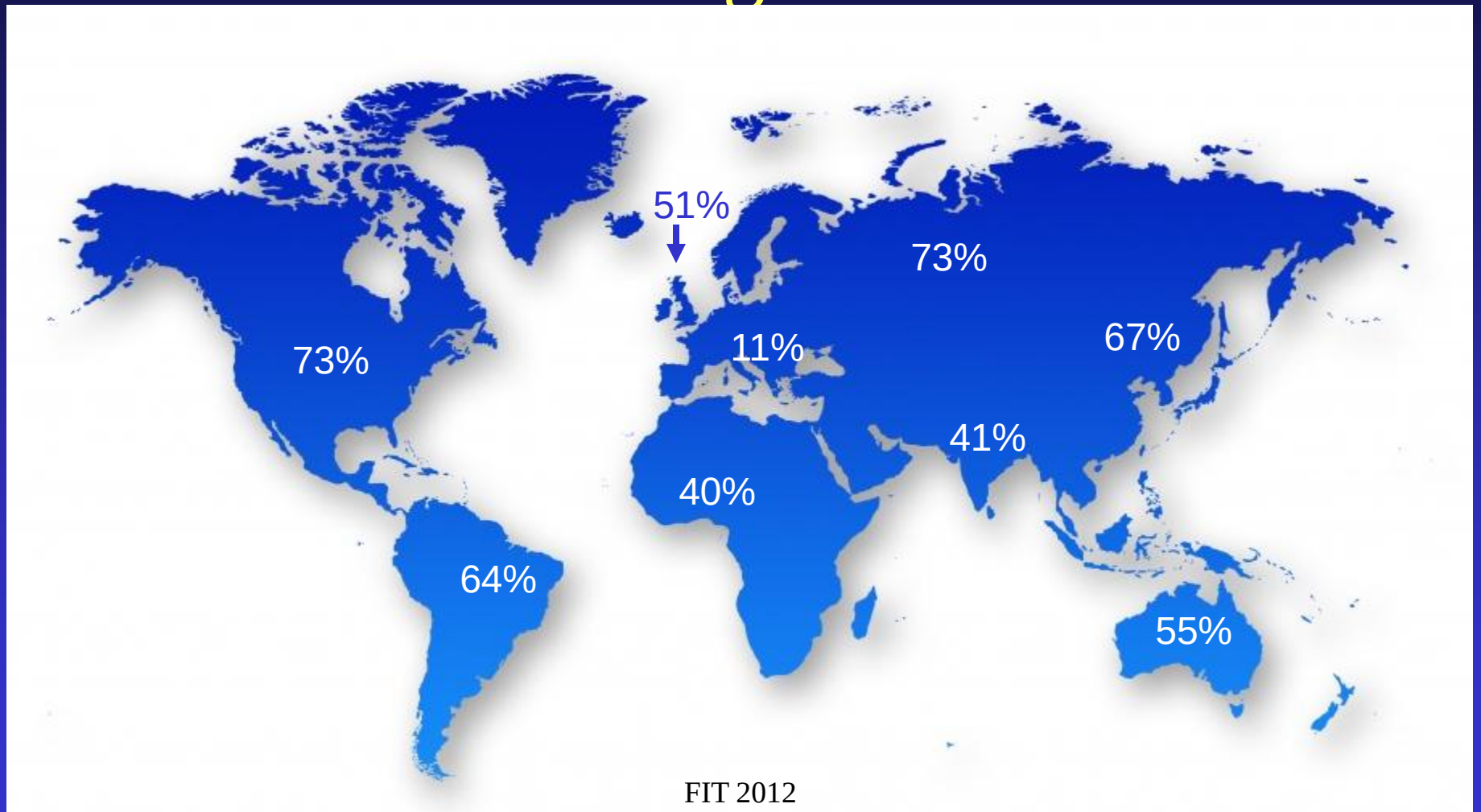
Armstrong, Wasley, Simard, et al. *Ann Intern Med.* 2006;144:705-714.

Prevalence of HCV among IDU in the U.S.

- Prevalence of anti-HCV among IDU in U.S. studies range 40-90%[1-2]
- Prevalence estimate in US/Canada: 73% (LL-UL: 70-77)[3]
  - HIV prevalence in IDU ~15%[4]
- 1.5 million HCV-infected IDU in US (v. 10 million infected world-wide)[3]

[1] Hagan, Pouget, Williams, et al. *J Infect Dis*. 2010;201:378-385.
[2] Page, Hahn, Evans, et al. *J Infect Dis*. 2009;200:1216-1226.
[3] Nelson, Mathers, Cowie, et al. *Lancet*. 2001;378:571-583.
[4] Mathers, Degenhardt, Phillips, et al. Lancet. 2008;372:1733-1745.

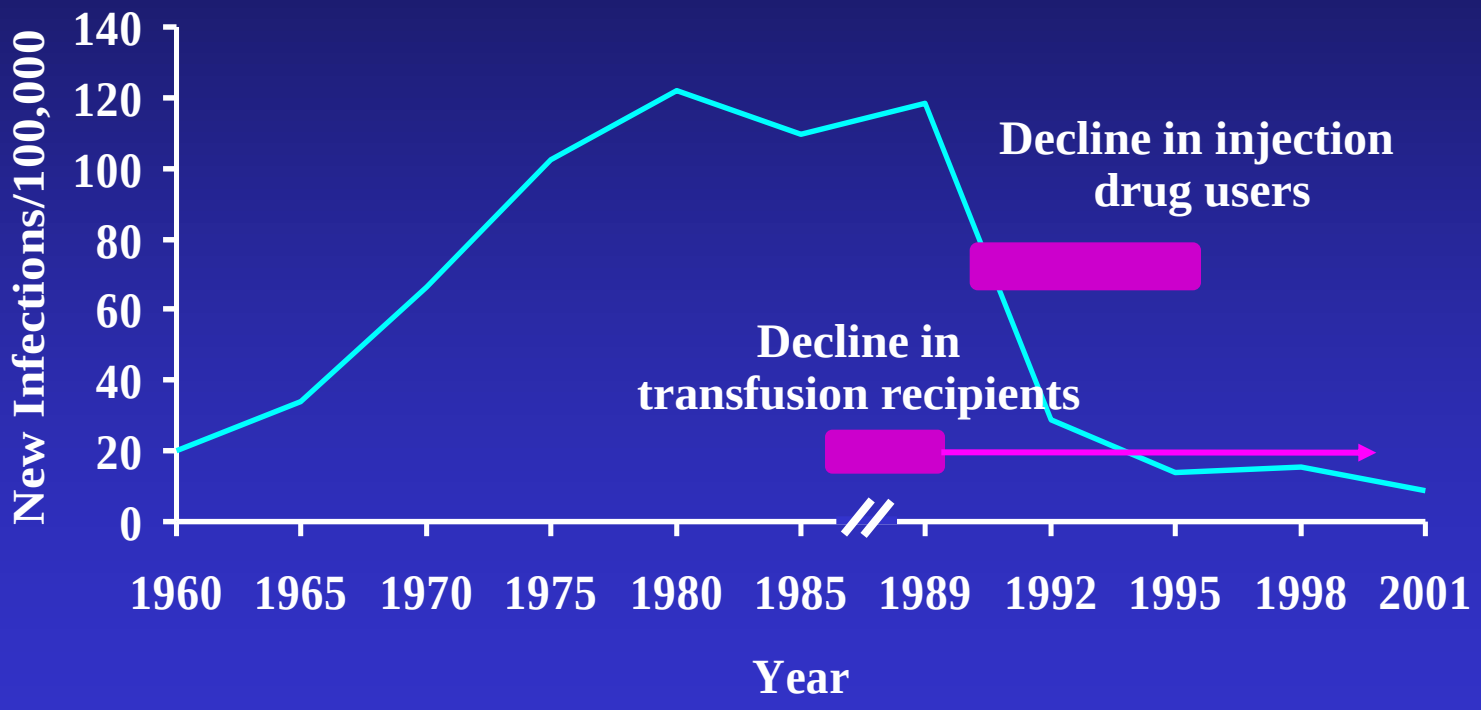
Global HCV Prevalence Among IDUs



FIT 2012

Nelson, Mathers, Cowie, et al. *Lancet*. 2001;378:571-583.

Incidence of Acute HCV Infection United States, 1960-2001



Armstrong, Alter, McQuillan, Margolis. *Hepatology.* 2000;31:777-82.
Alter. *Hepatology.* 1997;26:62S-65S.
CDC: unpublished data

HCV Incidence Among IDU in the U.S.

- Incidence of HCV ~10-30 cases/100 person-years[1-2]
- HCV incidence also declining in IDU, but not as dramatic as HIV[3]
- Proportion of cases reporting IDU has increased[4]
  - 31.8% cases 1982-1989
  - 33.5% cases 1990-1993
  - 45.6% cases 1994-2006
- IDU are the “core” of the HCV epidemic

[1] Hagan, Pouget, Williams, et al. *J Infect Dis*. 2010;201:378-385.
[2] Page, Hahn, Evans, et al. *J Infect Dis*. 2009;200:1216-1226.
[3] Mehta, Astemborski, Kirk, et al. *J Infect Dis*. 2011;203:587-9.
[4] Williams, Bell, Kuhnert, Alter. Arch Intern Med. 2011;171:242-248.

HCV Incidence in the U.S. Among IDU

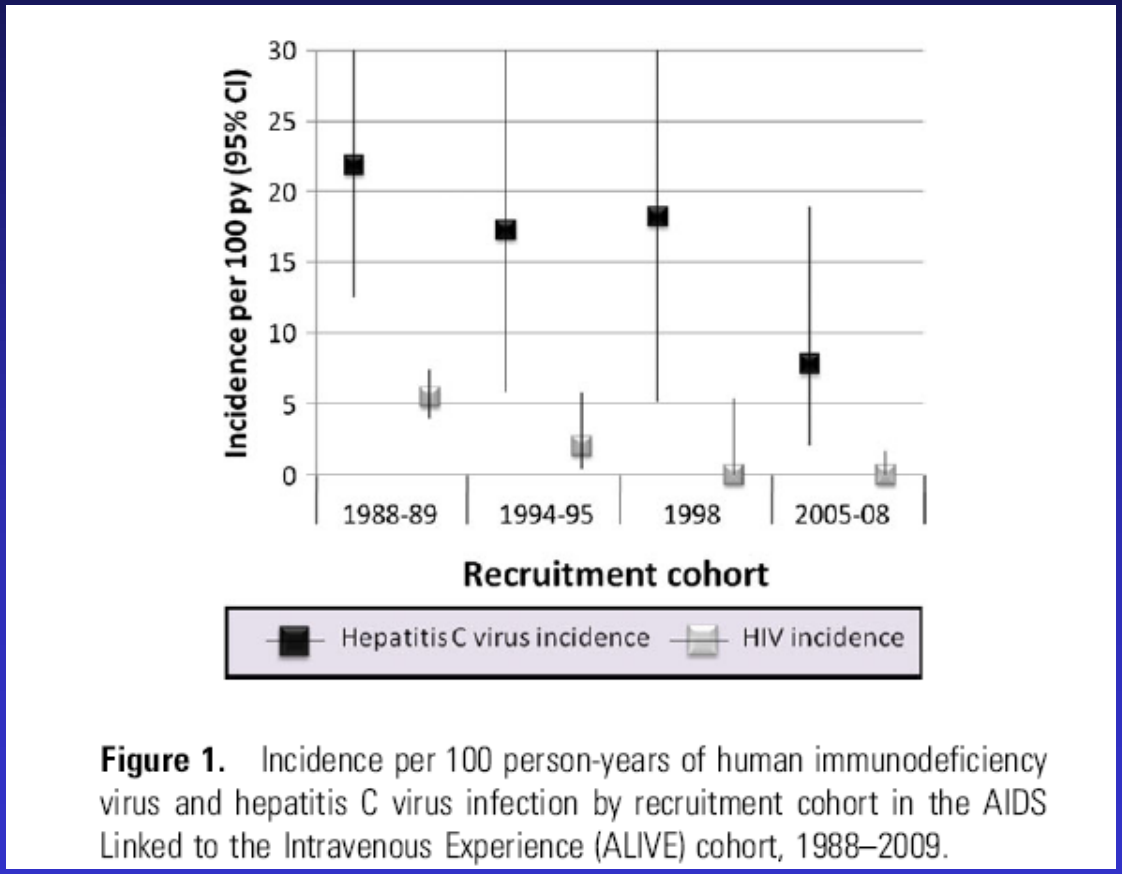


Figure 1. Incidence per 100 person-years of human immunodeficiency virus and hepatitis C virus infection by recruitment cohort in the AIDS Linked to the Intravenous Experience (ALIVE) cohort, 1988–2009.

FIT 2012

Mehta, Astemborski, Kirk, et al. *J Infect Dis*. 2011;203:587-589.

Risk Factors for HCV in IDU

- Age
- Duration of IDU
  - Narrow window for intervention: 20-50% infected within first 2 years of IDU[1,2]
- Severity of IDU
- Risky IDU behaviors

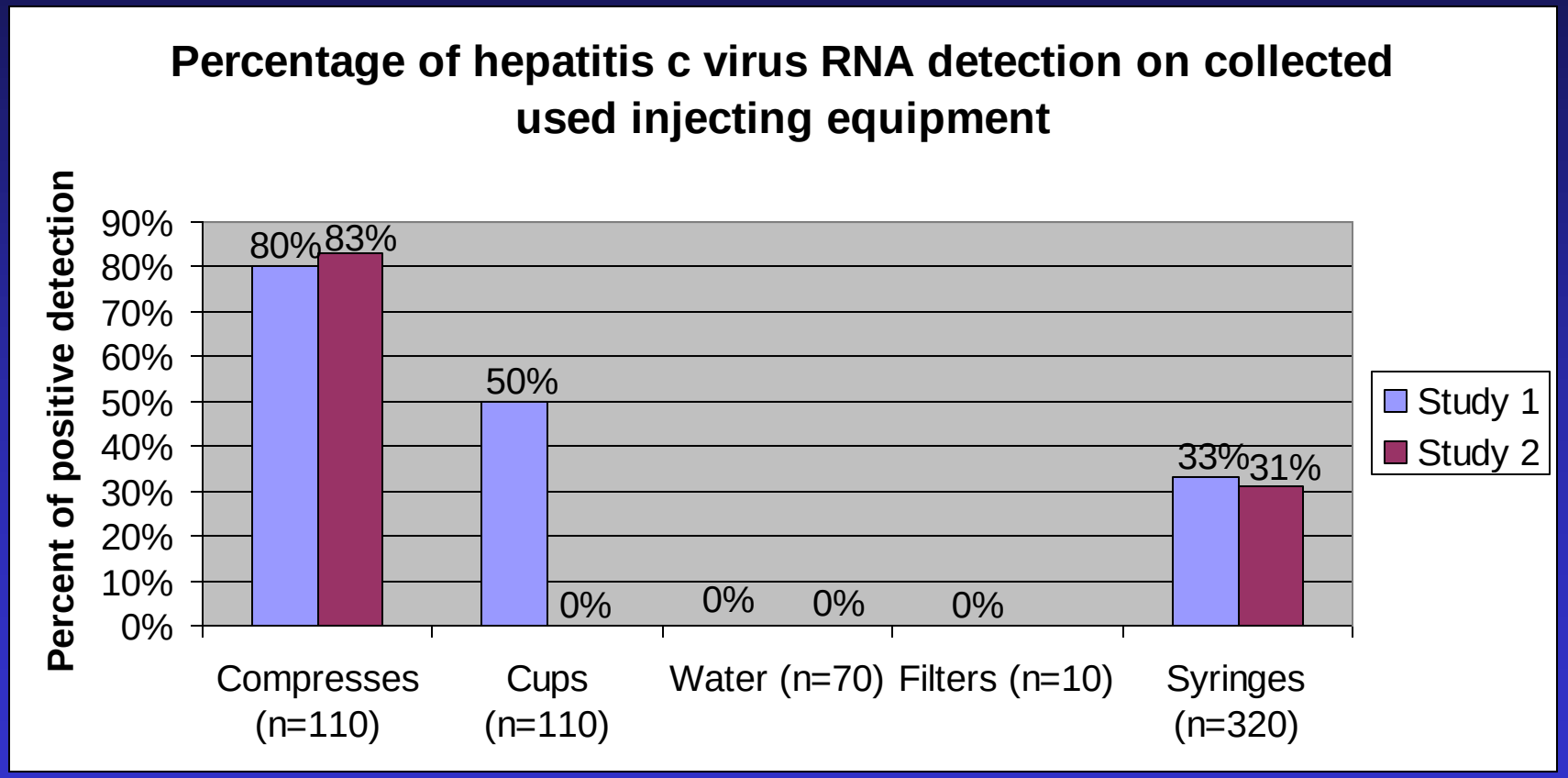
[1] Hagan, Pouget, Williams, et al. *J Infect Dis*. 2010;201:378-385.
[2] Amon, Garfein, Ahdieh-Grant, et al. *Clin Infect Dis*. 2008;46:1852-1858.

Factors that Facilitate HCV Transmission in IDU

- High concentration of virus in blood of chronic carriers
- High prevalence of disease in IDU
- Stability of virus in the environment
  - Persists as dried sample up to 1 week[1]
  - Persists up to 60 days in syringes[2]
- Sharing of injecting equipment
  - Swabs, cookers, syringes, filters, water[3]

[1] Doerrbecker, Friesland, Ciesek, et al. *J Infect Dis*. 2011;232:51-62.
[2] Paintsil, He, Peters, et al. *J Infect Dis*. 2010;202:984-90.
[3] Pouget, Hagan, Des Jarlais, et al. *Addiction*. In press.

Percentage of Hepatitis C Virus RNA Detection on Used Injecting Equipment



Thibault, Bara, Nefau, Dupleesy-Garson. *J Infect Dis*. 2011;204:1839-1842.

Interventions to Prevent HCV Transmission in IDU

- Meta-analysis of behavioral and treatment interventions, including opioid agonist treatment (OAT) and needle and syringe programs (NSP)[1]
  - 26 studies pooled
  - Combined interventions reduced risk of seroconversion by 75% (RR 0.25; 95% CI: 0.07-0.83)
- Meta-analysis of 6 UK studies of OAT and NSP[2]
  - Full harm reduction (OAT plus NSP) reduced odds of seroconversion by 79% (OR=0.21; 95% CI: 0.08-0.52)
- ***Data suggest that combined OAT and NSP programs are effective in decreasing HCV transmission in IDU***

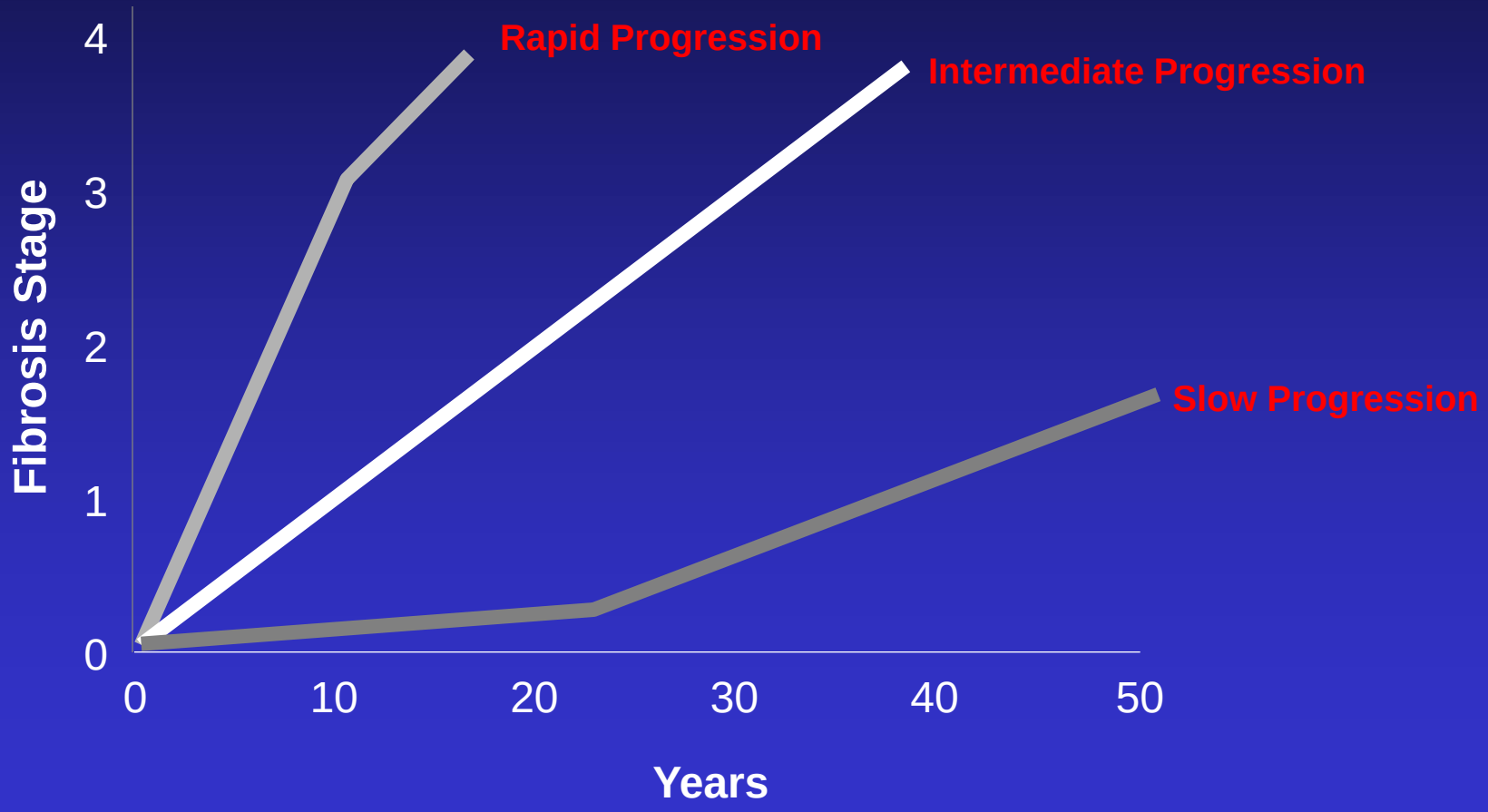
[1] Hagan, Pouget, Des Jarlais. *J Infect Dis.* 2011;204:74-83.
[2] Turner, Hutchinson, Vickerman, et al. *Addiction.* 2011;106:1978-1988.

HCV Natural History: Hepatic Complications

- **Chronic hepatitis**
  - Occurs in approximately 80% of patients infected
- **Cirrhosis**
  - 5-25% develop cirrhosis over 20-30 years
- **Hepatocellular Cancer**
  - 1-3% of cirrhotic patients develop HCCa per year
  - Rarely occurs outside the setting of cirrhosis

Ghany, Strader, Thomas, Seeff, AASLD/IDSA/ACG. *Hepatology.* 2009;49:1335-1374.

HCV Natural History: Hepatic Fibrosis



Poynard, Bedossa, Opolon. *Lancet.* 1997;349:825-832.
Slide Adapted from Roche Presentation: "Understanding Hepatitis C and Its Treatment"

Factors Associated with Progressive Fibrosis

- **Alcohol**
- Duration of infection
- Older age at infection
- Male
- Co-infection with HBV or HIV
- Being overweight/liver steatosis
- smoking

Bialek, Terrault. *Clin Liver Dis*. 2006;10:697-715.

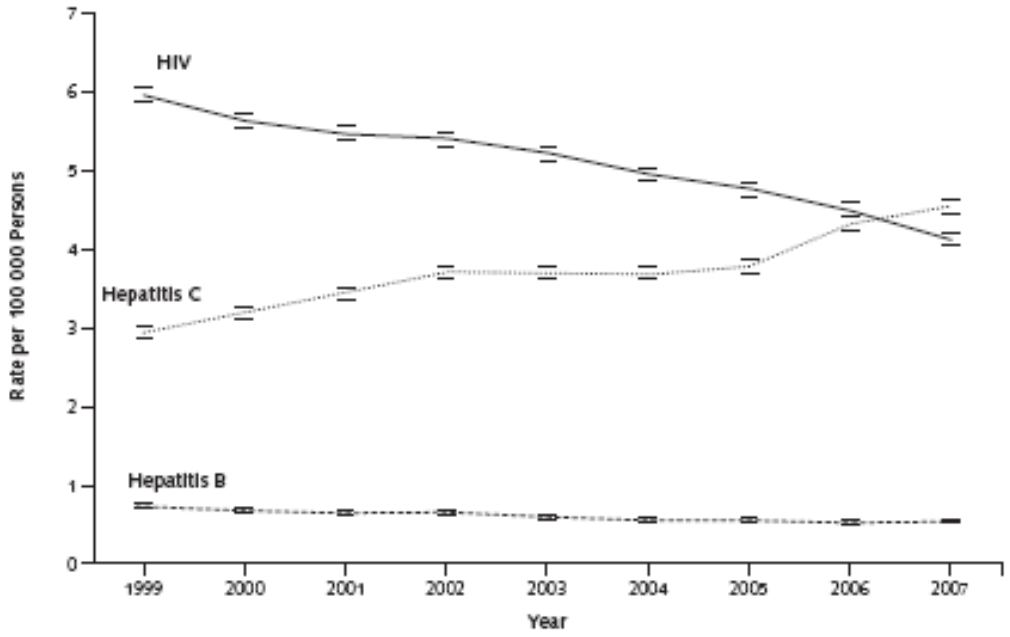
HCV Morbidity and Mortality

- Chronic liver disease is 12th leading cause of death in U.S. in 2009[1]
  - approx 1/2 is HCV-related
- Incidence of HCCA has tripled in the past 2 decades, primarily from HCV[2]
- HCV is the #1 cause for liver transplants in the US[3]
- HCV-related mortality projected to increase 2000-20[4]

[1] *CDC MMWR Rep*. 1998;47(RR-19):1-39.
[2] El-Serag. *New Eng J Med*. 2011;365:1118-11127.
[3] Berg, Steffick, Edwards, et al. *Am J Transplant*. 2009;9:907-931.
[4] Wong, McQuillan, McHutchison, et al. *Am J Public Health*. 2000;90:1562-1569.

HCV Mortality: 1999-2007

Figure. Annual age-adjusted mortality rates from hepatitis B and hepatitis C virus and HIV infections listed as causes of death in the United States between 1999 and 2007.



Because a decedent can have multiple causes of death, a record listing more than 1 type of infection was counted for each type of infection.

FIT 2012

Ly, Xing, Klevens, et al. *Ann of Int Med.* 2012;156:271-8.

HCV Mortality

- Increased mortality observed for liver and non-liver causes
  - Study of 20,000+ blood donors, ½ HCV+ and ½ matched HCV-
  - Vital status from U.S. NDI, mean follow-up 7 years
  - Hazards ratios (HR) for death associated with HCV:
    - Liver: HR=45.99 (95% CI: 11.32-186.74)
    - CV: HR=2.21 (1.41-3.46)

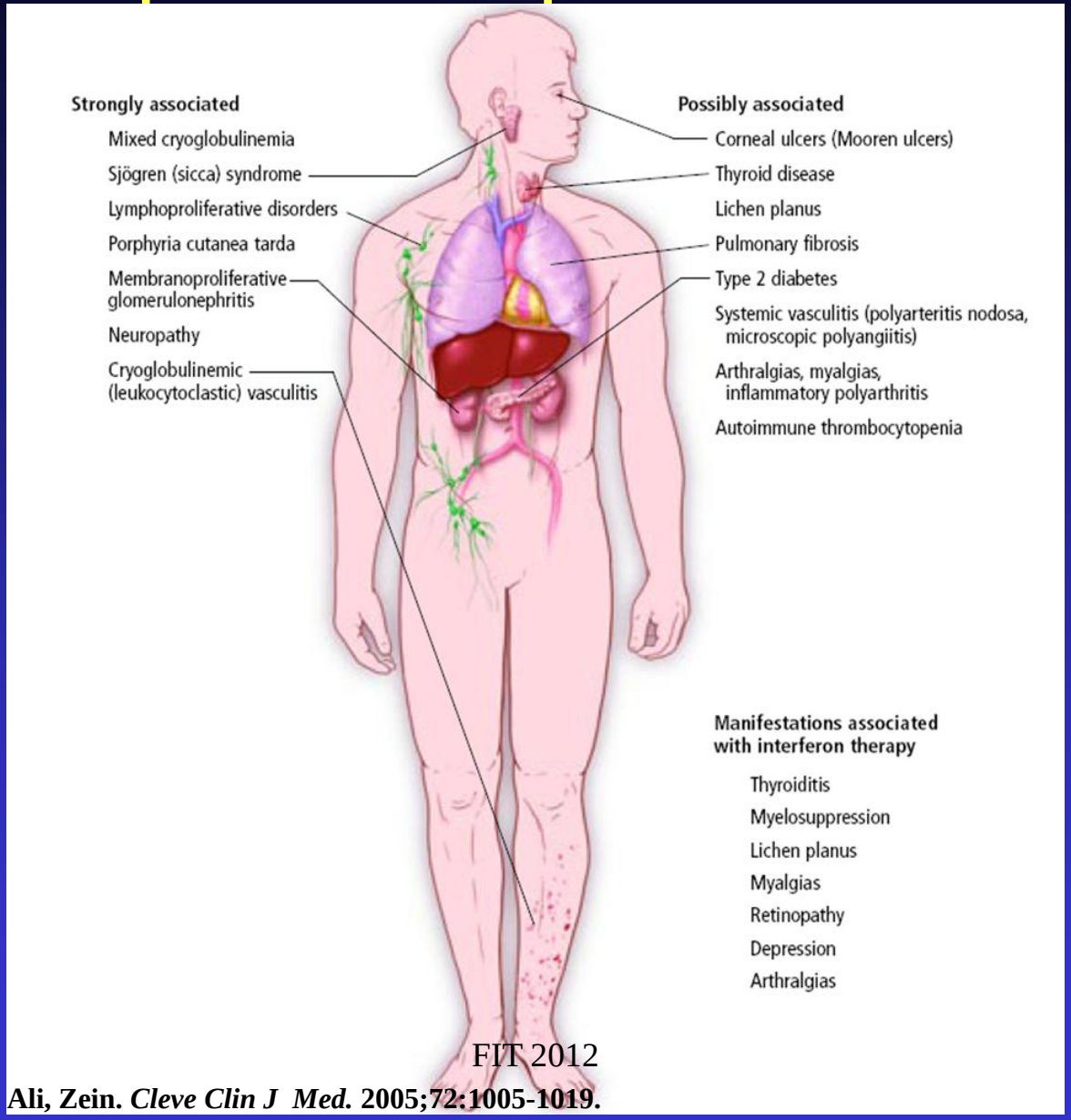
Guiltinan, Kaidarova, Custer, et al. *Am J of Epidem*. 2008;167:743-750.

HCV Mortality

- Increased mortality observed for liver and non-liver causes
  - Study NHANES participants with linked mortality file (n=9378), median follow-up 14.8 years
  - Adjusted mortality rate ratio for HCV+ v. HCV-
    - Liver: RR=26.46 (95% CI: 8.00-87.48)
    - All-cause: RR=2.37 (1.28-4.38)

El-Kamary, Jhaveri, Shardell. *Clin Infec Dis.* 2011;53:150-158.

Non-Hepatic Complications of HCV



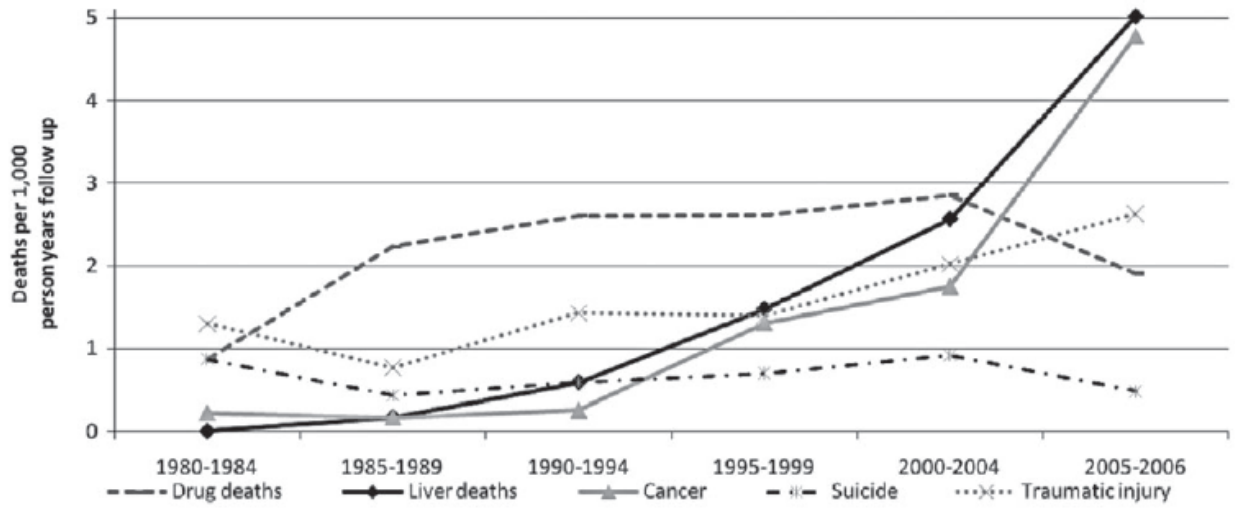
Ali, Zein. *Cleve Clin J Med.* 2005;72:1005-1019.

HCV Mortality in IDU

- Research suggests HCV is becoming a major cause of mortality in IDU
  - Cohort study of 2654 patients entering methadone treatment in Australia 1980-5
  - Linked to NDI death data up to 2008
  - Liver-related deaths increased over time, was most common cause last year of follow-up
    - 1/5 deaths (17%) from liver causes, hepatitis
    - Rate of death 17 from liver causes 17 x higher than general population

Gibson, Randall, Degenhardt. *Addiction.* 2011;106:2186-2192.

HCV Mortality in IDU



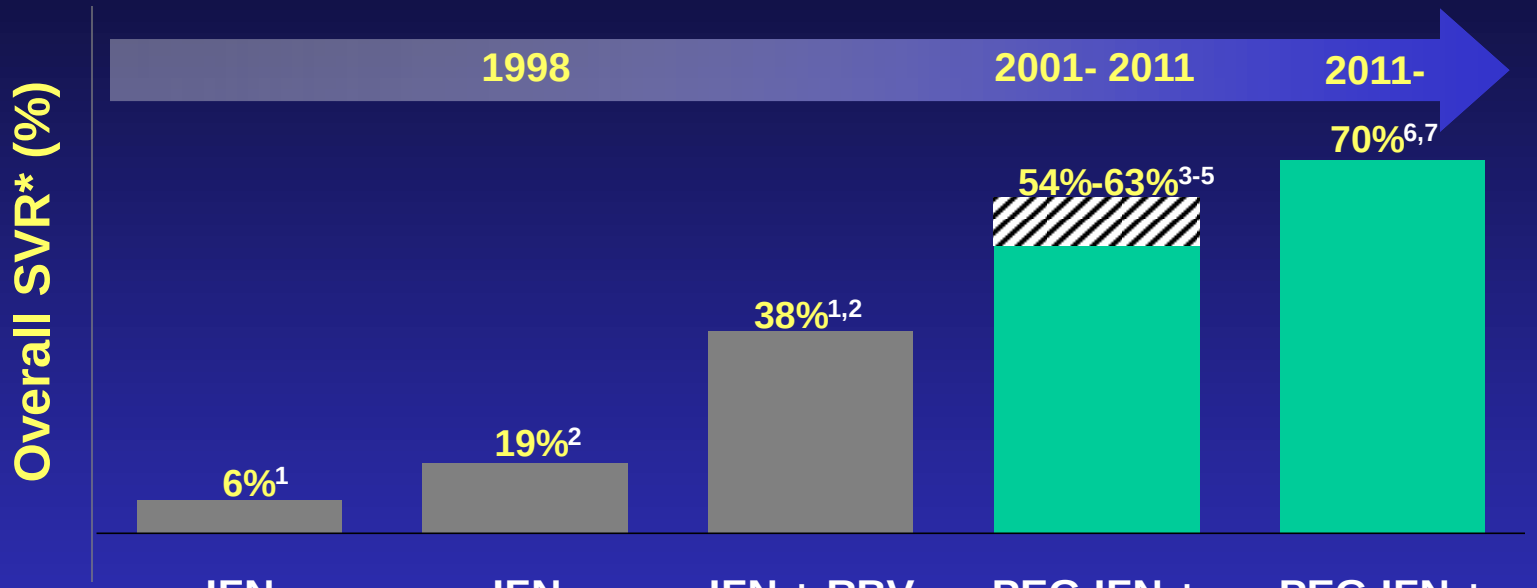
	1980-1984 deaths per 1000 PY (95%CI)	1985-1989 deaths per 1000 PY (95%CI)	1990-1994 deaths per 1000 PY (95%CI)	1995-1999 deaths per 1000 PY (95%CI)	2000-2004 deaths per 1000 PY (95%CI)	2005-2006 deaths per 1000 PY (95%CI)
Drug-induced	0.87(0.24-2.22)	2.23(1.46-3.27)	2.61(1.77-3.71)	2.62(1.77-3.74)	2.85(1.93-4.00)	1.91(0.83-3.77)
Liver-related	0.0(0.00-0.02)	0.17(0.02-0.62)	0.59(0.24-1.21)	1.48(0.86-2.38)	2.57(1.71-3.72)	5.02(3.11-7.68)
Cancer	0.22(0.01-1.21)	0.17(0.02-0.62)	0.25(0.05	1.31(0.73-2.16)	1.75(1.05-2.73)	4.78(2.92-7.39)
Suicide	0.87(0.24-2.22)	0.43(0.14-1.00)	0.59(0.24-1.21)	0.7(0.30-1.38)	0.92(0.44-1.69)	0.48(0.06-1.73)
Traumatidnjury	1.3(0.48-2.83)	0.77(0.35-1.47)	1.43(0.83-2.29)	1.4(0.80-2.27)	2.02(1.27-3.06)	2.63(1.31-4.71)

Figure 2 Trends across time in deaths per 1000 person-years (PY) for the most common underlying causes of death (participants with death causes recorded, $n = 432$); CI: confidence interval

FIT 2012

Gibson, Randall, Degenhardt. *Addiction.* 2011;106:2186-2192.

The Evolution of HCV Therapy



*SVR rates for all genotypes combined.

[1] McHutchison, Gordon, Schiff, et al. *N Engl J Med.* 1998;339:1485-1492.
[2] Poynard, Marcellin, Lee, et al. *Lancet.* 1998;352:1426-1432.
[3] Manns, McHutchison, Gordon, et al. *Lancet.* 2001;358:958-965.
[4] Fried, Shiffman, Reddy, et al. *N Engl J Med.* 2002;347:975-982.
[5] Hadziyannis, Sette, Morgna, et al. *Ann Intern Med.* 2004;14:346-355.
[6] Poordad, McCone, Bacon, et al. *N Engl J Med.* 2011;364:1195-1206.
[7] Jacobson, McHutchison, Dusheiko, et al. *N Engl J Med.* 2011;364:2405-2416.

Slide Adapted from Roche Presentation: "Understanding Hepatitis C and Its Treatment"

Benefits of SVR

- Durable effect, <1% have relapse ("cure")[1]
- Reduces progression of liver disease and development of hepatocellular CA[2]
- Ameliorates HCV-related extrahepatic manifestations
- Improves Quality of Life[3]
- May be associated with mortality benefit[4]

[1] Swain, Lai, Shiffman, et al. *Gastroenterology*. 2010;139:1593-1601
[2] Papatheodoridis, Papadimitropoulos, Hadziyannis. *Aliment Pharmacol Ther*. 2001;15:689-698.
[3] Spiegel, Younossi, Hays, et. al. *Hepatology* 2005;41:790-800.
[4] Butt, Wang, Moore. *Hepatology.* 2009:50:387-392.

Are Current Efforts for Screening and Treatment Adequate?

- National estimates: NHANES 2001-2008
  - 393 anti-HCV positive; 170 (43%) interviewed[1]
  - Only 49.7% were aware of HCV status prior to notification
    - Awareness twice as likely if health insurance, five times as likely if had usual source of medical care
- Among IDU:
  - Single study street recruited 197 IDU, only 61% of HCV+ were aware infected[2]

[1] Denniston, Monina, McQuillan, Jiles. *Hepatology.* E-pub 2011.
[2] Kwiatkowski, Corsi, Booth, et al. *Addiction.* 2002;97:1289-1294.

Risk Factor Based Screening

- ***Persons who have injected drugs***
- Persons with high prevalence conditions:
  - HIV
  - Hemophilia
  - Hemodialysis
  - Elevated transaminases
- Recipients of blood or organs prior to 1992
- Children born to HCV-infected mothers
- Healthcare workers with a needle stick
- Current sexual partners of HCV-infected persons

Ghany MG Hepatology 2009 AASLD, IDSA, ACG

Treatment Rates in IDU

- Studies suggest very low rates of HCV treatment are low among current/former IDU (1-16%)[1-3]
- Guidelines state that IDU is not an absolute contraindication to treatment
- Numerous barriers to treatment exist for IDU

[1] Mehta, Genberg, Astemborski, et al. *Journal of Community Health*. 2008;33: 126-133.
[2] Grebely, Genoway, Raffa, et al. *Drug and Alcohol Dependence*. 2008;93: 141–147.
[3] Stein, Maksad, Clarke. *Drug and Alcohol Dependence*.2001;61: 211-215.

Barriers to HCV Treatment in IDU

Individual barriers
Low patient motivation
Unstable lifestyle
Mod-severe depression
Active drug use
Heavy alcohol use

Provider barriers
Perceived non-adherence
Perceived risk of re-infection
Knowledge of HCV

Environmental barriers
No health insurance
No physician
No transportation

Adapted from Mehta, Thomas, Sulkowski, et al. *AIDS.* 2005;19:S179-S189.

Integration of Care for Substance Abuse and HCV

- Linking services for substance use and medical care may reduce barriers to treatment
- Study by Litwin, et al.
  - Provided HCV treatment on-site in methadone clinics in the Bronx, NY
    - 73 patients treated
    - 55% achieved ETR, 45% achieved SVR

Litwin, Harris, Nahvi, et al. *J Subst Abuse Treat*. 2009;37:32-40.

Treatment Outcomes for Opioid Dependent Patients/IDU

- Recent systematic review of HCV treatment in IDU:
  - 10 studies of IDU that included non-IDU comparison
  - Median rate of SVR among IDUs was 54.3% (range, 18.1%–94.1%)
    - Comparable to responses (54%–63%) in clinical trials
  - Only one small study restricted to active IDU, not informative

Hellard, Sacks-Davis, Gold. *CID*. 2009;49:561-573.

Additional Reasons to Screen for HCV if Not a Treatment Candidate

- Modify behaviors
  - Transmission risk behaviors
    - Sharing equipment/syringes, sexual behaviors
  - Behaviors that impact HCV progression
    - Alcohol, body weight, smoking
- Offer HCV related care
  - Immunizations for HAV and HBV

Awareness of HCV and Risk Behaviors

- Injecting drug practices
  - Studies suggest that HCV+ have more severe addiction, no consistent change in sharing practices with awareness[1-4]
- Alcohol
  - Some studies suggest awareness of HCV associated with less alcohol use[5-7]

[1] Korthuis, Feaster, Gomez, et al. *Addict Behav.* 2012;37:552-555.
[2] Norden, Saxon, Kaberg, et al. *J Infect Dis.* 2009;41:727-734.
[3] Kwiatkowski, Corsi, Booth. *Addiction.* 2002;97:1289-1294.
[4] Ompad, Fuller, Vlahov, et al. *CID.* 2002;35:783-788.
[5] Tsui, Saitz, Cheng, et al. *J Gen Int Med.* 2007;22:822-825.
[6] Tsui, Vittinghoff, Hahn, et al. *Drug Alc Dep*. 2009;105:160-163.
[7] McCusker. *Addiction.* 2001;96:1007-1014.

Awareness of HCV and Risk Behaviors

- "Risk behaviors after HCV seroconversion in young injection drug users in San Francisco"
  - Data from prospective study of young IDU
  - 112 participants seroconverted during study
  - Examined behaviors before/after seroconversion

Tsui, Vittinghoff, Hahn, et al. *Drug Alc Dep.* 2009;105:160-163.

Awareness of HCV and Risk Behaviors

Table 2
Adjusted relative odds for behaviors/depression associated with awareness of HCV seroconversion in 112 young IDU who seroconverted using conditional logistic regression[a].

	Immediately After Seroconversion[b]			6 months After Seroconversion			12 months After Seroconversion		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Past Month Alcohol Use	0.52	0.27–1.00	0.05	0.67	0.36–1.26	0.21	0.85	0.43–1.69	0.65
Past Month Injection Drug Use	0.84	0.35–2.05	0.7	0.85	0.36–1.98	0.71	0.86	0.33–2.20	0.75
Past 3 Month Non-injection Drug Use	0.4	0.20–0.81	0.01	0.48	0.23–1.00	0.05	0.57	0.25–1.32	0.19
Past 3 Month Lending of Syringes	0.80	0.29–2.25	0.68	0.49	0.21–1.16	0.10	0.3	0.08–1.09	0.07
Past 3 Month Sharing of Injecting Equipment	0.61	0.22–1.71	0.35	0.6	0.23–1.58	0.3	0.59	0.15–2.30	0.45
Past 3 Month Sex without Condom	1.65	0.77–3.58	0.2	1.57	0.72–3.40	0.26	1.48	0.63–3.48	0.37
Current Depression	0.76	0.23–2.53	0.65	0.78	0.28–2.16	0.63	0.8	0.19–3.29	0.76

[a] Adjusted for secular trends plus drug use, recent incarceration and homelessness; fixed covariates (age, sex, race, etc.), which represent between- rather than within-subject differences, have no influence in the conditional logistic model.

[b] OR for behavior immediately after seroconversion; model assumes change at seroconversion followed by linear trend.

Tsui, Vittinghoff, Hahn, et al. *Drug Alc Dep.* 2009;105:160-163.

Future Research Opportunities

- Interventions to prevent transmission (treatment as prevention?)
- Interventions to improve screening and linkage to care
- Improving systems for delivery of care/expanding access to care for HCV in IDU
- Monitoring/improving adherence in IDU
- Elucidating non-hepatic effects of HCV
- Finding an effective vaccine for HCV