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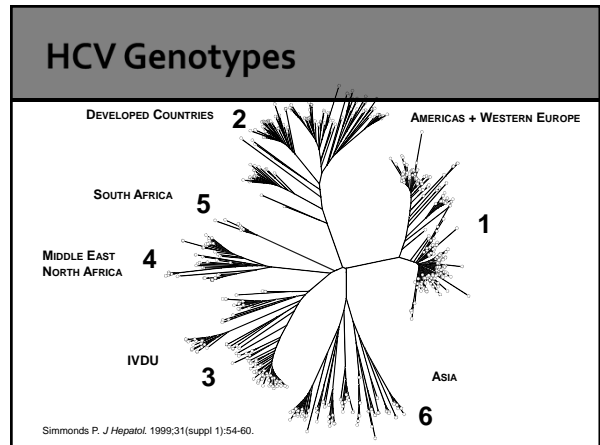
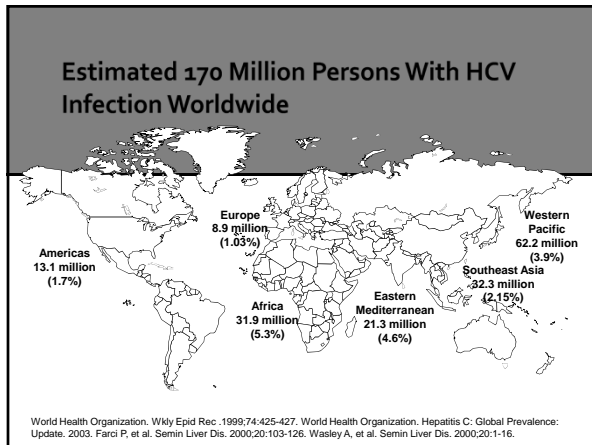


Hepatitis C

Objectives

Upon completion of this session, the participant will be able to:

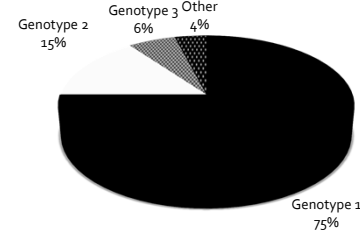
- Describe the natural history of hepatitis C
- Advocate for screening and treatment of hepatitis C
- Discuss treatment options for chronic hepatitis C infection
- Discuss the University of New Mexico's Project ECHO and how it could help your community



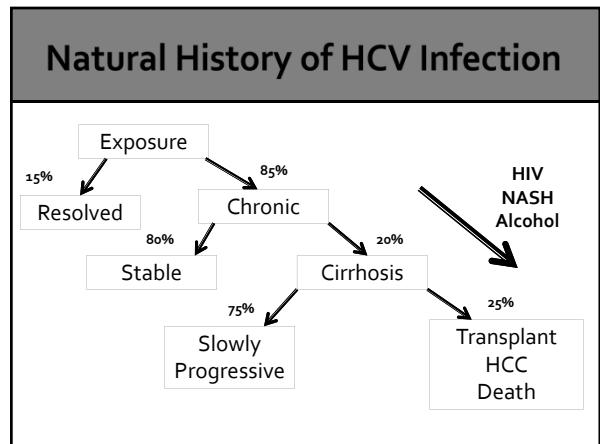
Clinical Significance of Genotypes

- All can lead to cirrhosis, end-stage liver disease (ESLD), hepatocellular carcinoma (HCC)
- Response to therapy is different
- Genotype 1 is greatest risk factor for not responding to treatment

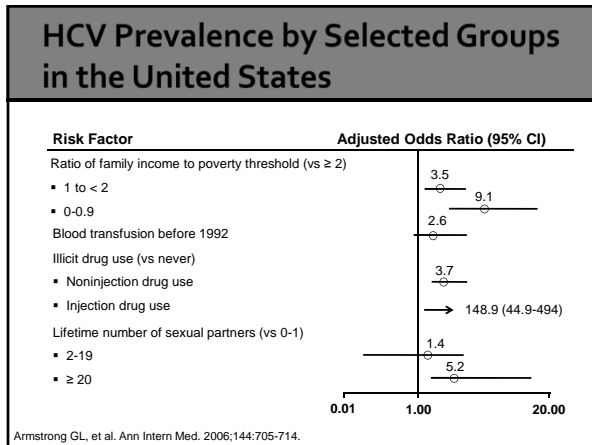
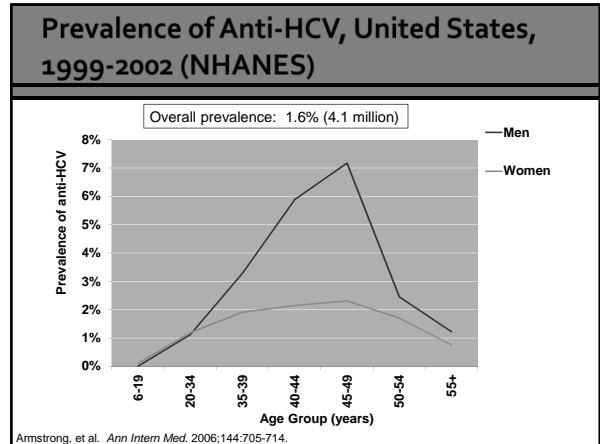
Genotypes in the U.S.



Genotype	Percentage
Genotype 1	75%
Genotype 2	15%
Genotype 3	6%
Other	4%



Epidemiology	
<p>5x as widespread as HIV</p> <p>75% of Patients Unaware of Infection</p>	



IOM Report 2010: Hepatitis and Liver Cancer

SUMMARY 3

1. There is a lack of knowledge and awareness about chronic viral hepatitis on the part of health-care and social-service providers.
2. There is a lack of knowledge and awareness about chronic viral hepatitis among at-risk populations, members of the public, and policy-makers.
3. There is insufficient understanding about the extent and seriousness of this public-health problem, so inadequate public resources are being allocated to prevention, control, and surveillance programs.

IOM (Institute of Medicine). 2010. *Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C.*

IOM Report 2010: Hepatitis and Liver Cancer

That situation has created several consequences:

- Inadequate disease surveillance systems underreport acute and chronic infections, so the full extent of the problem is unknown.
- At-risk people do not know that they are at risk or how to prevent becoming infected.
- At-risk people may not have access to preventive services.
- Chronically infected people do not know that they are infected.
- Many health-care providers do not screen people for risk factors or do not know how to manage infected people.
- Infected people often have inadequate access to testing, social support, and medical management services.

IOM (Institute of Medicine). 2010. *Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C.*

AASLD Practice Guidelines	Recommendations
<p>Offer diagnostic, therapeutic, and preventative recommendations</p> <p>Guidelines approved by the American Association for the Study of Liver Diseases (AASLD), Infectious Diseases Society of America, and the American College of Gastroenterology</p> <p>Guidelines revised in 2009</p>	<ol style="list-style-type: none"> 1. As part of comprehensive health evaluation, all persons should be screened for HCV infection risks 2. Persons who are at risk should be tested for the presence of HCV infection 3. Persons infected with HCV should be counseled on how to avoid HCV transmission to others

Ghany MG, et al. *Hepatology.* 2009;49:1335-1374.

HCV Household Transmission Concerns

- Avoid potential blood contact
 - No sharing toothbrush, razors, etc
- No known transmission:
 - Hugging
 - Kissing
 - Sharing of eating utensils
 - Breastfeeding

Ghany MG, et al. Hepatology. 2009;49:1335-1374.

Patient Case

- 22 yo female presents to clinic after donating blood and being told she is HCV positive
- What are risk factors for HCV exposure?

HCV Exposure Risks: AASLD Recommended Screening

- Current or former injection drug users
 - Even if one-time use
- Conditions associated with high prevalence of HCV
 - HIV positive
 - Hemodialysis
 - Hemophiliacs- received clotting factors <1987
 - Evidence of unexplained abnormal aminotransferase levels
- Transplants/ Transfusions <July 1992
- Children born to HCV infected mother
- Occupational exposure- needlestick or mucosal exposure
- Current sexual partners of HCV-infected persons

Ghany MG, et al. Hepatology. 2009;49:1335-1374.
Centers for Disease Control and Prevention. MMWR Recomm Rep. 1998;47:1-39.

Patient Case Continued

- Patient convinced false positive
 - Athletic
 - Pre-med
 - Denied history of illegal drug use, non-professional tattoos
- On exam she had evidence of liver disease
- Patient had multiple opportunities for diagnosis

Forecasting Morbidity and Mortality of HCV Patients in U.S.

- HCV infections reached a peak in late 1980s
 - 1989: 291,000 per year
 - 2006: 20,000 per year
- Chronically infected cohort
 - Long incubation period
 - Many undiagnosed/unaware of infection
 - Patients infected in 1960s-1980s approaching era of HCV related morbidity

Rein, DB et al. Dig Liver Dis. 2011;43:66-72.

Forecasted Annual Incident Cases of Decompensated Cirrhosis (DCC), Hepatocellular Carcinoma (HCC), Liver Transplants, and Deaths Associated with Persons with Chronic Hepatitis C Infection and No Liver Cirrhosis in the United States in 2005

Rein, DB et al. Dig Liver Dis. 2011;43:66-72.

Risks for Infection

- 2075 patients with acute HCV 1994-2006
- Known or potential exposures
 - Injection drug use 46.7%
 - No risk factor identified 29.3%
 - 14.5% had prior history of IDU (6.7%) or intranasal drug use (7.8%)
- Missed opportunities for identifying HCV
 - Among patients reporting drug use, 72% had been either in a substance abuse or treatment program and/or incarcerated

Williams et al. Arch Intern Med. 2011;171:242-248.

Current HCV Screening Research

- 3 large community based clinics in Bronx
- Study design:
 - Cross-sectional electronic medical record review for association of patient characteristics and HCV testing
 - >18 years old, primary care visit between Jan 08 through Feb 08
- Outcomes
 - Patient characteristics associated with HCV testing and positivity
 - Prevalence of HCV in urban setting

Southern, WN, et al. J of Viral Hepat 2010. doi: 10.1111/j.1365-2893.2010.01327

Current HCV Screening Research

- N=9579
 - 51% Latino
 - 32% Black
 - 5% White
- HCV Risk
 - 5.8% substance abuse diagnosis
 - 4.5% HIV diagnosis
- 39.7% tested at baseline for anti-HCV
- Among tested population, HCV+ prevalence 11.5%
- Estimated clinical population prevalence 7.7%

Southern, WN, et al. J of Viral Hepat 2010. doi: 10.1111/j.1365-2893.2010.01327

Current HCV Screening Research

- Risk factors associated with HCV
 - Born in high prevalence birth cohort (1945-64)
 - Male
 - Any substance abuse
 - Cirrhosis
 - Elevated ALT
- Among patients with no risk factor, HCV prevalence 3%
- Universal testing may be appropriate in high risk urban population

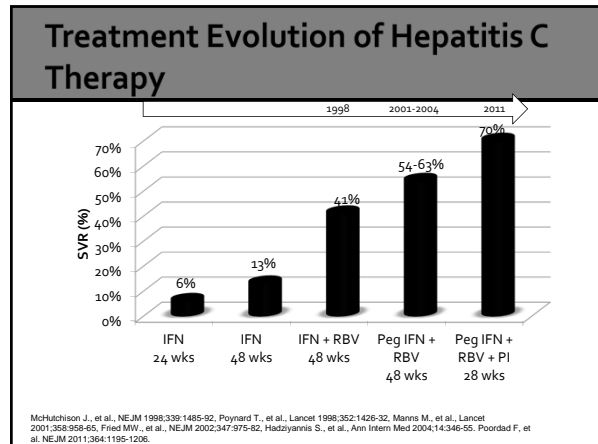
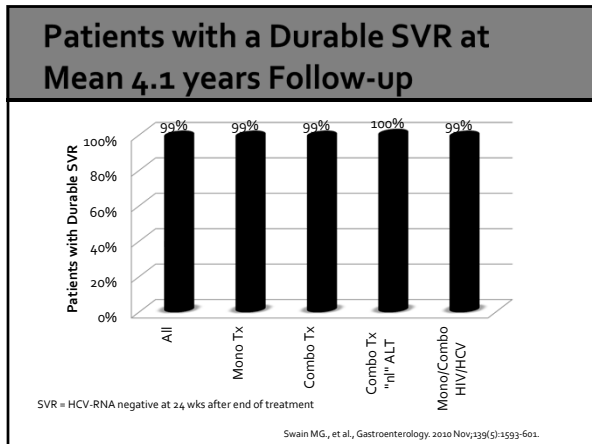
Southern, WN, et al. J of Viral Hepat 2010. doi: 10.1111/j.1365-2893.2010.01327

Birth-cohort Evaluation to Advance Screening and Testing for Hepatitis C: Best-C Study

- Evaluate effectiveness and implementation of one-time screening strategy of all patients born between 1945- 1965
- Large, primary care systems
 - New York
 - Detroit
 - Birmingham
 - Houston
- Updated screening guidelines expected 2012-2013

Goals of Therapy

1. Eradication of virus: sustained virological response
2. Prevent complications of HCV infection
 - Fibrosis
 - Cirrhosis
 - ESLD
 - HCC
3. Other: Histological improvements, patient quality of life



- ### Pegylated Interferon (Peg-IFN)
- Immunomodulatory protein associated with durable response
 - Prevent infection
 - Reduce HCV mutation
 - Stimulate proinflammatory response
 - Polyethylene glycol moiety increased half-life
 - Reduced dosing frequency from 3x per week to 1x per week
 - Increased SVR rates
 - Genotype 1: 38-50%
 - Genotypes 2 or 3: 76-82%

Pegylated Interferons

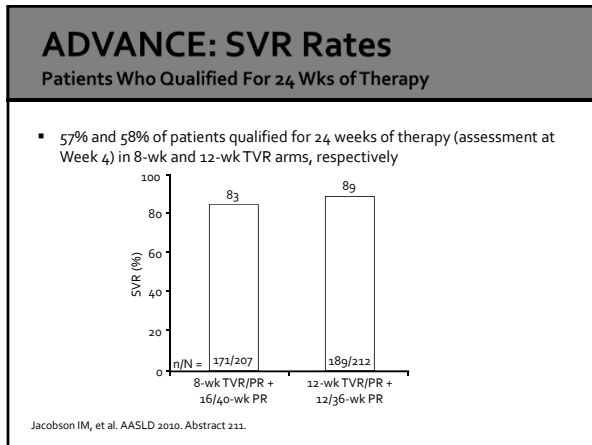
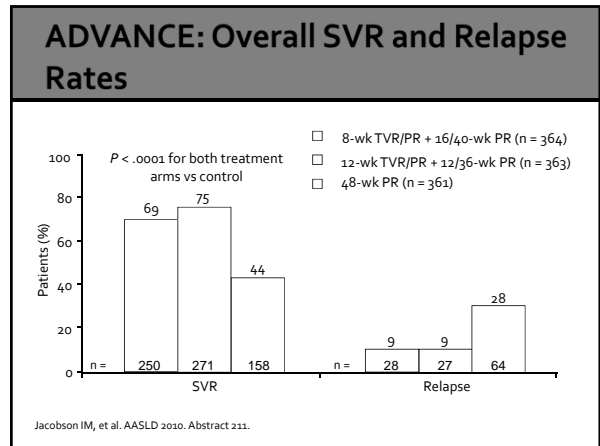
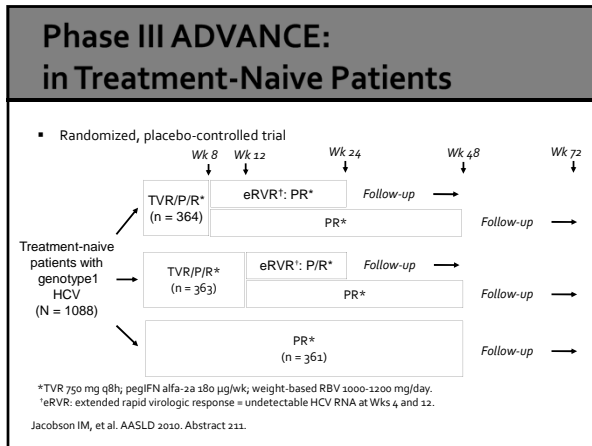
	Pegasys®	PegIntron®
Interferon	Alpha-2a	Alpha-2b
PEG moiety (Weight)	Branched (40 kD)	Linear (12 kD)
Distribution	8-12 L Highest concentration in liver, spleen, kidneys	Body weight dependent: 1 L/kg; distributes throughout body
Metabolism	Liver	Liver
Excretion	Renal	Renal
Dosing	Fixed: 180 mcg/week subcutaneously	Weight dependent: 1.5 mcg/kg/week subcutaneously

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- ### Ribavirin
- Mechanism of action in HCV unclear: inhibits viral replication
 - Synergistic effects with interferon to increase SVR rates
 - No efficacy as monotherapy
 - Oral medication
 - Dose not defined:
 - Weight based dosing for genotype 1
 - Standard 800 mg dose for genotypes 2,3
 - Shorter course of therapy with weight based dosing for genotypes 2,3 is possible
- Mangia et al. N Engl J Med 2005;352:2609-17.

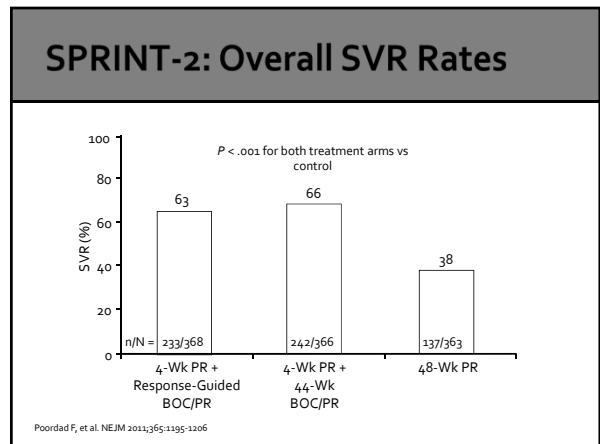
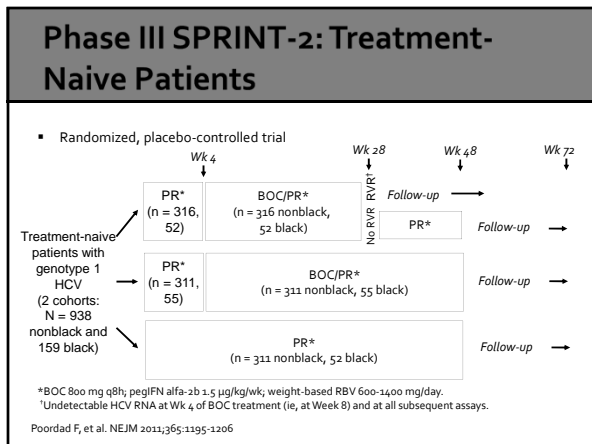
Telaprevir (Incivek™)

- Vertex Pharmaceuticals
- Oral HCV protease inhibitor for genotype 1 infections
- FDA approved on May 23, 2011
- Combined with IFN/RBV
 - Dosed 750 mg q8h
 - Resistance develops quickly if used alone
 - Do not dose adjust



Boceprevir (VICTRELIS™)

- Merck
- Oral HCV protease inhibitor for genotype 1 infections
- Approved by FDA on May 13, 2011
- Combined with IFN/RBV
 - Dosed 800 mg q8h
 - Resistance develops quickly if used alone
 - Do not dose adjust



SPRINT-2: SVR Rates

Patients Who Qualified For 28 Wks of Therapy

- 44% of patients qualified for 28 weeks of therapy (assessment at Week 4 of BOC, ie Week 8 of therapy) in response-guided arm

Race	n/N	SVR (%)
Non-blacks	143/147	97
Blacks	13/15	87

Poordad F, et al. NEJM 2011;365:1195-1206

Clinical Adverse Drug Reactions with Telaprevir

- Rash, anemia, and anal-rectal symptoms were most commonly reported

	Telaprevir + PR	PR
Rash	56%	34%
Pruritus	47%	28%
Anemia	36%	17%
Diarrhea	26%	17%
Hemorrhoids	12%	3%
Anorectal discomfort	11%	3%
Anal pruritus	6%	1%

PR: pegylated interferon/ribavirin therapy

Boceprevir: Adverse Events and Discontinuations

- Anemia and dysgeusia reported more frequently in BOC arms vs control in SPRINT-2 (P<0.001)

Outcome	4-Wk PR + Response-Guided BOC/PR (n = 368)	4-Wk PR + 44-Wk BOC/PR (n = 366)	48-Wk PR (n = 363)
Adverse event, %			
Anemia	49	49	29
EPO use	43	43	24
Dysgeusia	37	43	18
Discontinuations due to adverse events, %	12	16	16
Anemia	2	2	1

Poordad F, et al. NEJM 2011;365:1195-1206

Key Kinetics of HCV Protease Inhibitors

BOCEPREVIR	TELAPREVIR
<ul style="list-style-type: none"> Absorption <ul style="list-style-type: none"> Improved by 65% when taken with food (any kind) Metabolism <ul style="list-style-type: none"> Aldoketoreductase pathway Inhibits CYP3A4/5 and P-glycoprotein Elimination <ul style="list-style-type: none"> By liver 	<ul style="list-style-type: none"> Absorption <ul style="list-style-type: none"> Improved by 237% when taken with meal of 20 g fat Metabolism <ul style="list-style-type: none"> CYP3A4 major player, also P-glycoprotein Inhibits both May inhibit CYP2C, 1A, 3A Elimination <ul style="list-style-type: none"> By liver

Drugs That Are Contraindicated with PIs

Boceprevir and Telaprevir	Clinical Comment
St. John's Wort	May lead to loss of virologic response
Rifampin	May lead to loss of virologic response
Alfuzosin	Increased alfuzosin concentrations can result in hypotension
Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Potential for acute ergot toxicity (peripheral vasospasm or ischemia)
Cisapride	Potential for cardiac arrhythmias
Lovastatin, simvastatin (Atorvastatin with TVR also)	Potential for myopathy including rhabdomyolysis
Pimozide	Potential for cardiac arrhythmias
REVATIO® (sildenafil) or ADCIRCA® (tadalafil) for treatment of PAH	Potential for PDES inhibitor-associated AEs
Triazolam; midazolam (oral)	Prolonged or increased sedation or respiratory depression
Boceprevir	Clinical Comment
Carbamazepine, phenobarbital, phenytoin	May lead to loss of virologic response to BOC
Drospirone (oral contraceptive)	Potential for hyperkalemia

Improving Outcomes: Adherence and Compliance

FREQUENT DOSING	PILL BURDEN
<ul style="list-style-type: none"> Boceprevir <ul style="list-style-type: none"> Four 200 mg capsules by mouth every 8 hours Telaprevir <ul style="list-style-type: none"> Two 375 mg tablets by mouth every 8 hours 	<ul style="list-style-type: none"> Both protease inhibitors must be taken every 8 hours <ul style="list-style-type: none"> Concerns for virological breakthrough with missed dose Both protease inhibitors should be taken with food <ul style="list-style-type: none"> Telaprevir requires a snack or meal with 20 grams of fat

Protease Inhibitor Stopping Rules

Telaprevir*		
Timepoint	Criteria for Stopping	Action
Week 4 or 12	HCV-RNA > 1000 IU/mL	Discontinue TVR/PEG-IFN/RBV
Week 24	HCV-RNA detectable	Discontinue PEG-IFN/RBV

Boceprevir**		
Timepoint	Criteria for Stopping	Action
Week 12	HCV RNA \geq 100 IU/mL	Discontinue BOC/RBV/Peg-IFN
Week 24	Confirmed, detectable HCV RNA	Discontinue BOC/RBV/ Peg-IFN

*INCIVEK® (telaprevir) tablets [package insert]. Cambridge, MA: Vertex Pharmaceuticals Incorporated, 2011
 **VICTRELIS® (boceprevir) capsules [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2011

Direct Economic Burden of HCV

- Assess all-cause healthcare utilization and costs for patients with chronic HCV
- Data from Integrated Health Care Information Services Managed Care Benchmark Database
 - Medical and pharmacy claims data
 - Data from 30 managed care organizations across US
- Patient data from Jan. 1 2002-Dec. 31 2006
- Patients with chronic HCV matched to control group
 - 20,662 patients evaluated

Davis et al. *J Clin Gastroenterol.* 2011;45:e17-e24.

Financial Burden: Costs of HCV

- Compared to controls, HCV patients had higher costs
 - All cause: \$20,961 vs \$5451 ($p < 0.0001$)
 - Mean inpatient costs: \$5892 vs \$1315 ($p < 0.001$)
 - Higher hospitalization rates 24% vs 7% ($p < 0.0001$)
- HCV related costs nearly doubled as disease progressed from mild to severe
 - \$6839 vs \$12,481 ($p < 0.0001$)

Davis et al. *J Clin Gastroenterol.* 2011;45:e17-e24.

Financial Burden: Costs of HCV

- Patients with chronic HCV have higher annual costs as compared to other common chronic conditions (cardiovascular disease or diabetes)
- Patients who achieved SVR demonstrated reduced healthcare costs

Davis et al. *J Clin Gastroenterol.* 2011;45:e17-e24.

The mission of Project ECHO is to develop the capacity to safely and effectively treat chronic, common and complex diseases in rural and underserved areas and to monitor outcomes.



Supported by Agency for Health Research and Quality HIT grant 1 UC1 HS015135-04, and MRIS R24HS16510-02 and the New Mexico Legislature, Robert Wood Johnson Foundation.

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 HEALTH SCIENCES CENTER
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 DEPARTMENT OF
 INTERNAL MEDICINE

Methods

- Use technology (telemedicine and internet) to leverage scarce healthcare resources
- Disease Management Model focused on improving outcomes by reducing variation in processes of care and sharing "best practices"
- Case based learning: co-management of patients with UNMHSC specialists
- Centralized database HIPAA compliant to monitor outcomes





HCV in New Mexico

- Racial and ethnic minorities less likely to receive care
- In 2004, patients across NM had a 6 month wait list to receive care at UNM
 - Travel up to 250 miles

Project ECHO

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Outcomes of Treatment for Hepatitis C Virus Infection by Primary Care Providers

Sanjeev Arora, M.D., Karla Thornton, M.D., Glen Murata, M.D., Paulina Deming, Pharm.D., Simone Kalkbrenner, Ph.D., Denise Diaz, Ph.D., Brooke Parish, M.D., Thomas Burke, B.S., Wesley Pak, M.B.A., Jeffrey Dunkelberg, M.D., Martin Kottin, M.D., John Brown, M.B.A., Steven Jenks, M.D., Miriam Komaromy, M.D., and Clifford Qualls, Ph.D.

Hypothesis: treatment for HCV delivered in the community with the use of the ECHO model is as effective as that provided at the academic medical center

Project ECHO initiated in 2003
 >5000 patients presented
 >800 patients treated

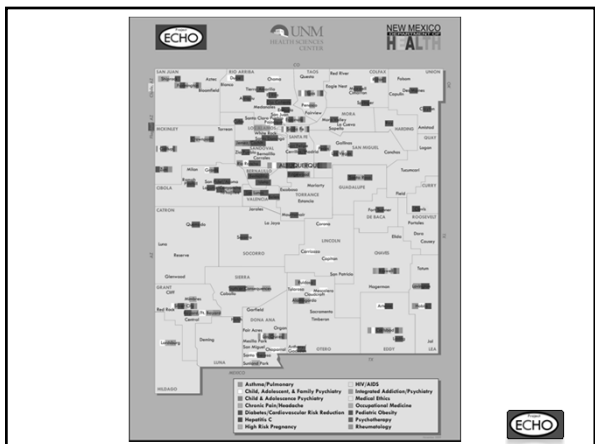
N Engl J Med 2011;364:2199-207.

Results

- 407 patients included in analysis
 - 261 patients at ECHO sites and 146 at UNM
- Patient characteristics
 - Predominantly Hispanic (n= 216 patients)
 - 156 (64.5%) at ECHO sites vs. 60 (41.4%) at UNM
 - Age
 - 41.9±9.8 at ECHO sites vs. 45.4±9.8 at UNM
 - Male sex
 - 190 at ECHO sites vs. 66 at UNM
 - HCV genotype 1
 - 147 (56.3%) at ECHO sites vs. 83 (56.8%) at UNM

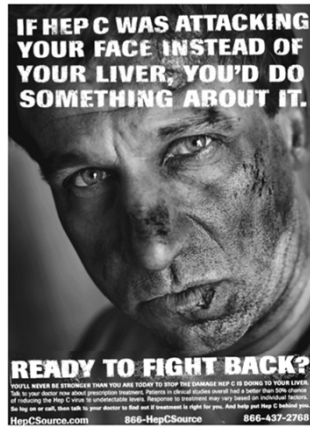
SVR Results

<p>ECHO MODEL</p> <ul style="list-style-type: none"> ▪ SVR rate <ul style="list-style-type: none"> ▪ 58.2% overall ▪ 49.7% for genotype 1 ▪ No difference in SVR for Hispanic patients 	<p>OTHER COMMUNITY TRIALS</p> <ul style="list-style-type: none"> ▪ WIN-R <ul style="list-style-type: none"> ▪ 34.1% SVR for genotype 1 ▪ Veterans Affairs <ul style="list-style-type: none"> ▪ 20% SVR for genotype 1 ▪ Latino Study Group <ul style="list-style-type: none"> ▪ 34% SVR for Hispanic patients vs 49% for non-Hispanic patients
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Benefits to Rural Clinicians

- No cost CMEs and nursing CEUs
- Professional interaction with colleagues with similar interest
 - Less isolation with improved recruitment and retention
- A mix of work and learning
- Obtain HCV certification
- Access to specialty consultation with GI, hepatology, psychiatry, infectious diseases, addiction specialist, pharmacist, patient educator



Questions?