The HIV/HCV Co-Infected Patient and Future Treatment Options

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November 14, 2012

Disclosure Statement

I have served as a consultant for Vertex Pharmaceuticals

I will discuss the following off-label use in this presentation:
Telaprevir / Boceprevir for HIV-1 / HCV co-infection
Other direct-acting agents

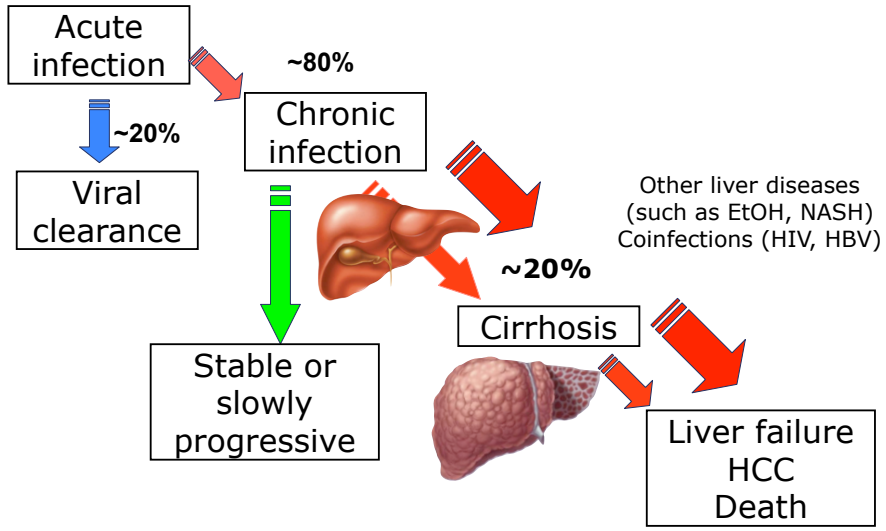
Funding: National Institutes of Health
(National Institute of Allergy and Infectious Diseases,
National Institute of Drug Abuse)

Objectives

Upon Completion of this program, the participant will be able to:

3. State the special considerations in caring for the HIV/HCV co-infected patient
4. Describe the emerging therapeutic options available for HCV treatment

Natural history of HCV



HIV / HCV co-infection is double trouble

For HCV, compared to HIV-negative individuals, those with HIV suffer from:

1. Higher rates of persistence (lower rates of spontaneous clearance)
2. Accelerated rate of fibrosis, higher rates of cirrhosis
3. Higher rates of decompensation & higher liver-related mortality
4. Higher viral titers and lower rates of response to therapy

Challenge 1: Prevention & Screening

Problem: Higher rates of persistence (lower rates of spontaneous clearance)

Key challenges:

- **Prevention**: Decreasing risky behaviors, reducing harm
- **Vaccines**: Developing immunity that can prevent infection or enhance clearance
- **Diagnosis**: Identifying infection that is asymptomatic or minimally symptomatic

A tale of two viruses

HIV

Sex > Blood

Targets immune cells

Years to clinical illness

High levels of viremia

10^9 particles/day

Low fidelity of reverse transcriptase

Frequently mutates

HCV

Blood > Sex

Targets hepatocytes

Decades to clinical illness

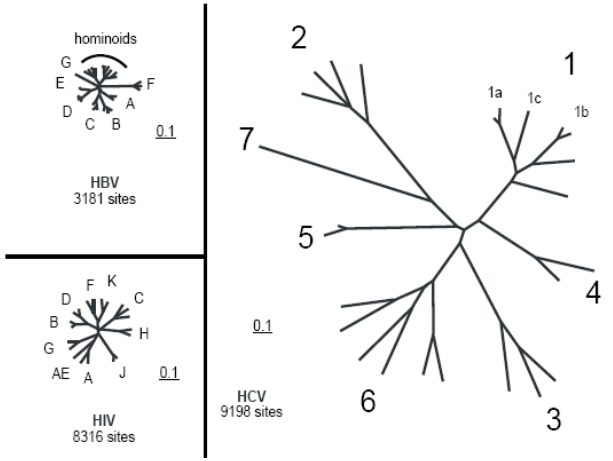
High levels of viremia

10^12 particles/day

Low fidelity of RNA-RNA polymerase

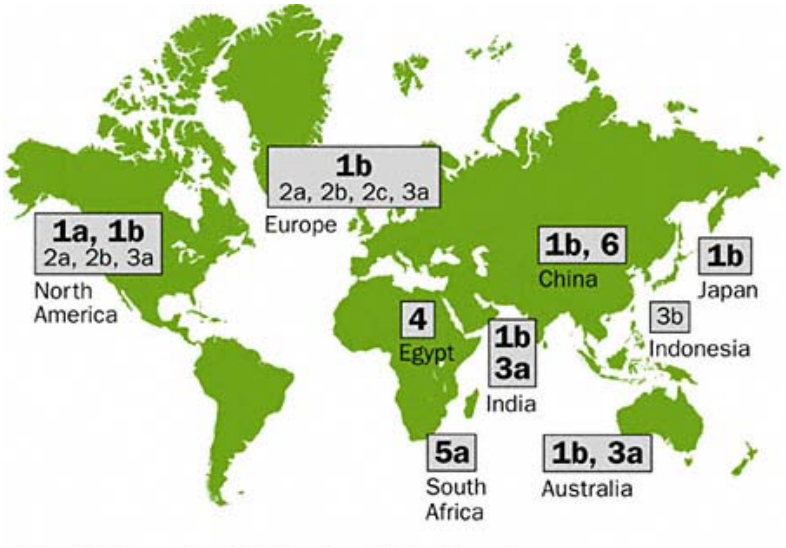
Frequently mutates

HCV Sequence Diversity Relative to Hepatitis B and HIV



Ray SC, Thomas DL. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases, 7th ed. Philadelphia, PA: Churchill Livingstone/Elsevier; 2010.

Worldwide genotype distribution

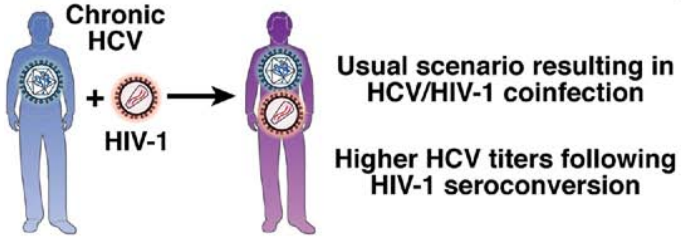


A tale of two viruses

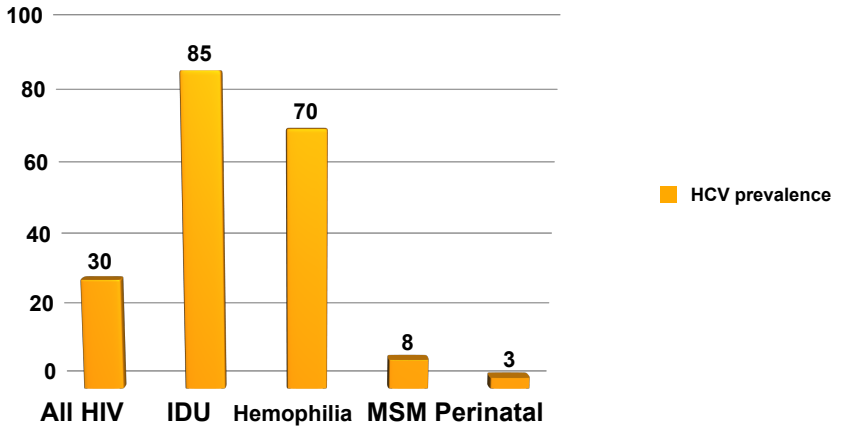
HIV	HCV
Sex > Blood	Blood > Sex
Targets immune cells	Targets hepatocytes
Years to clinical illness	Decades to clinical illness
High levels of viremia	High levels of viremia
10^9 particles/day	10^12 particles/day
Low fidelity of reverse transcriptase	Low fidelity of RNA-RNA polymerase
Frequently mutates	Frequently mutates

Usual scenario for HCV/HIV co-infection

HCV is more transmissible via bloodborne than sexual exposure



HCV prevalence if HIV+ depends on risk factor



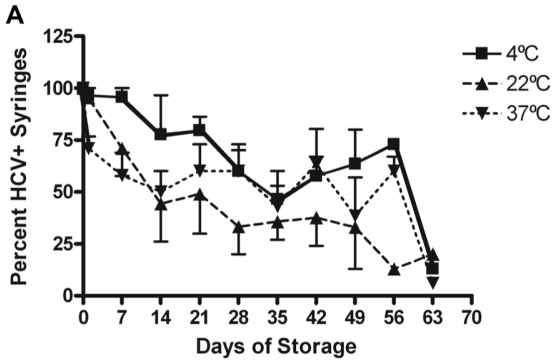
Rules of 3: risk after needlestick

HBV 30%

HCV 3% (~1-2%)

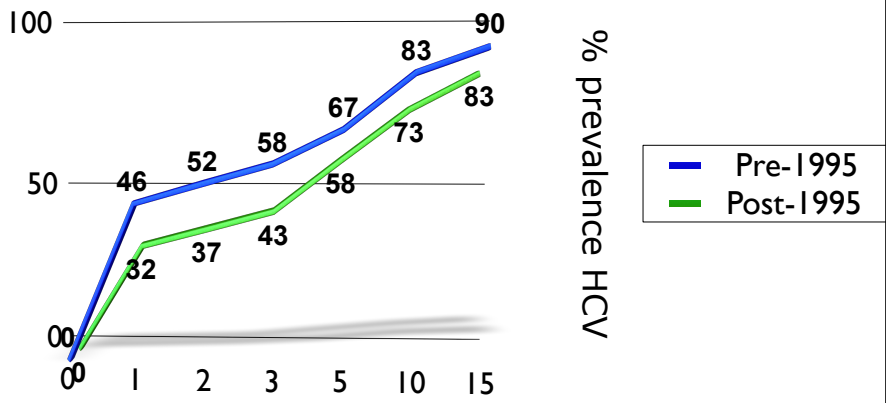
HIV 0.3%

Infectivity of JFH-1 strain of HCV in syringes

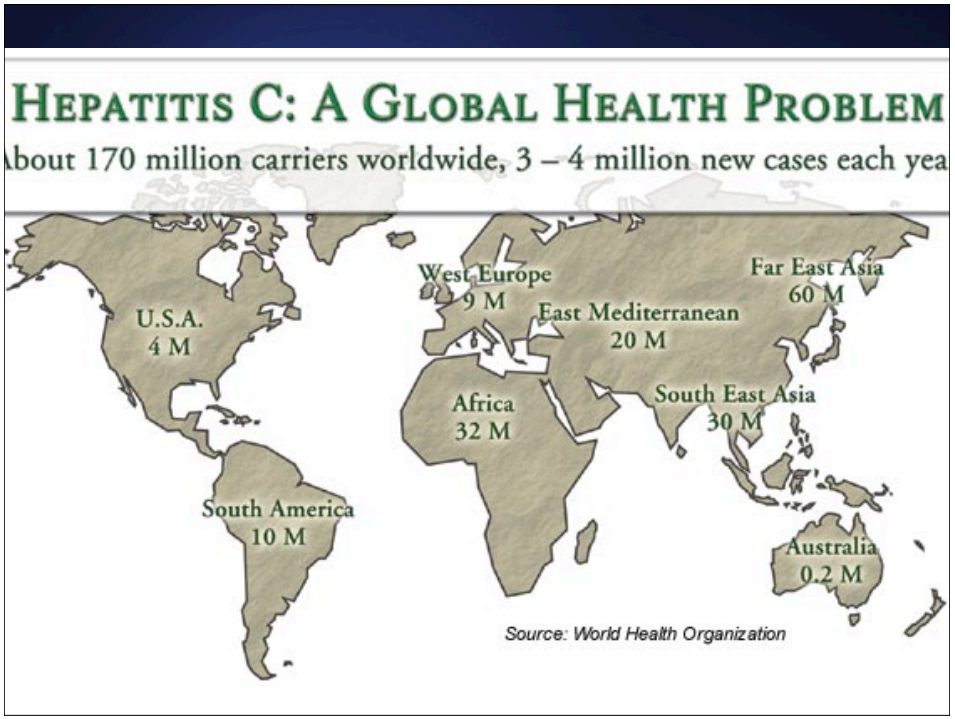


Paintisil et al. J Infect Dis 2010;202(7):984–990

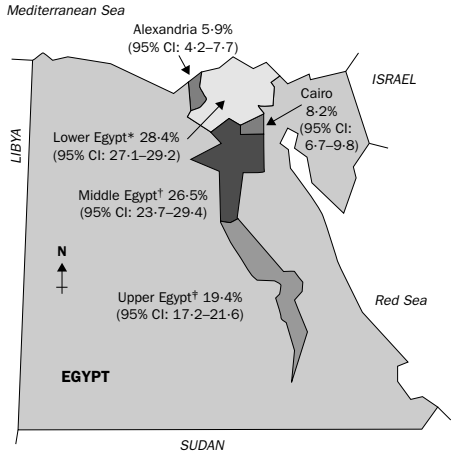
Likelihood of HCV infection: duration of IDU



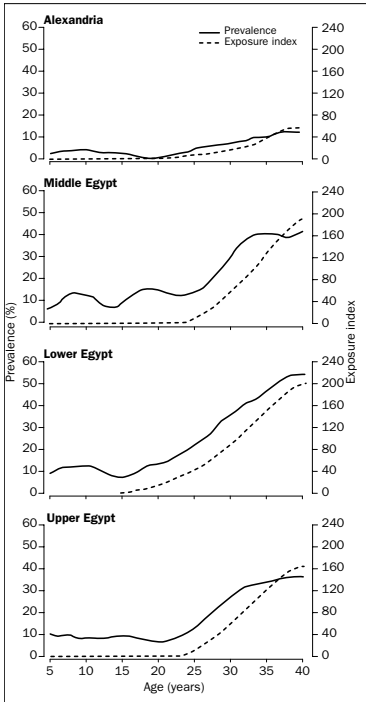
Hagan et al. Am J Epidemiol 2008; 167:1099



The prevalence of HCV in Egypt is >10%



Frank et al. Lancet 2000

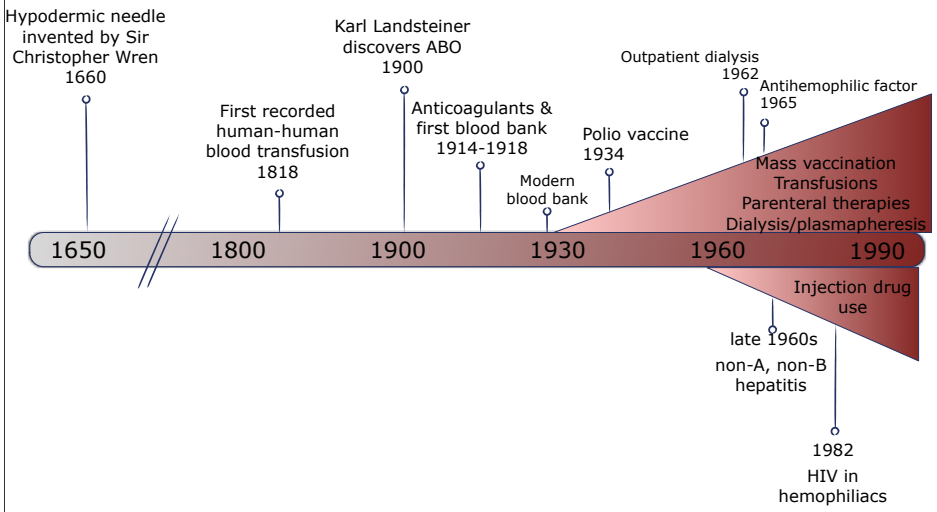


Correlation of HCV prevalence to exposure to parenteral antischistosomal therapy

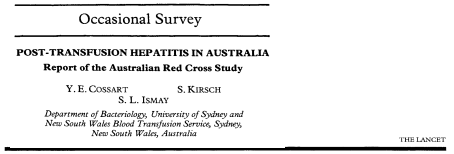
Lining up for tartar emetic to treat bilharzia, upper Nile

Frank et al. Lancet 2000
Jordan Acta Tropica 2000

Injections/parenteral therapies in medicine - rise in 20th century



The 70s and 80s were scary times



Occasional Survey

POST-TRANSFUSION HEPATITIS IN AUSTRALIA
Report of the Australian Red Cross Study

Y. E. Cossart S. Kirsch
S. L. Ismay

Department of Bacteriology, University of Sydney and New South Wales Blood Transfusion Service, Sydney, New South Wales, Australia

THE LANCET

Frequent patient-to-patient transmission of hepatitis C virus in a haematology ward

Tobias Allander, Astrid Gruber, Mojgan Naghavi, Aster Beyene, Tommy Söderström, Magnus Björkholm, Lena Grillner, Mats A A Persson

Original Articles

Hepatitis C Virus Infection in Medical Personnel After Needlestick Accident

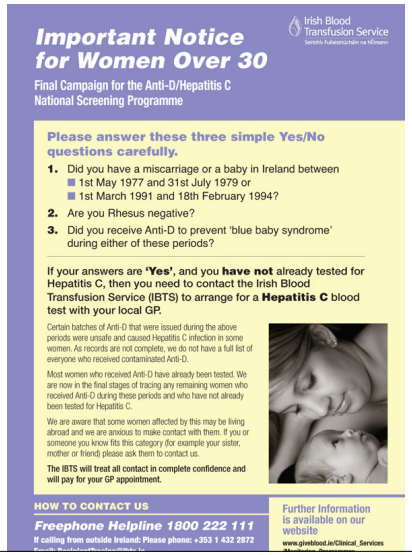
Takehiro Mitsui,[1,2] Keiko Iwano,[1,2] Kazuo Masuko,[1,2] Chikao Yamazaki,[1,2] Hiroaki Okamoto,[3] Fumio Tsuda,[4] Takeshi Tanaka[5] and Shunji Mishiro[6]

TRANSMISSION OF HEPATITIS C VIRUS BY A CARDIAC SURGEON

Juan I. Esteban, M.D., Jordi Gómez, Ph.D., María Martell, Ph.D., Beatriz Cabot, Ph.D., Josep Quer, Ph.D., Joan Camps, M.D., Antonio González, M.D., Teresa Otero, M.T., Andrés Moya, Ph.D., Rafael Esteban, M.D., and Jaime Guardia, M.D.

Cossart Lancet 1982
Mitsui Hepatology 1992
Allender Lancet 1995
Esteban NEJM 1996

The Irish and East German anti-D outbreak



Important Notice for Women Over 30

Irish Blood Transfusion Service

Final Campaign for the Anti-D/Hepatitis C National Screening Programme

Please answer these three simple Yes/No questions carefully.

1. Did you have a miscarriage or a baby in Ireland between
   - 1st May 1977 and 31st July 1979 or
   - 1st March 1991 and 18th February 1994?
2. Are you Rhesus negative?
3. Did you receive Anti-D to prevent 'blue baby syndrome' during either of these periods?

If your answers are **'Yes'**, and you **have not** already tested for Hepatitis C, then you need to contact the Irish Blood Transfusion Service (IBTS) to arrange for a **Hepatitis C** blood test with your local GP.

Certain batches of Anti-D that were issued during the above periods were unsafe and caused Hepatitis C infection in some women. As records are not complete, we do not have a full list of everyone who received contaminated Anti-D.

Most women who received Anti-D have already been tested. We are now in the final stages of tracing any remaining women who received Anti-D during these periods and who have not already been tested for Hepatitis C.

We are aware that some women affected by this may be living abroad and we are anxious to make contact with them. If you or someone you know fits this category (for example your sister, mother or friend) please ask them to contact us.

The IBTS will treat all contact in complete confidence and will pay for your GP appointment.

HOW TO CONTACT US

Freephone Helpline 1800 222 111

If calling from outside Ireland: Please phone: +353 1 432 2872

Further information is available on our website

www.giveblood.ie/Clinical_Services

Anti-D used to prevent hemolytic disease of newborn

early suspicious cases were not centrally reported

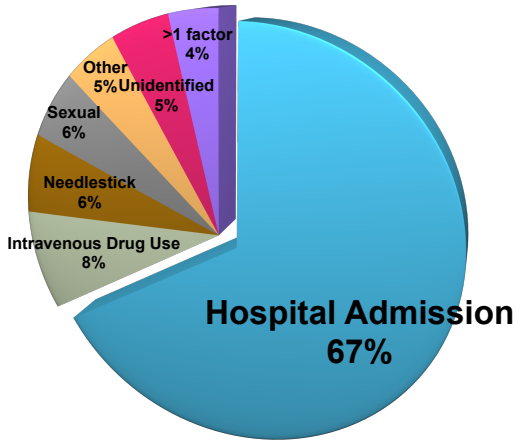
affected women:
400 in 1976-7 in Ireland
1018 in 1978-9 in EastGermany

Higher rate of spontaneously clearing the virus (~45-50%)

Kenny-Walsh NEJM 1999

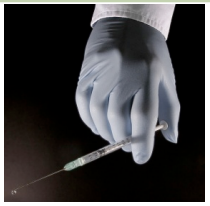
Acute HCV in Spain

- Of documented cases of acute HCV between 1998-2005 (n=109):



Martínez-Bauer et al J Hepatology 2008

Medical exposures may account for the majority of HCV transmission worldwide



- Nosocomial & occupational
  - Suboptimal infection control practices
    - Recapping needles
    - Reuse of syringes
    - Reuse of multi-dose vials
- Brazilian cohort (Oswaldo Cruz Institute)
  - Symptomatic acute HCV (n=65)
  - 49% major risk factor was medical procedure

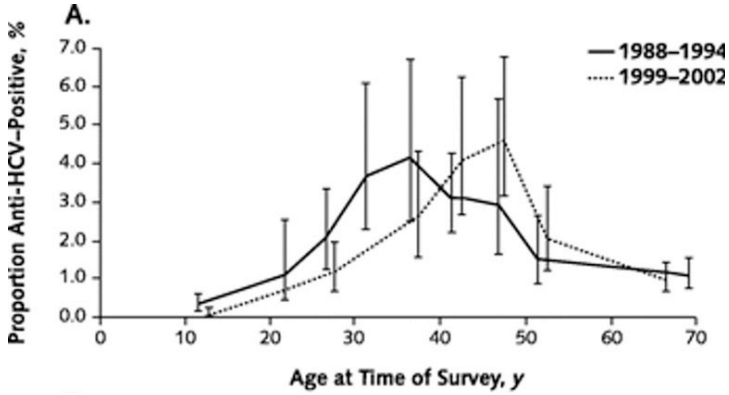
Martínez-Bauer et al J Hepatology 2008
Lewis-Ximinez et al. Clin Infect Dis 2010

Nosocomial transmission in the 21st century?

- Las Vegas 2007-2008
  - HCV Infections from Unsafe Injection Practices at an Endoscopy Clinic
  - 10,000 persons notified
- Florida 2007-2008
  - Diversion of fentanyl by radiology technician
- Colorado 2009
  - Ex-Medical Technician is Held Without Bail in Hepatitis C Outbreak

Fischer et al. Clin Infect Dis 2010
New York Times, July 9 2009

Prevalence of antibodies to hepatitis C virus by Age (NHANES III, 1988-1994) and the current NHANES (1999-2002)

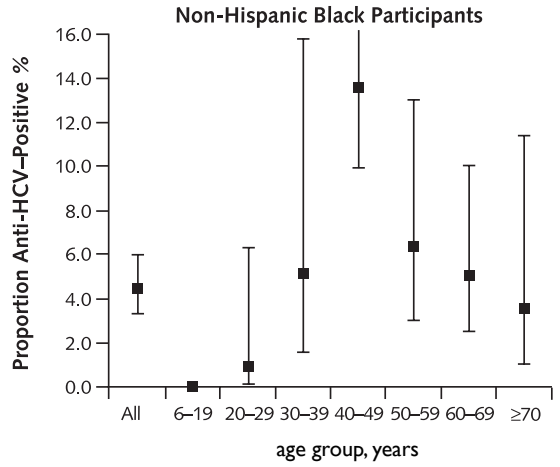


CDC data. Ann Intern Med 2006

Prevalence of HCV in various groups

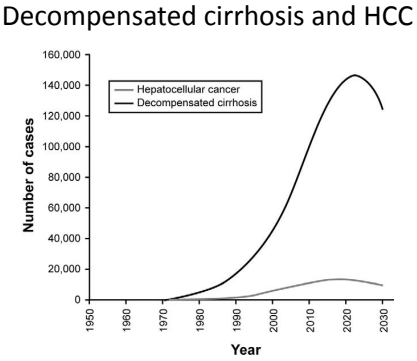
General population	1.6%
Males	2.1%
Non-hispanic blacks	3.0%
Below poverty line	3.2%
Transfusion before 1992	5.8%
20-50 lifetime sexual partners	7.5%
ALT 40-80	8.4%
HIV-positive	13-30%
H/o incarceration	15-41%
Any history of IVDU	57.5%

HCV prevalence in African-American males



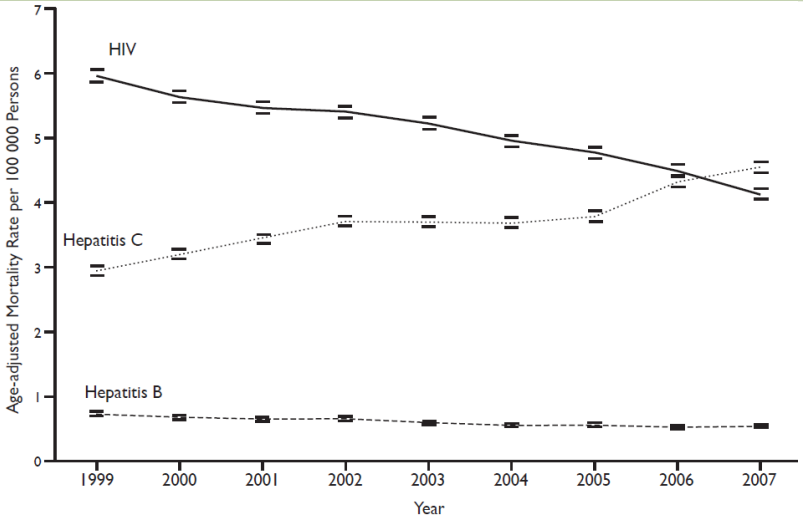
Armstrong et al. Ann Intern Med 2006

Tidal wave of persons at risk for ESLD complications due to HCV infection



Davis et al. (2010) Gastroenterology 138: 513.

HCV Exceeds HIV as Cause of Death in USA



Adapted by S. Ray, Source: Ly, et al. *Ann Intern Med* 2012; 271

CDC and AASLD Guidelines for HCV screening

- Should be screened
  - Intravenous drug use (even if used once)
  - Recipient of plasma derivative before 1987
  - Recipient of organ transplant, transfusion before 1992
  - Healthcare worker with needlestick or mucosal exposure
  - Chronic hemodialysis
  - HIV
  - Persistently elevated ALT
  - Child of an HCV + mother
- Should be considered for screening
  - Intranasal cocaine users
  - Recipients of tattoos / body piercing
  - Recipients of transplanted epithelial tissue (e.g. corneas)
  - People with multiple sexual partners
  - Monogamous sex partners of HCV + people

AASLD/IDSA 2009 Guidelines

Reasons why current practices guiding HCV screening fails

- LFTs normal in up to ~25% despite chronic infection
- CDC data suggest ~10% HCV positive without discernible risk factor
- Primary risk factor of IDU is underreported

Volk et al. Hepatology 2009

What were you doing in the 70's / 80's?

- *Providers rarely ask about past use*
- *Patients forgot or do not wish to admit*
  - *"I only used a few times" (used once or twice - ~9% HCV)*
  - *"I used a long time ago" (any use ~57% HCV)*
  - *"I am ashamed"*

Kallman et al. Aliment Pharmacol Ther 2009
O'Brien et al. Transfus Med 2010

Reasons why risk-factor based screening fails us

- Intravenous drug use
  - Current: fragmented health care
  - Past: underreporting
- Nosocomial
  - Blood product exposure usually not asked at routine physical
  - Hospital exposure in 60s/70s/80s very common
- Sexual
  - Common behavior, underreporting of high-risk
- Perinatal
  - HCV may be underrecognized in pregnant women

A new proposal: screening all "baby-boomers"

- ~66% of those living with HCV are 45-64 years of age
  - 75% of HCV-related deaths are aged 45-64
- As antibodies remain elevated for duration of infection, and these patients usually lack ongoing risk, a one-time antibody test will suffice
- Chance to intervene with antiviral therapies

Why should we screen for HCV?

- Public Health
  - Those infected may transmit to others
  - ESLD due to HCV great burden on health care system
- Personal Health
  - Leading cause of end-stage liver disease / cirrhosis
  - 18,000 deaths/year by 2020, 35,000 deaths/year by 2030
- We can do something about it
  - Over half (70-80%) of those with chronic HCV can be cured

Wise et al. Hepatology 2008
Veldt et al. Ann Intern Med 2008

Annals of Internal Medicine | ORIGINAL RESEARCH

The Cost-Effectiveness of Birth-Cohort Screening for Hepatitis C Antibody in U.S. Primary Care Settings

David B. Rein, PhD; Bryce D. Smith, PhD; John S. Wittenborn, BS; Sarah B. Lesesne, BS; Laura D. Wagner, MPH; Douglas W. Roblin, PhD; Nita Patel, DrPH; John W. Ward, MD; and Cindy M. Weinbaum, MD, MPH

- Assumptions
  - 66.9 million Americans born 1945-1965 visiting PCP
  - ~90% accepted screening
  - ~90% received results
  - those with insurance offered treatment
  - ~40% accepted and initiated treatment

Rein et al. Ann Intern Med 2012;156:263-270

Annals of Internal Medicine | Original Research

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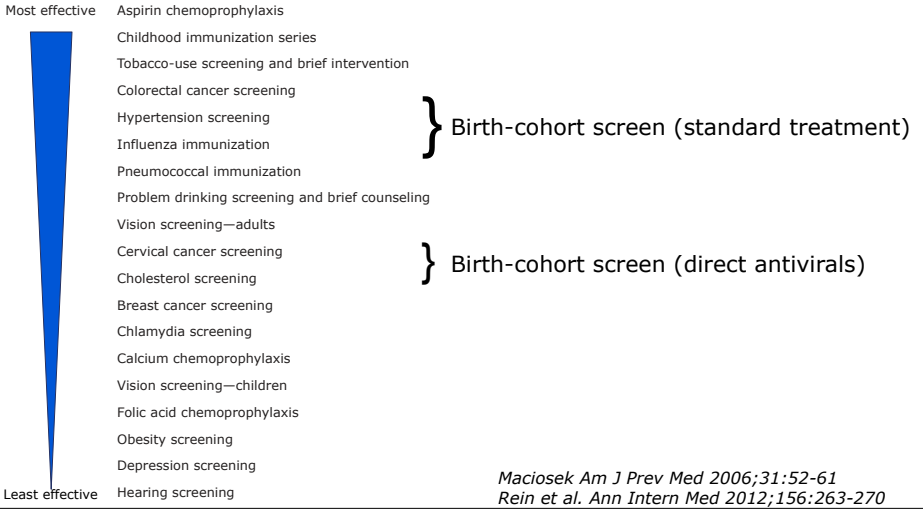
	Deaths	ICER($ per QALY saved)
No screening	618,000	
Risk-based	592,000	Base case
Birth cohort PEG-Ribavirin	509,000	$15,700
Birth cohort Direct-acting	470,000	$35,700

Rein et al. Ann Intern Med 2012;156:263-270

What is the relative cost-effectiveness to other preventive services?

National Committee on Prevention Priorities
Combining clinically-preventable burden & cost-effectiveness:



Maciosek Am J Prev Med 2006;31:52-61
Rein et al. Ann Intern Med 2012;156:263-270

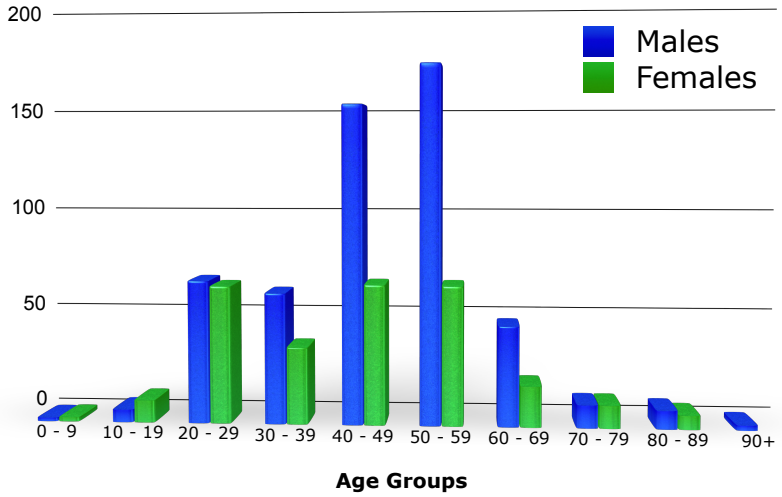
HCV and HIV screening

- Baby boomer screening - all those identified with HCV should have HIV testing
- 15% of new HIV infections in the U.S. occur in persons over 50
- CDC already recommends a one-time screen of all adults for HIV

Do not abandon risk-factor based screening

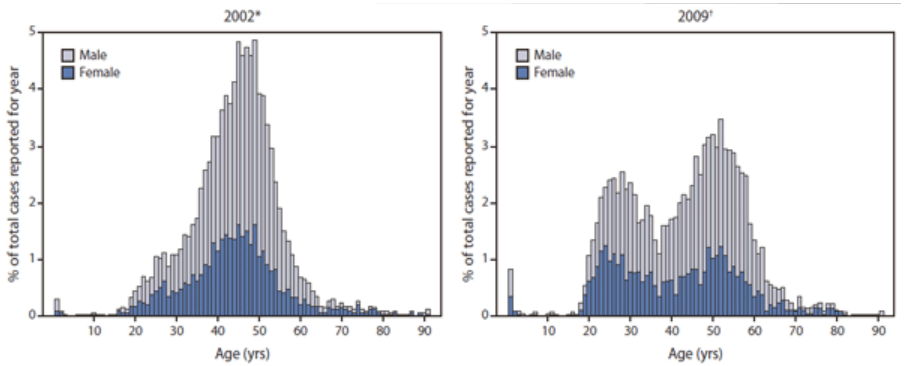
High-risk groups remain at risk

Incidence Rates (per 100,000 population) for Reported Confirmed Hepatitis C Infections by Age Groups



Courtesy Dan Church, MA DPH

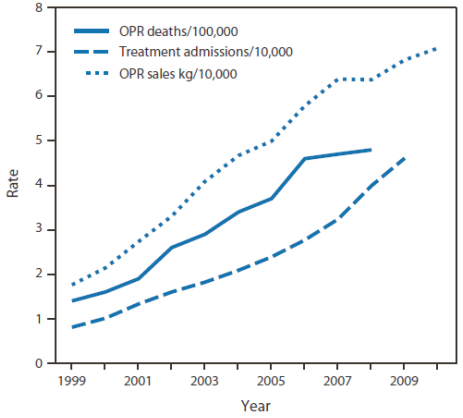
MMWR: Age distribution of newly reported confirmed cases of hepatitis C virus infection --- Massachusetts, 2002 and 2009



* N = 6,281; excludes 35 cases with missing age or sex information.
† N = 3,904; excludes 346 cases with missing age or sex information.

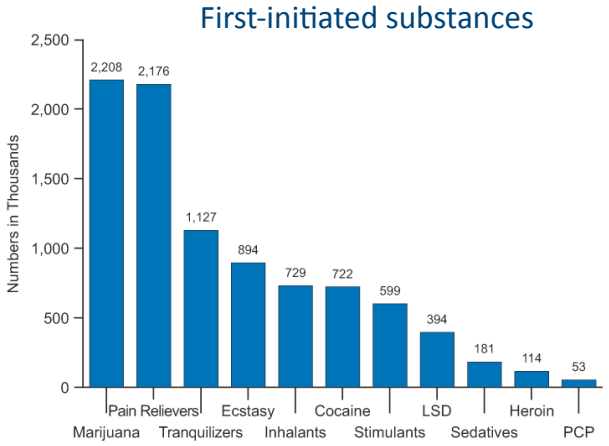
Source: Onofrey et al MMWR: **May 6, 2011 / 60(17);537-541**

National Opioid Prescription Sales and Deaths on the Rise



MMWR / November 4, 2011 / Vol. 60 / No. 43

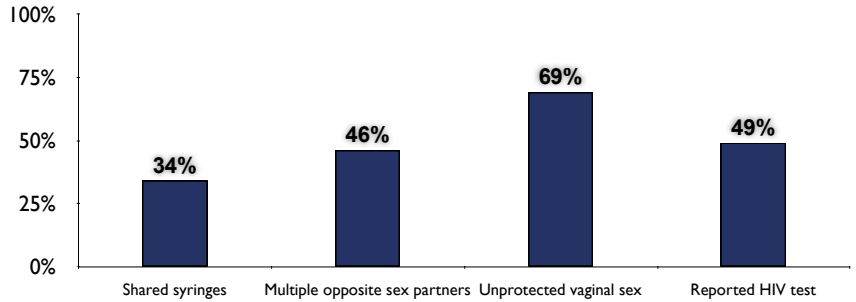
Past Year Initiates for Specific Illicit Drugs among Persons Aged 12 or Older: 2007



2007 National Survey on Drug Use & Health

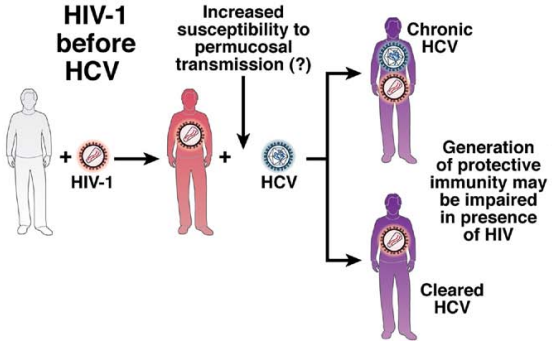
IDU at highest risk for HCV are also at risk for HIV

- 9% of new U.S. HIV infections in 2009 occurred in IDU
- 9% of 10,073 IDU tested were positive for HIV (NHBS)
- Among 9,565 IDUs at risk for acquiring HIV
- Among male IDUs: 5% reported unprotected male-male anal sex

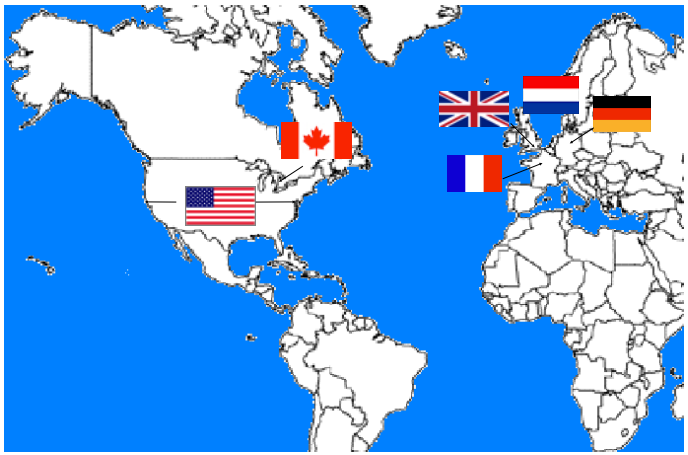


Prejean et al. PLoS One 2011, CDC MMWR 2012;61:133-138

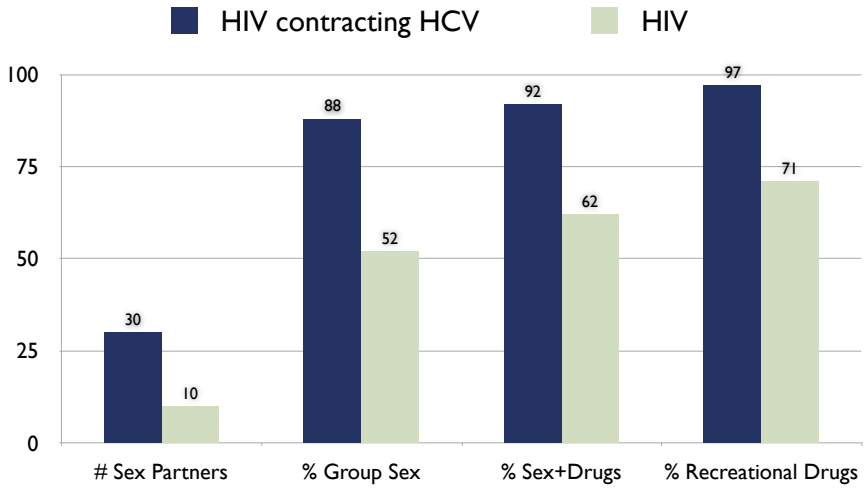
HIV before HCV



HIV before HCV: International Outbreaks of HCV in HIV+ MSM



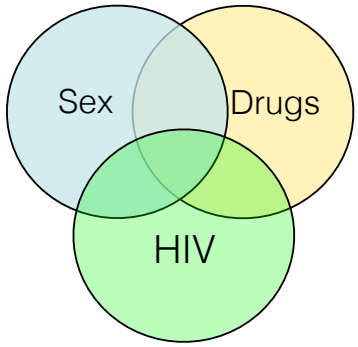
Risk factors in London outbreak



Danta et al. AIDS 2007

A perfect storm for HCV transmission

- Bloody practices
- Semen exposure
- Other STDs
- Sildenafil
- Internet

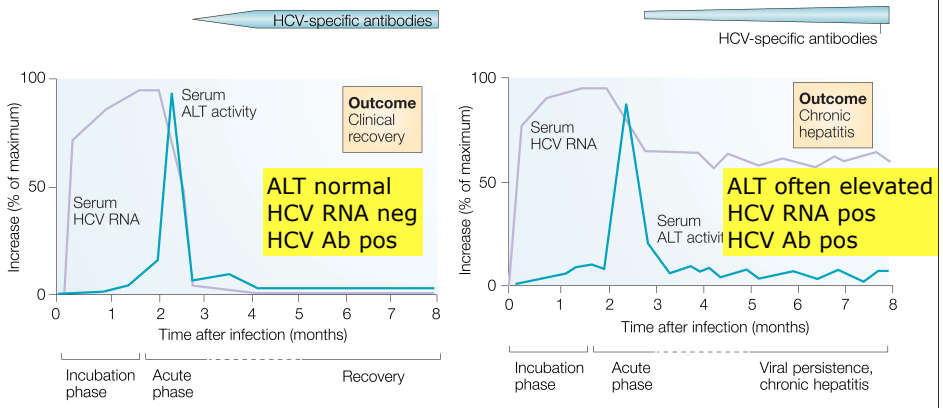


- Crystal methamphentamine

– Higher levels of virus in plasma and semen

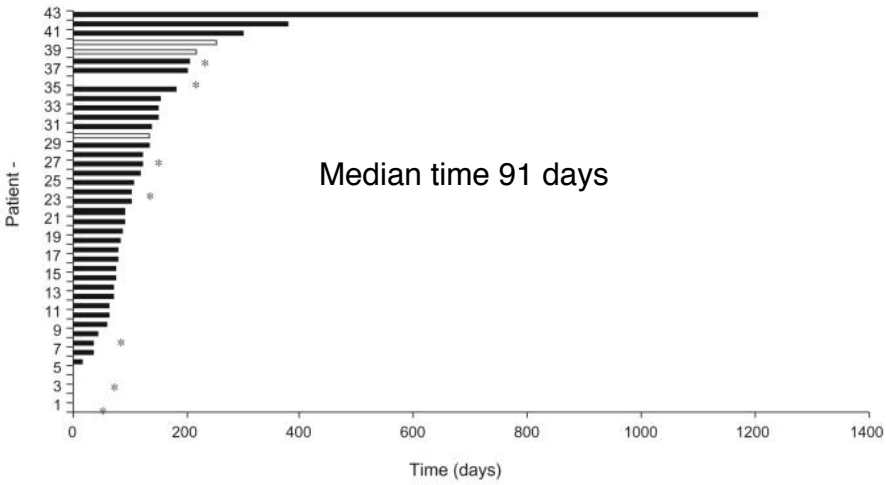
– Immune deficiency, especially at GI mucosa

Outcomes of acute HCV



Rehermann and Nascimbeni. Nat Rev Immunol 2005

Delayed HCV EIA seroconversion in HIV+ MSM



Thomson et al. AIDS 2009

Diagnosis of acute HCV

- History: Risk factor and timing
  - Underreporting of risk
- Seroconversion
  - Past antibody testing
  - Antibody seroconversion may be delayed in setting of HIV
- Serial checks of ALT, HCV RNA
  - Viral fluctuations and/or low viral loads are suggestive of acute phase

Why identify acute HCV?

Opportunities for:

Risk reduction

Education

Immunizations for HAV/HBV

Interrupt transmission

Better treatment outcomes

HCV in HIV+ MSM

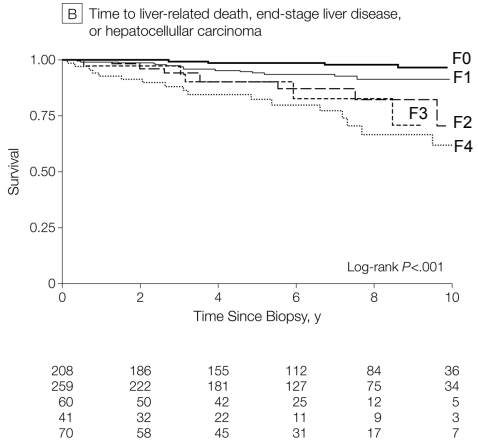
- Screen for high-risk behaviors
  - Bloody practices, exposure to semen[1]
  - Ulcero-genital STDs
- Screen those engaging in high-risk behaviors
  - Yearly antibodies recommended[2]
    - Cost-effective[3]
- React to minor changes in LFTs[3]
  - HCV RNA for seronegative window
  - HCV RNA for re-infections

[1]Schmidt et al. PLoS One 2011; [2]EASL (2010), NY State (2010); [3]Linas et al. Clin Infect Dis 2012 (accepted)

Challenge of accelerated fibrosis

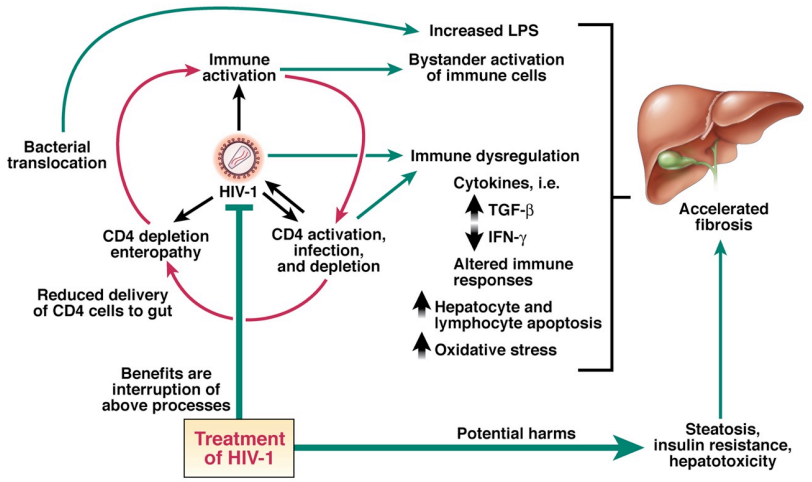
- Opportunities to:
  - Stage fibrosis more frequently
    - Noninvasive tests, serum Fibrosure/Fibrotest or transient elastrography
  - Slow progression
    - HIV suppression
    - Avoidance of other liver insults (such as alcohol, steatosis)
    - Role of caffeine, vitamin D replenishment

Staging of the liver in co-infected patients is prognostic of ESLD/HCC/death



Limketkai et al. JAMA 2012

Mechanisms of accelerated HCV-related fibrosis in HIV

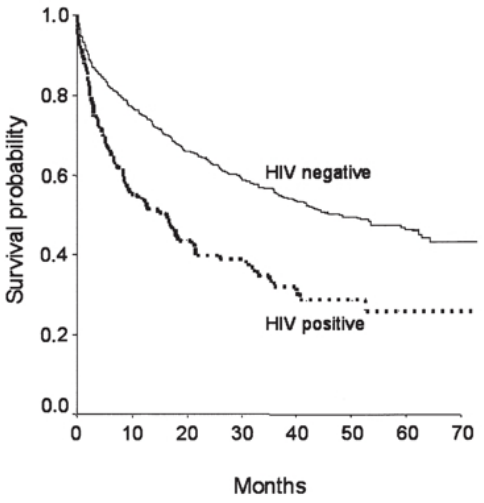


Kim and Chung Gastroenterology 2009

DHHS Antiretroviral Guidelines in 2012

The effect of ART on preserving or restoring immune function and reducing HIV-related immune activation and inflammation may slow the progression of liver disease. The benefits of ART in most HIV/HCV-coinfected patients outweigh concerns regarding drug-induced liver injury (DILI). **Therefore, ART should be considered for all HIV/HCV-coinfected patients regardless of CD4 count (BII).**

Survival after first episode of liver decompensation is decreased in HIV/HCV patients



75% mortality over ~6 years

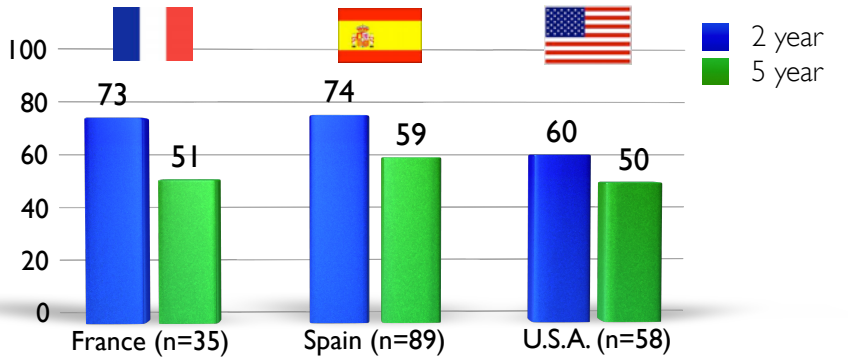
Pineda et al. Hepatology 2005

Challenges of higher rates of decompensation and higher mortality

Opportunity to:

Perform liver transplantation for HIV/HCV

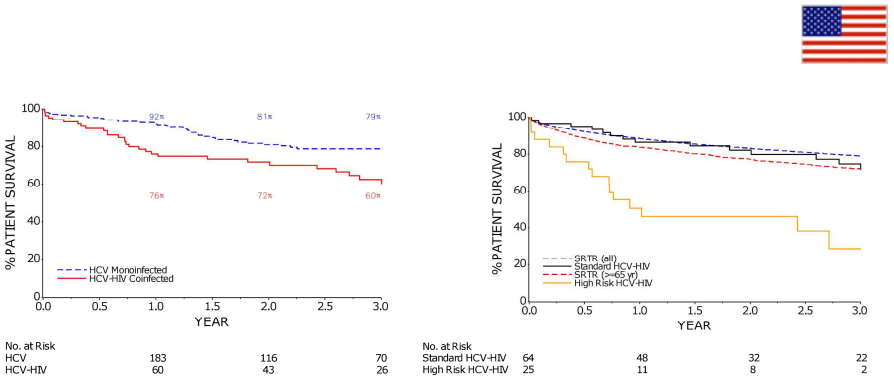
Survival rates for HIV+/HCV+ OLT



In absence of transplant, after decompensation,
2 year survival only ~**40**%
5 year survival only ~**20**%

Duclos-Vallée et al. Hepatology 2008
Miró et al. CROI 2008
Mindikoglu et al. Transplantation 2008

NIH multicenter trial of liver transplantation for HIV/HCV coinfection + ESLD



Highest risk patients had the worst outcomes (low BMI, older donor age, need for renal tx)

Terrault et al. Liver Transplantation 2012

Higher rates of decompensation & higher liver-related mortality
Higher viral loads and lower response rates to treatment

Opportunity to:

Treat with antivirals and achieve cure

Antiviral HCV treatments (FDA-approved)

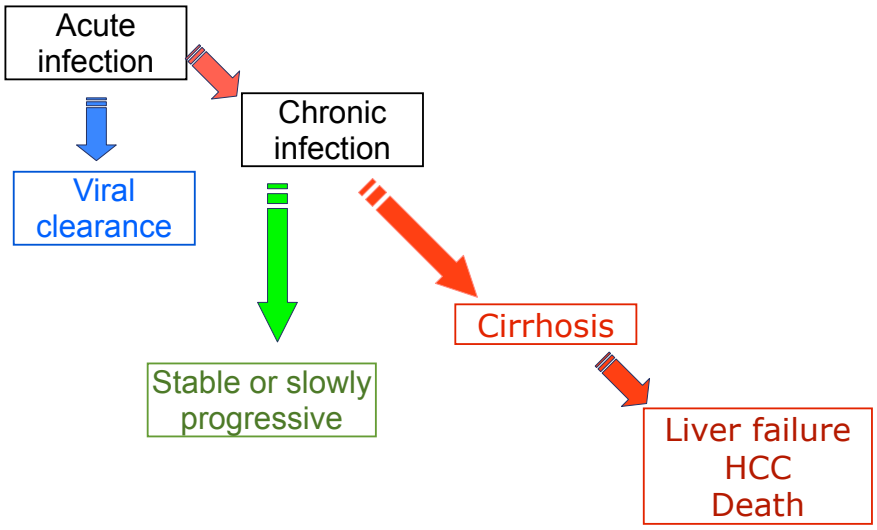
- Monotherapy
  - –IFN-2a (Roferon)
  - –IFN-2b (Intron)
  - –PEG-IFN 2a (Pegasys)
  - –PEG-IFN 2b (Peg-Intron)
  - –Consensus IFN

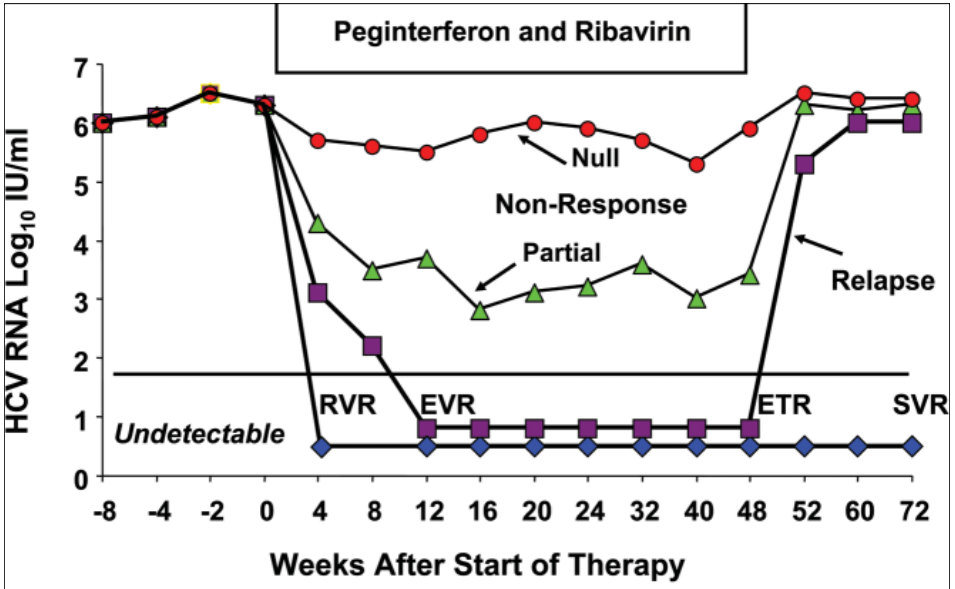
Combination Therapy
IFN-2a + Ribavirin
IFN-2b + Ribavirin
PEG-IFN 2a + Ribavirin*
PEG-IFN 2b + Ribavirin

Boceprevir (with PEG/RBV)
Telaprevir (with PEG/RBV)

* Indication for HIV/HCV coinfection

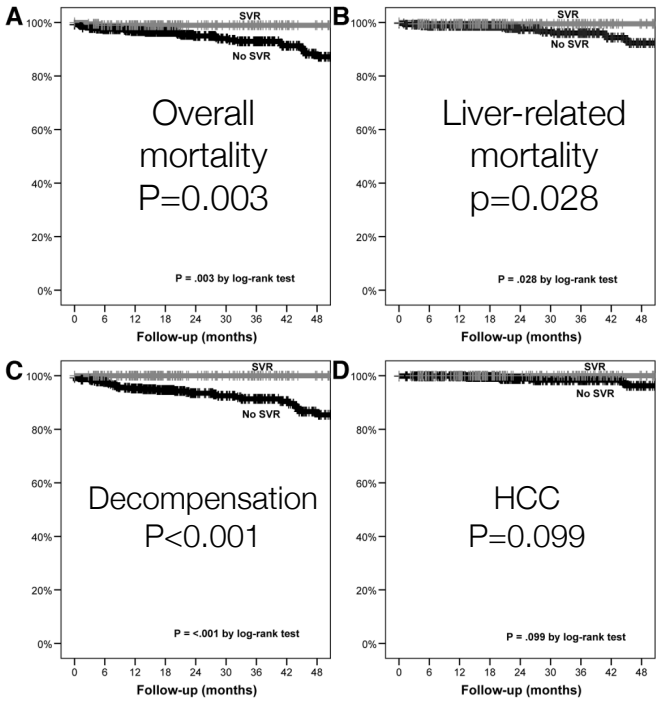
Natural history of HCV





RVR = rapid virologic response= negative HCV RNA at week 4
pEVR = partial early virologic response = 2 log drop at week 12 compared to baseline
cEVR = complete early virologic response = negative HCV RNA at week 12
ETR = end of treatment response
SVR = sustained virologic response = negative HCV RNA 24 weeks after therapy

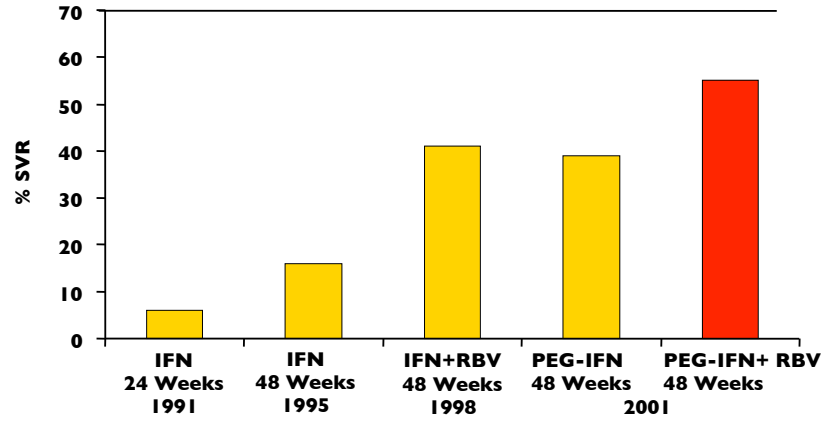
AASLD/IDSA 2009 Guidelines



SVR and outcomes in advanced fibrosis (HIV/HCV)

Berenguer et al. Hepatology 2009

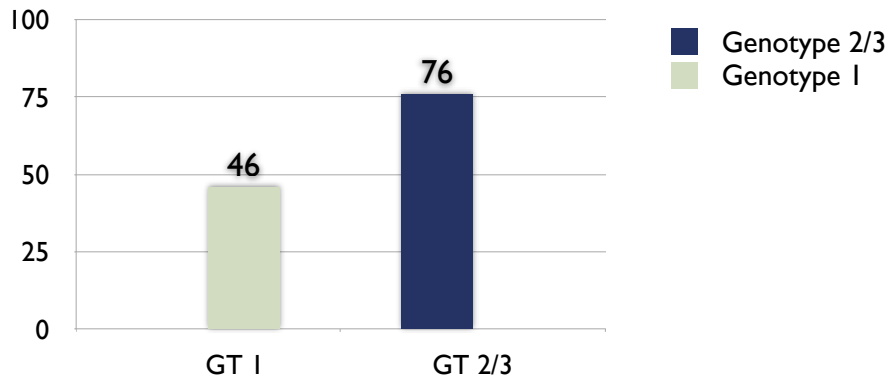
Evolution of the Treatment for Chronic Hepatitis C



IFN, interferon; PEG-IFN, pegylated interferon; RBV, ribavirin; SVR, sustained virologic response

Poynard T et al. Gastroenterology. 2002

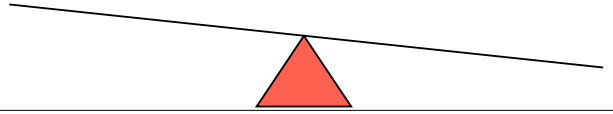
Sustained virologic responses with PEG IFN/RBV by genotype



Fried et al. NEJM 2002

Likelihood of success on interferon-based treatments

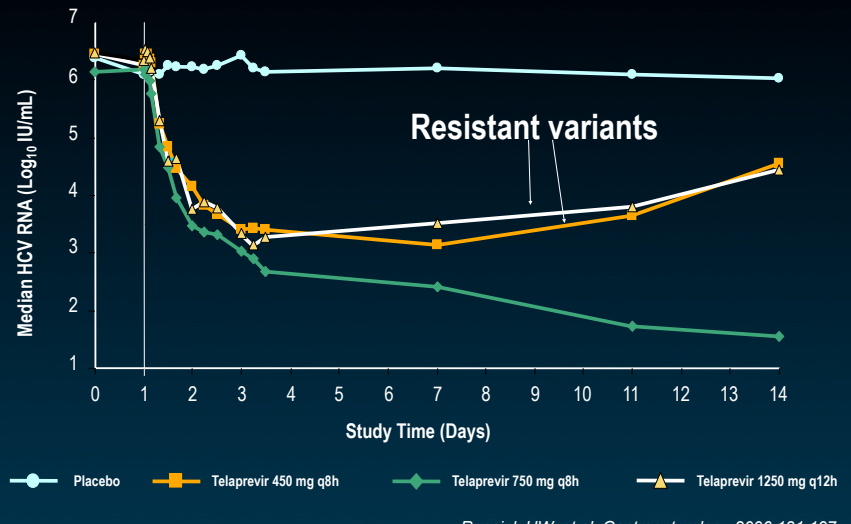
Higher likelihood of success:	Lower likelihood of success:
Non genotype 1 status	Genotype 1 status
Low HCV VL	High HCV VL
IL-28B genotype favorable	IL-28B genotype unfavorable
Less fibrosis on biopsy	More fibrosis on biopsy
No steatosis or insulin resistance	Steatosis and/or insulin resistance
vitamin D replete	vitamin D deficient
non-African-American	African-American
Female	Male
Adherence	Non-adherence



Comparison of two currently-approved protease inhibitors

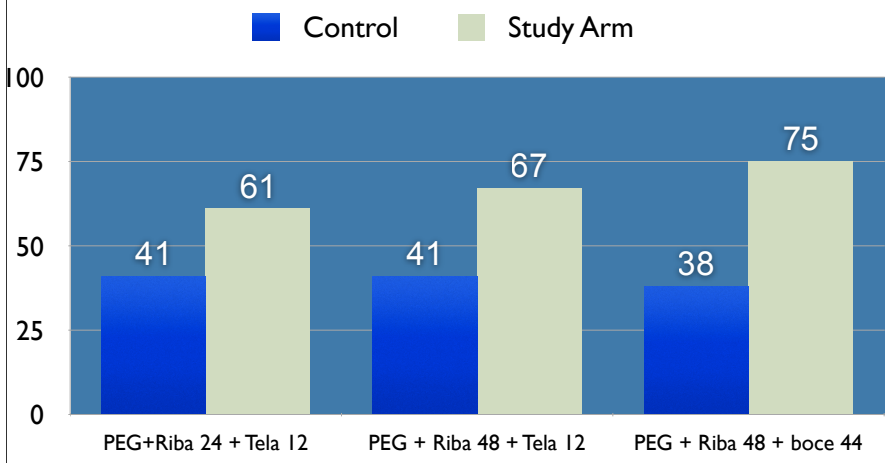
	Boceprevir	Telaprevir
Genotype activity	GT 1 (-2)	GT 1 (-2)
PEG-IFN regimen	PEG-IFN-2b	PEG-IFN-2a
Dosing	q7-9h (with food)	q7-9h (with food)
Pharmacology	CYP3A4, p-glycoprotein	CYP3A4, p-glycoprotein
Lead-in phase	Yes	No
Duration of PI	24-44 weeks	12 weeks
Additive side effects	Dysgeusia, anemia	Rash, pruritus, anal sx, anemia
Cost	$1300/week	$4100/week

Telaprevir Monotherapy—Phase Ib Trial



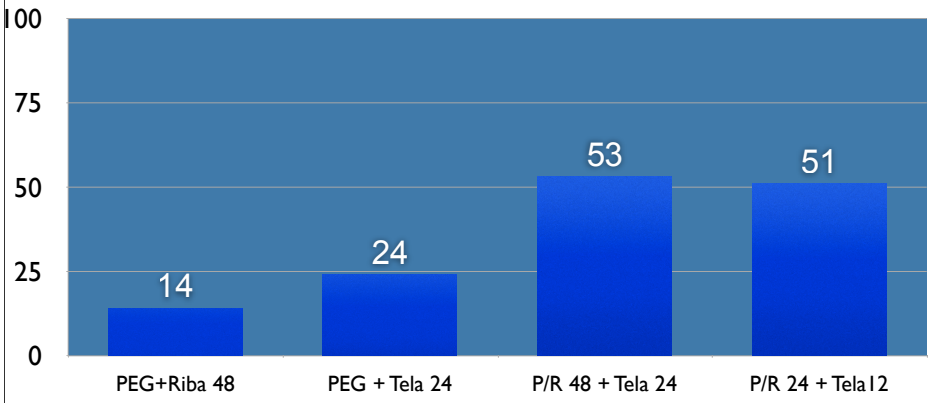
Reesink HW, et al. Gastroenterology 2006;131:197

SVR rates for genotype 1 HCV infection: PEG-IFN, ribavirin, plus telaprevir or boceprevir



McHutchinson et al. NEJM 2009
Kwo et al. Lancet 2010

SVR rate for nonresponders genotype 1 HCV infection: telaprevir, HIV negative



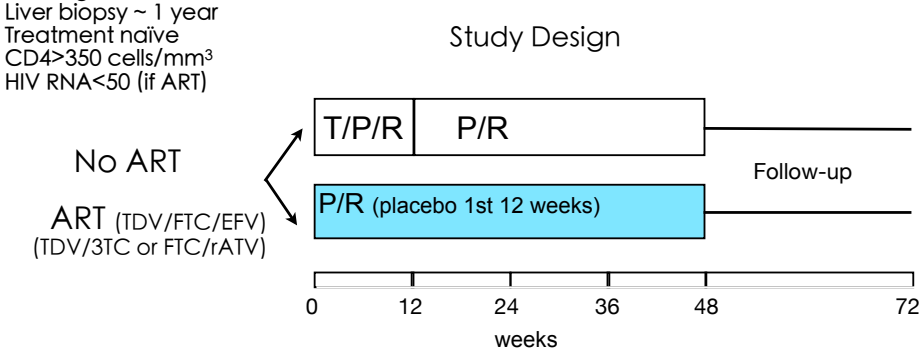
McHutchinson et al. NEJM 2010

Novel drugs, pharmacology

- Pregnancy category B
- No dosing change for renal impairment
- Both an inhibitor and substrate of cytochrome P450 (CYP3A) and P-glycoprotein (P-gp)
- Contraindicated with drugs that are:
  - Highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events
  - Strongly induce CYP3A, which lead to lower exposure and loss of efficacy of telaprevir

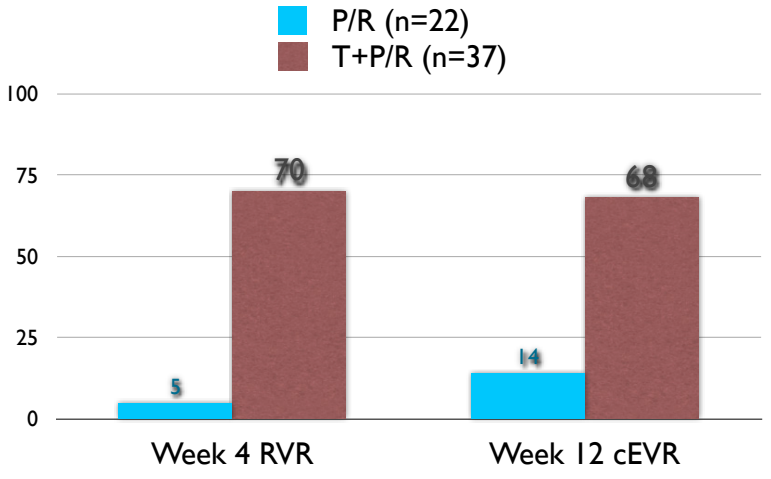
Telaprevir 750-1125 mg TID + standard of care for HCV in HIV coinfected persons

Eligibility:
HIV+ age 18-65
Liver biopsy ~ 1 year
Treatment naïve
CD4>350 cells/mm^3
HIV RNA<50 (if ART)



Sulkowski et al. CROI 2011, Boston, MA
Dieterich et al. CROI 2012, Seattle, WA

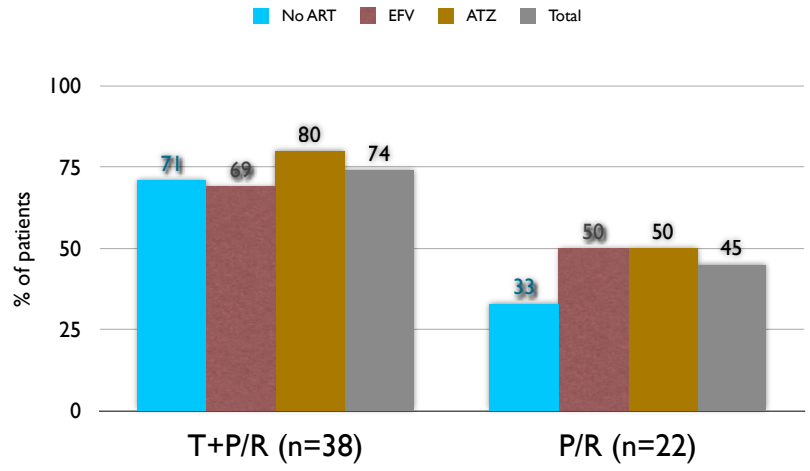
Telaprevir for HCV in HIV coinfected persons: interim results from CROI 2011



Only efavirenz and boosted atazanavir tested

Sulkowski et al. CROI 2011, Boston, MA

Telaprevir for HCV in HIV coinfected persons: SVR12 results



Only efavirenz and boosted atazanavir tested

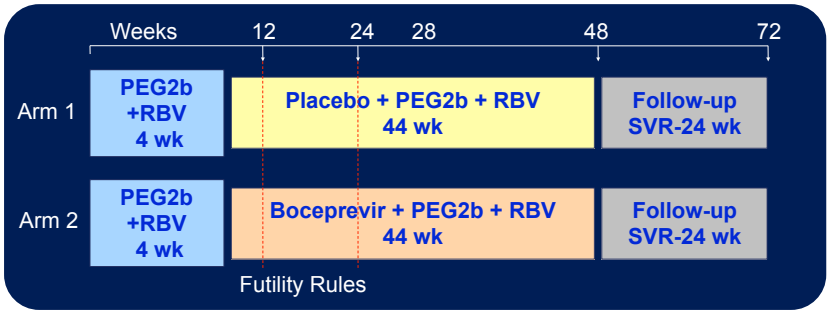
Dieterich et al. CROI 2012, Seattle WA

Adverse events, telaprevir/PEG-IFN/ribavirin in co-infected individuals

	T+P/R (n=38), %	P/R (n=22), %
Fatigue	16 (42)	9 (41)
Pruritus	**15 (39)**	**2 (9)**
Headache	**14 (37)**	**6 (27)**
Nausea	**13 (34)**	**5 (23)**
Rash	**13 (34)**	**5 (23)**
Diarrhea	9 (24)	4 (18)
Dizziness	8 (21)	3 (14)
Pyrexia	**8 (21)**	**2 (9)**
Neutropenia	**8 (21)**	**2 (9)**
Depression	8 (21)	5 (23)
Anemia	7 (18)	4 (18)
Vomiting	7 (18)	2 (9)
Myalgia	6 (16)	5 (23)
Chills	6 (16)	4 (18)
Insomnia	**5 (13)**	**5 (23)**
Decreased appetite	4 (11)	4 (18)
Weight decreased	**4 (11)**	**5 (23)**

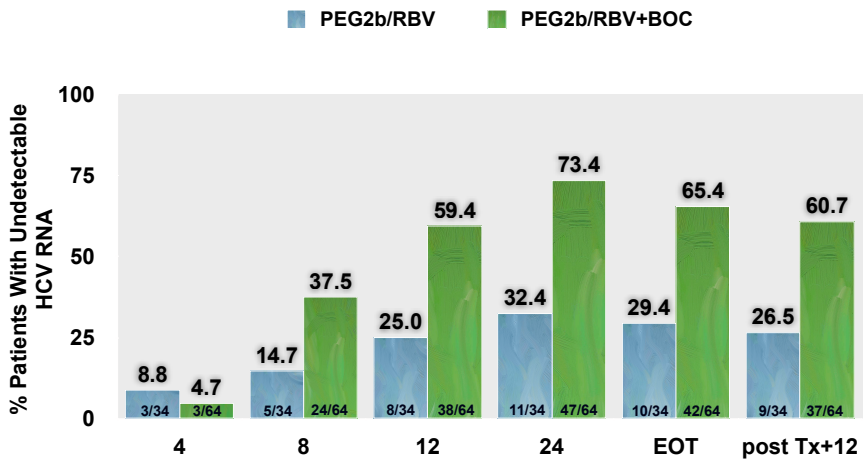
Sherman et al. AASLD 2011, San Francisco, CA

Boceprevir for HIV/HCV coinfection: Study Design



- Two-arm study, double-blinded for BOC, open-label for PEG2b/RBV
  - 2:1 randomization (experimental: control)
  - Boceprevir dose 800 mg, TID
- 4-week lead-in with PEG2b/RBV for all patients
  - PEG-2b 1.5 µg/kg QW; RBV 600-1400 mg/day divided BID
- Control arm subjects with HCV-RNA ≥ LLQ at TW 24 were offered open-label PEG2b/RBV+BOC via a cross-over arm

Virologic Response Over Time (% HCV RNA Undetectable)



Sulkowski et al. CROI 2012, Seattle, MA

Summary of Safety

	PEG2b/RBV (N = 34)	PEG2b/RBV + BOC (N = 64)
Days on study, median	166	211
Any AE, n (%)	34 (100)	63 (98)
Serious AEs, n (%)	7 (21%)	5 (8%)
Treatment-related Treatment-emergent AEs, n (%)	34 (100%)	61 (95%)
Study Discontinuation Due to an AE, n (%)	3 (9%)	9 (14%)
Any Drug Modification Due to an AE, n (%)	7 (21%)	12 (19%)

Sulkowski et al. IDSA 2011, Boston MA

Most Common Adverse Events With a Difference of ≥10% Between Groups*

	PEG2b/RBV (N=34)	PEG2b/RBV + BOC (N=64)
Days on study, median	166	211
Neutropenia, (%)	3%	13%
Dysgeusia, (%)	15%	25%
Vomiting, (%)	15%	25%
Pyrexia, (%)	21%	34%
Headache, (%)	12%	28%
Decreased Appetite, (%)	18%	30%

*A difference of ≥10% for patients receiving PEG2b/RBV+BOC when compared with PEG2b/RBV.

Sulkowski et al. IDSA 2011, Boston MA

Hematologic Adverse Events

	PEG2b/RBV (N=34)	PEG2b/RBV + BOC (n=64)
Anemia		
AEs, n (%)	9 (26)	19 (30)
SAEs, n (%)	2 (6)	1 (2)
AEs leading to discontinuation, n (%)	1 (3)	1 (2)
Grade 2 (8.0 to <9.5 g/dL), n (%)	7 (21)	10 (16)
Grade 3 (6.5 to <8.0 g/dL), n (%)	1 (3)	3 (5)
Erythropoietin use, n (%)	7 (21)	17 (27)
Transfusions, n (%)	2 (6)	4 (6)
Neutropenia		
AEs, n (%)	1 (3)	8 (13)
Grade 3 (<0.75x10^9/L), n (%)	3 (9)	10 (16)
Grade 4 (<0.5x10^9/L), n (%)	*	*

Sulkowski et al. IDSA 2011, Boston MA

Use of Antiretroviral Therapy

	PR	B/PR
Any*	34 (100)	64 (100)
HIV Protease Inhibitors†	31 (91)	54 (84)
ATV/r	13 (38)	20 (31)
Lopinavir/r	10(29)	16 (25)
Darunavir/r	7 (21)	12 (19)
NRTIs††	33 (97)	60 (94)
Integrase Inhibitors	4 (12)	11 (17)
CCR5 antagonists	1 (3)	1 (2)

* To maintain blinding in this continuing study, data is only shown where at least 1 patient in each treatment group is represented.

† HIV PIs included ATVr, DRV/r, LPV/r, fAMP/r, SAQ/r

†† NRTIs included TDF, ABC, 3TC, FTC

Sulkowski et al. IDSA 2011, Boston MA

Drug-drug interactions & toxicities between antiretrovirals and anti-HCV agents

- PEG-IFN/RBV + AZT additive anemia
- d4T/ddI - avoid co-administration with ribavirin
- Telaprevir
  - Compatible with TDF/3TC orFTC + boosted atazanavir or efavirenz
  - Raltegravir
- Boceprevir
  - Recent FDA warning - decreased levels of antiretrovirals
  - HIV breakthroughs were equal in both PEG/RBV and PEG/RBV/BOC groups (Sulkowski et al. CROI 2012)

HIV breakthroughs while on B/PR therapy

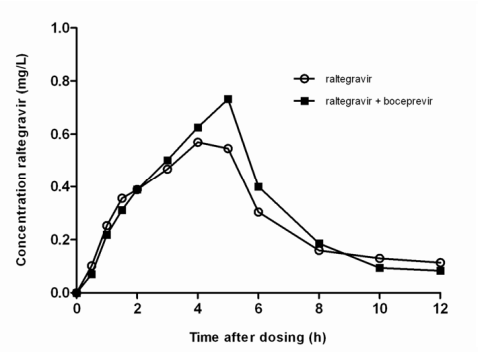
Overall 7 HIV breakthroughs (>50 copies on 2 consecutive occasions), 4 on P/R and 3 on B+P/R

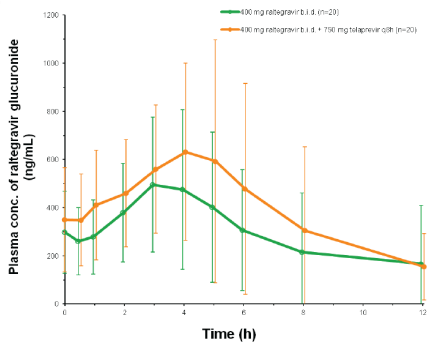
Regimen	HIV RNA						
	BL	TW4	TW12	TW24	TW36	EOT	FW4
ATV/r	<50	<50	---	659	---	53	2990
LPV/r	<50	<50	<50	55	59	67	68
ATV/r	<50	<50	<50	<50	243	---	7870

Sulkowski et al. IDSA 2011, Boston MA

Raltegravir lacks interactions with HCV protease inhibitors

- No clinically significant interaction between raltegravir and either boceprevir or telaprevir





Raltegravir appears safe in HIV/HCV cirrhosis
Moreno et al. J AIDS 2012

de Kanter et al. Clin Infect Dis 2012
van Heeswijk et al. J Infect Dis 2012

Preliminary recommendations for the use of boceprevir or telaprevir in HIV patients coinfected with HCV genotype 1 based on current ART use

ART	Boceprevir	Telaprevir
None	Standard dose	Standard dose
Raltegravir + 2NRTIs	Standard dose	Standard dose
ATV/r + 2NRTIs	Do not use*	Standard dose
EFV + 2NRTIs	Do not use*	Increased dose (1125 mg q7-9h)
Other ART regimens	Consider deferral of HCV treatment if HCV disease minimal	

* Only under clinical trial supervision

DHHS Antiretroviral Guidelines

- Consider use of pegylated interferon/ribavirin without HCV (PI) if good prognostic factors for HCV treatment response (i.e. IL28B cc genotype or HCV RNA < 400,000 IU/mL)
- If possible, based on ART history and HIV genotype results, consider switching to a regimen listed above
- Consult an expert in the management of HIV and HCV co-infection for patients with complex ART history or resistance

Guidelines for use of boceprevir/telaprevir for HIV/HCV genotype 1 coinfected patients

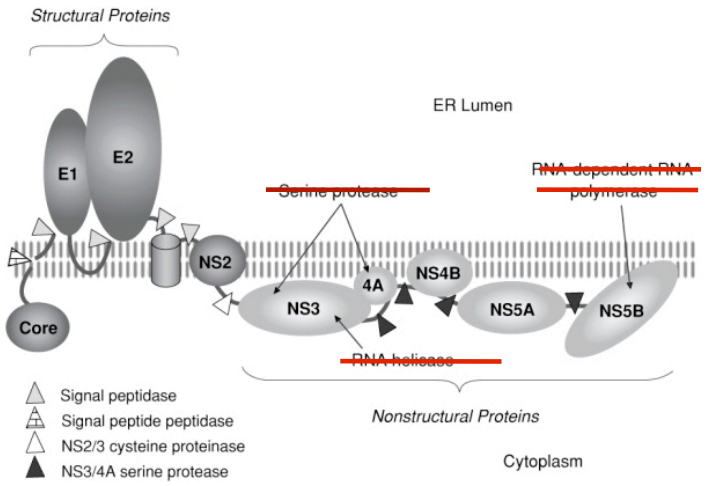
- Stable & compatible HIV regimen
- If possible, refer to clinical trials
- 48 week course (no data re: response-guided therapy)
- IL28B data for DAA/triple therapy not yet available
- No data re: efficacy of nonresponders
- Counseling re: pill burden, dosing frequency, duration of tx
- Close monitoring of HCV and HIV RNA
- Follow stopping rules

Thomas et al. Clin Infect Dis 2012
Naggie & Sulkowski, Gastroenterology 2012

Treatment summary

- New standard of care for genotype 1 infections include protease inhibitors
- Regimens are more complicated but more effective
- Therapy is highly individualized
- Availability of more effective treatment paradigms may drive more screening
- How will we overcome barriers to evaluate and treat?

Specifically-targeted antiviral therapy against HCV



Pipeline of direct acting agents-HCV

Protease inhibitors
- Telaprevir
- Boceprevir
- TMC-435
- BI-201335
- Vaniprevir
- Narlaprevir
- Danoprevir
- GS-9256
- BMS-650032
- ACH-1625
- VX-500
- BIT-225
- ABT-450

NS5A inhibitors
- BMS-790052
- BMS-824383
- PPI-461
- AZD-7295

Entry inhibitors
- ITX-5061

NS4B inhibitors
- Clemizole

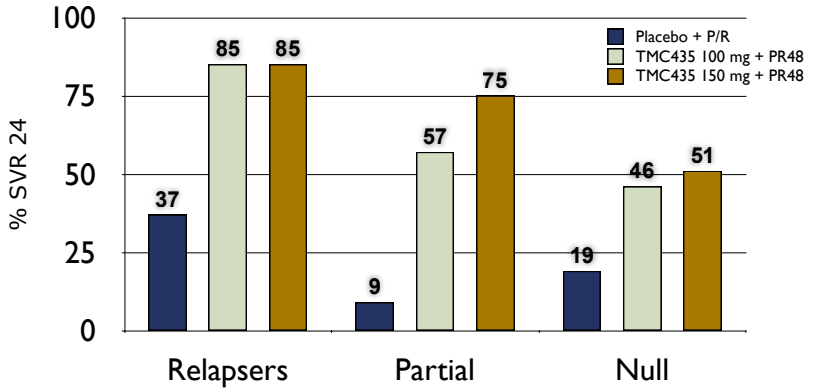
Polymerase inhibitors
- Filibuvir
- ANA-598
- BI-207127
- BMS-791325
- GS-9190
- PSI-7977 / GS-7977 sofosbuvir
- RG7129
- VX-222
- VX-759
- VX-916
- TMC-649128
- PSI-7977
- PSI-938
- MK-3281
- INX-189
- IDX-375
- ABT-072
- ABT-333

Future Strategies for HCV Therapy

- 2nd wave PIs
- Polymerase inhibitors
  - Nucleoside
  - Nonnucleoside
- NS5A inhibitors
- Alternative IFNs
- Combinations of DAAs with complementary MOAs and resistance
  - High barrier with high potency
  - Quadruple therapy: PEG + RBV + 2 DAAs
- Host cofactor inhibitors
  - High genetic barrier

Next generation protease inhibitor: simeprevir (TMC-135) - ASPIRE

- Randomized nonresponders QD 100 mg or 150 mg



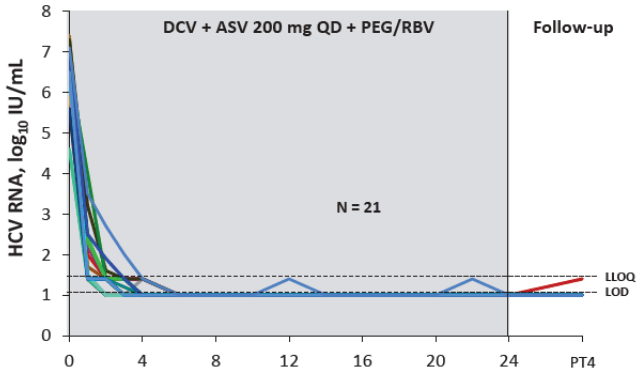
TMC435 associated with mild, transient, asymptomatic increases in bilirubin

TMC435 has interactions with EFV, DRV/r

Zeuzem S, et al. EASL 2012. Abstract 2. Lenz O, et al. EASL 2012. Abstract 9. Ouwerkerk-Mahadevan S et al. IDSA 2012

"Quad" = 2 DAAs + PEG/RIBA: GT1 null responders

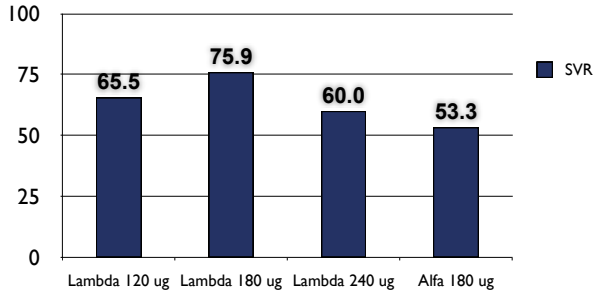
Figure 3b. HCV RNA by Patient: DCV 60 mg QD + ASV 200 mg QD + PEG/RBV



Barcelona EASL 2012

Interferon-lambda- a kinder, gentler interferon

- PEG-IFN-lambda-1a versus PEG-IFN alfa-2a (w/ RBV)
  - Alfa receptors multiple cell types, lambda hepatocytes/immune cells
- EMERGE data for genotype 2/3
- lambda 180 ug group had no RBV dose reduction, no significant neutropenia or thrombocytopenia

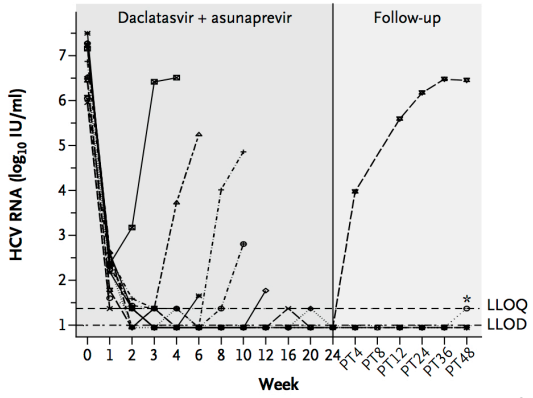


Zeuzem S, et al. EASL 2012. Abstract 10.

ORIGINAL ARTICLE

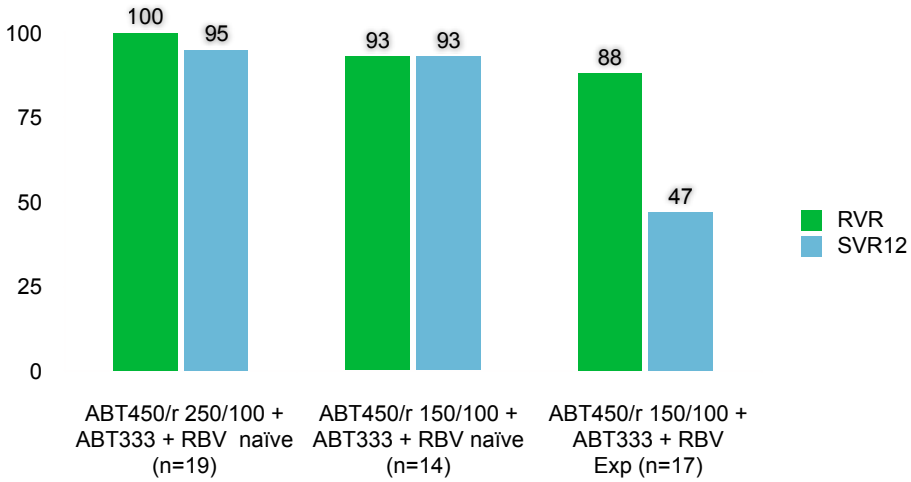
Preliminary Study of Two Antiviral Agents for Hepatitis C Genotype 1

A HCV RNA Levels, Group A

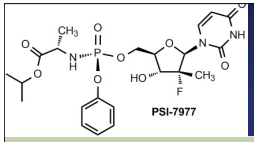


Lok et al. NEJM 2012

ABT450/r (PI) +ABT333 (NNI) + RBV x 12W in gt1 HCV



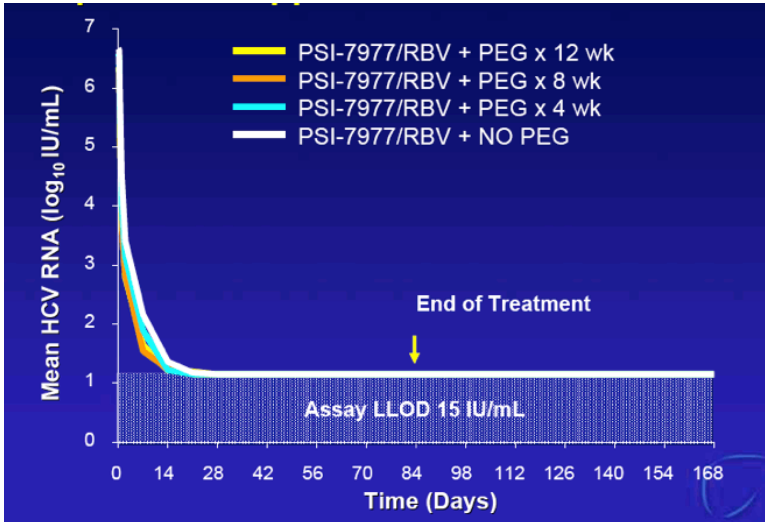
Poordad F et al.; Lawitz E et al. EASL 2012



sofosbuvir GS-7977

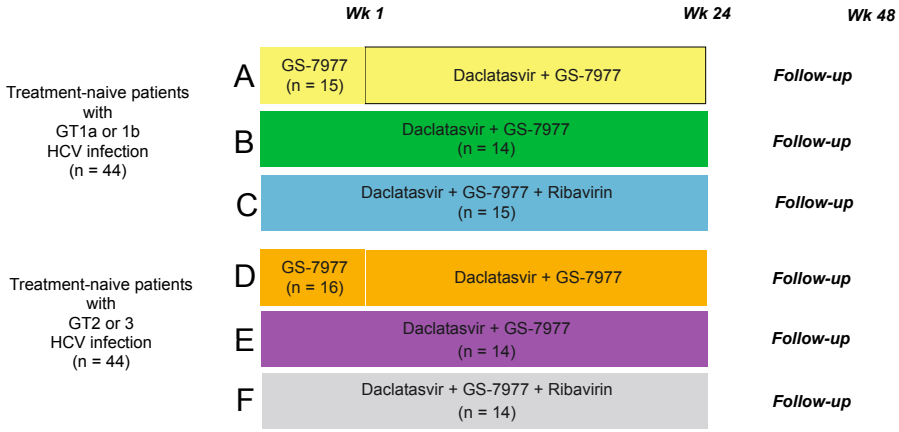
- sofosbuvir is a potent, specific HCV nucleotide
- Safe and well-tolerated
- Once daily, with or without food
- Broad HCV genotype coverage
- High barrier to resistance, no known breakthrough to date

sofosbuvir or GS-7977: ELECTRON



Gane et al. AASLD 2011

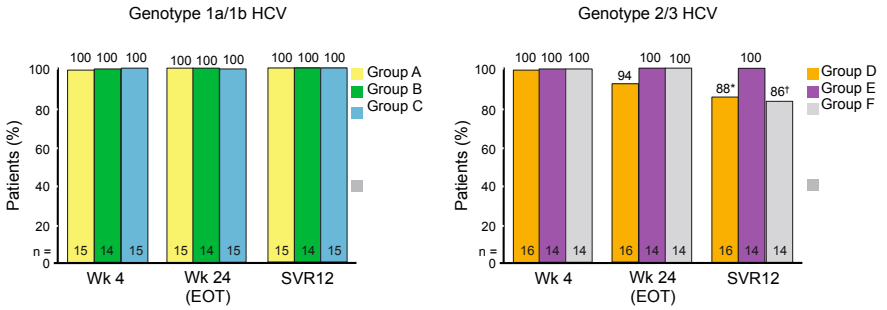
Daclatasvir + Sofosbuvir ± RBV in Tx-Naive GT1, 2/3 Pts



GS-7977 dosed 400 mg QD. Daclatasvir dosed 60 mg QD. RBV dosed by body weight for GT1 pts (1000 -1200 mg/day); 800 mg/day for GT 2/3 pts.

Sulkowski M, et al. EASL 2012. Abstract 1422. AASLD 2012 Abstract LB-2

Daclatasvir + Sofosbuvir ± RBV: Efficacy Analysis According to Genotype



Sulkowski M, et al. EASL 2012. Abstract 1422. AASLD 2012 Abstract LB-2

The "informed deferral"

- Patients / providers may together elect to defer therapy
- Particularly if earlier stage F0-F2, or contraindications to interferon
- Consider restaging those who are at risk for accelerated fibrosis (eg HIV)
- Continue prevention i.e. antiretrovirals, alcohol, nutrition

Opportunities to address HIV/HCV coinfection in 2012

- Prevention of new cases
- Identification of new cases
- Access to care, liver transplantation
- Less invasive tools for fibrosis assessment
- Access to novel and effective treatments
  - Addressing provider shortage
  - Addressing patient barriers

Barriers to addressing & treating HCV

Biologic
High viral loads
Fibrosis / cirrhosis, HIV

Psychosocial
Stigma
Lack of awareness
Fear of evaluation and treatment
Substance abuse
Neuropsychiatric comorbidities
Poor adherence to treatment

Medications
Side effects of treatment
Drug Interactions
Lack of insurance
High cost

Provider
Dearth of providers
Lack of provider knowledge