

HCV/HIV COINFECTION *Soup to Nuts*

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Learning Objectives

At the conclusion of this presentation, participants should be able to:

- State the epidemiology and natural history of HCV/HIV coinfection
- Appraise the efficacy of current treatment modalities for patients with HCV/HIV in order to better counsel patients about management options

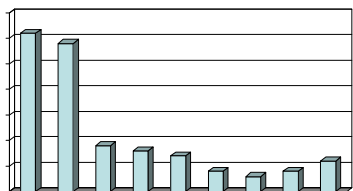
Disclosures (Activity w/i 12 months)

- Research Support (to institution):
 - Roche, Schering, SciClone, Vertex, GSK, HGS, Gilead, BMS
- Advisory Board/Consultation:
 - BMS, SciClone, Vertex, Merck, Valeant, Anadys

WHY DISCUSS HCV/HIV COINFECTION?

- People living with HIV are increasing in number
- Liver disease is an IMPORTANT outcome that ID caregivers are often ill-prepared to evaluate and manage
- Gastroenterologists are frequently uncomfortable with HIV management and with HIV-infected patients

Causes of Death in Coinfection French Mortality 2000 Cohort



Among patient with markers of HBV or HCV infection

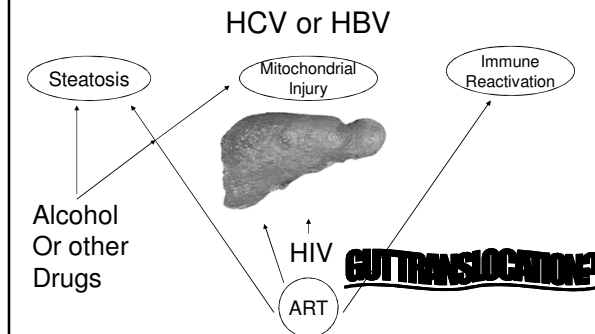
Salmon-Ceron et al., J HEPATOL 2005

HCV/HIV Effect on Health Utilization in A5001

	HCV/HIV rate* (95% CI)	HIV rate* (95% CI)	Adjusted rate ratio (95% CI)
Nights in hospital	14.2 (13.4–14.9)	5.8 (5.6–5.9)	2.5 (1.7–3.6)
Emergency department visits	6.3 (5.8–6.8)	3.4 (3.2–3.5)	1.5 (1.2–2.0)
Disability days	112.5 (110.3–114.7)	67.6 (67.0–68.2)	1.6 (1.2–2.2)

Linus et. al. CROI 2008 Oral #102

ETIOLOGIES OF LIVER INJURY



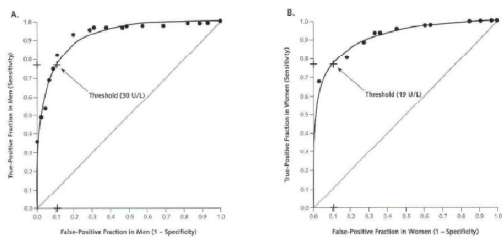
WHO SHOULD BE TESTED?

HIV-infected patients should be tested routinely for evidence of chronic HCV infection

Initial testing for HCV should be performed using the most sensitive immunoassays licensed for detection of antibody to HCV (anti-HCV)

USPHS GUIDELINES, MMWR, 2009

Updated ALT Ranges



Newly calculated healthy limits are indicated in each panel. A) Male participants. B) Female participants. To convert the alanine aminotransferase thresholds to $\mu\text{kat/L}$, multiply by 16.667.

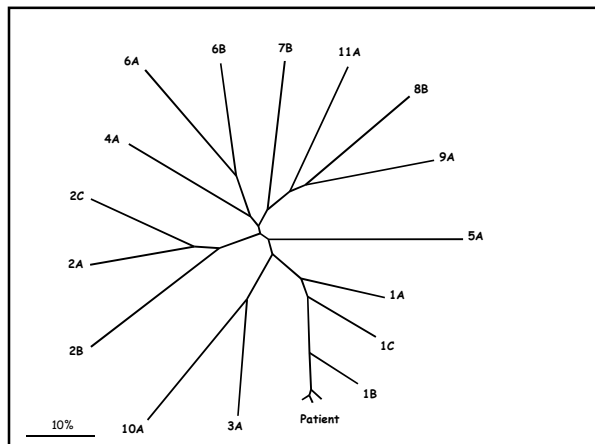
Prati, et al. 2002, Ann of Int Med

ROLE OF HCV RNA TESTING

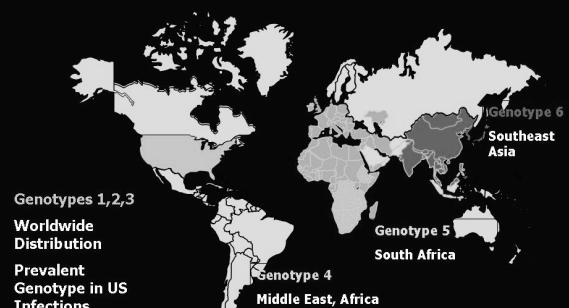
To confirm the presence of chronic infection, all HCV-seropositive persons should be tested for plasma HCV RNA using a qualitative or quantitative assay

Quantitative HCV RNA level (i.e., viral load) does not correlate with degree of liver damage and does not serve as a surrogate for measuring disease severity, but it does provide important prognostic information about the response to antiviral therapy

USPHS GUIDELINES, MMWR, 2009



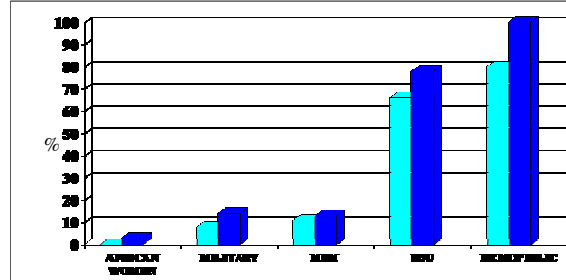
HCV Infection: Worldwide Genotype Distribution



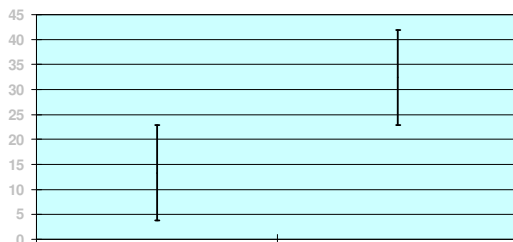
HCV FactSheet, Version 2.0 February (2006) Accessed via www.hcvadvocate.org

EPIDEMIOLOGY & NATURAL HISTORY

HCV ANTIBODY PREVALENCE in HIV-INFECTED PATIENTS

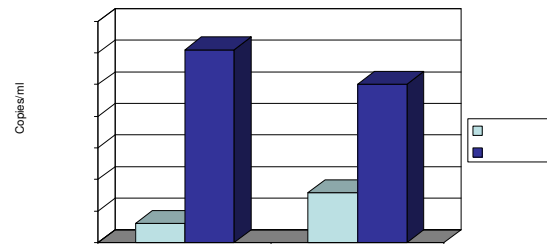


HCV/HIV Prevalence Composite Estimates



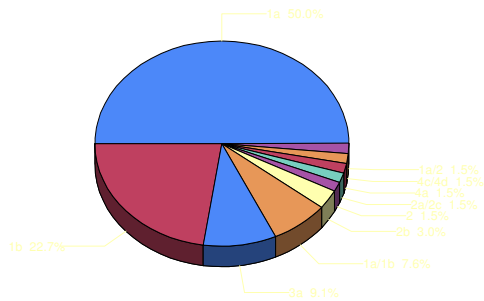
Sherman KE et. al., CID 2002
Rockstroh JK et. al. JID, 2005

HCV VIRAL LOAD



Sherman et. al., CID, 2002
Bonacini et. al., J VIRAL HEP, 1999

GENOTYPE DISTRIBUTION



Sherman et. al., CID, 2002

EVALUATION OF FIBROSIS

- Liver biopsy is the only reliable method to assess degree of hepatic fibrosis and is useful to provide prognostic information and guide therapeutic decisions

Advanced fibrosis/cirrhosis

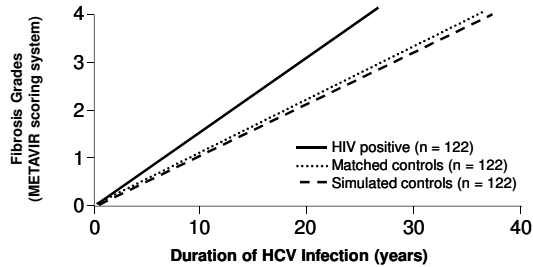
Consider treatment sooner

Screen for HCC

Screen for Portal Hypertension

MMWR, 2009

Rates of Liver Fibrosis Progression



Benhamou Y et al., Hepatology, 1999

FACTORS ASSOCIATED WITH FIBROTIC PROGRESSION IN HIV-INFECTED PATIENTS

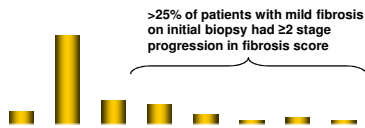
- Alcohol > 50 gms/day
- CD4+ < 200 cell/mm³
- Age at Time of HCV Infection (>20)
- No Protease Inhibitor Therapy

Benhamou et. al., HEPATOLOGY, 2001

Rapid Progression of Liver Disease in HIV/HCV-Coinfected Patients

- Prospective study of fibrosis progression in 67 coinfecting patients
- 2 biopsies; median time between biopsies was 2.84 years

Patients With Mild Fibrosis (≤F1) on First Biopsy



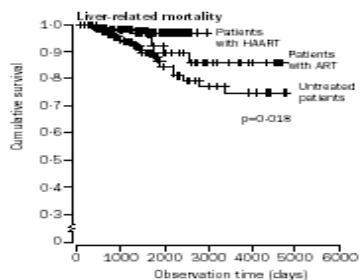
Change in Ishak Score From First to Second Biopsy

Sulkowski M et al. AIDS, 2007

PREVENTION STRATEGIES

- Vaccinate ALL HCV/HIV patients for
 - Hepatitis A
 - Hepatitis B
- Screen for HCV in HCV negative patients
- Discuss safe sexual practices and high risk sexual and parenteral exposure behaviors

EFFECT OF HAART ON LIVER RELATED MORTALITY IN HCV/HIV INFECTED PATIENTS

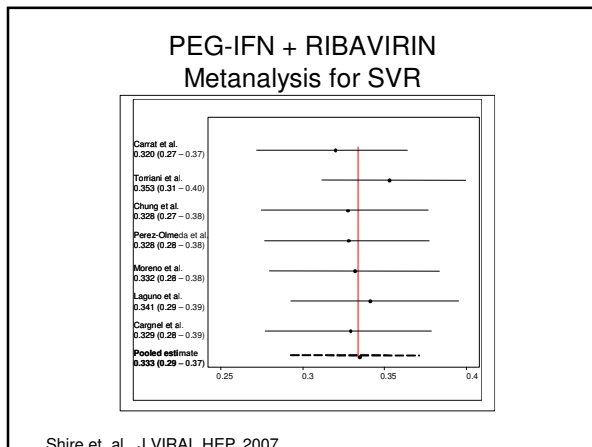
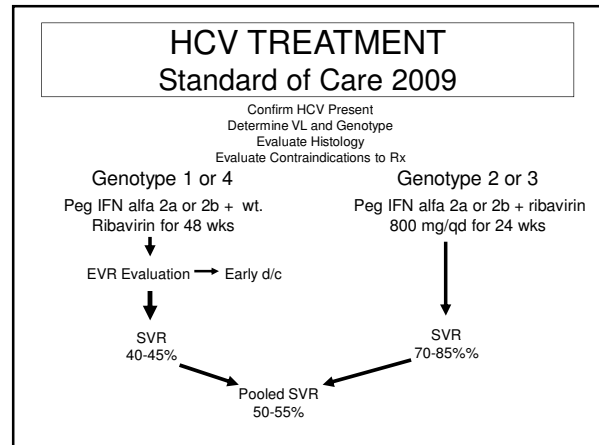
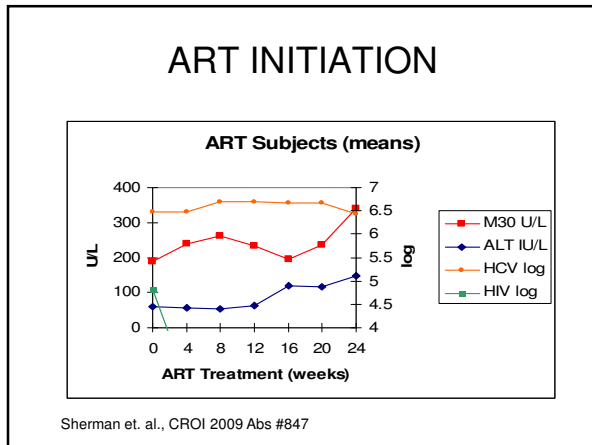
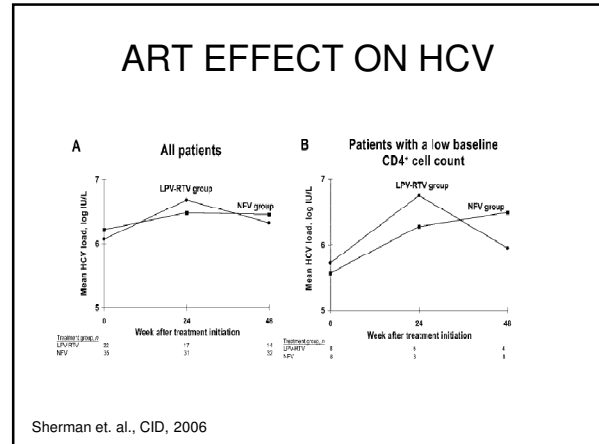


Qurishi N et al. LANCET, 2003

TREATMENT & MANAGEMENT PRINCIPLES

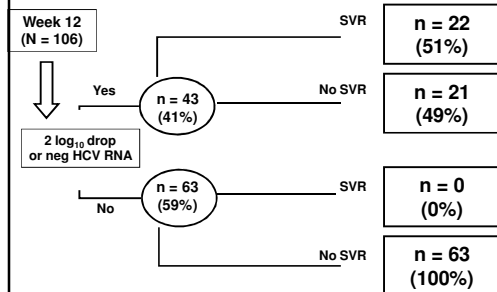
HIV
HCV

ART HEPATOTOXICITY		
DRUG	MECHANISM	MANIFESTATION
NRTI AZT d4T ddl ddC Abacavir	Impaired mitochondrial polymerase gamma function	Lactic Acidosis Steatosis
Protease Inhibitors Ritonovir Tipranovir Darunavir Atazanavir Indinavir	?Inhibition of retinoic acid binding protein UDP-glucuronyl transferase competition	Hepatocellular injury Steatosis Unconjugated hyperbilirubinemia
NNRTI Nevirapine	Impaired mitochondrial polymerase gamma Immune-mediated hypersensitivity	Lactic Acidosis Steatosis Eosinophilic injury



- ### TREATMENT RECOMMENDATIONS in HIV
- PegIFN + Ribavirin is the recommended treatment (A1)
 - Genotype 1 SVR 14-29%
 - Genotype 2, 3 SVR 43-73%
 - Many experts recommend weight-based ribavirin (A2)
 - 48 Weeks of Therapy in All Patients (A1)
 - Acute HCV should be treated with same regimen for >24 weeks (B3)
- USPHS GUIDELINES, MMWR, 2009

Early virologic response has 100% negative predictive value

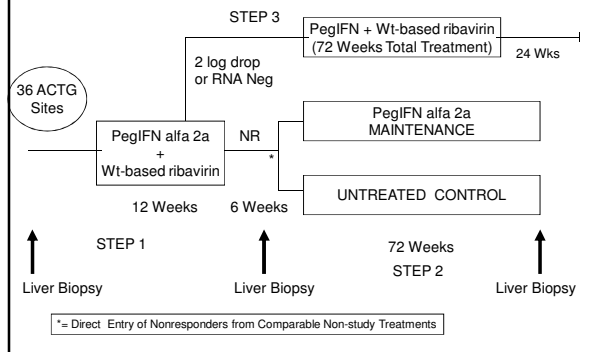


Chung et. al., 2004, NEJM

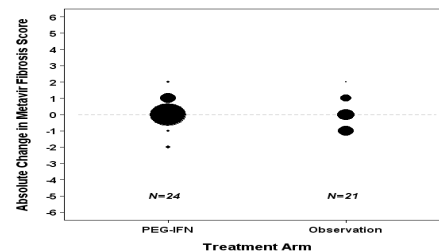
Issues Limiting Treatment of HCV

- Inexperience using agents
- Liver Disease too Advanced
- Psychiatric complications
- Anemia
- Neutropenia
- Weight loss
- Drug Interactions

STUDY DESIGN

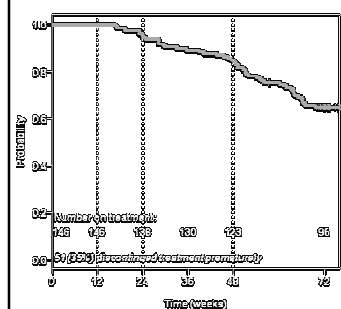


FIBROSIS CHANGE Paired Sample Analysis



Sherman et. al., CROI, 2008

Timing of Discontinuation of Treatment



- Of those who prematurely D/C'd Rx, 55% D/C'd between W48-72
- 95 (65%) subjects completed 72 wks
- SVR rate 63% (95% CI: 53% -73%)
 - Naïve 48/67 (72%)
 - Prev Tx 12/28 (43%)

Chung et. al. CROI 2009

NEW HCV AGENTS

- Entry Inhibitors
- Protease Inhibitors
- Polymerase Inhibitors
 - Nuc
 - Non-nucs
- Cyclophilin Inhibitors
- Immune modulators and DNA vaccines

Pre-existing mutation HCV/HIV Coinfected Patients

- Comparison of signature mutations for NS3 protease inhibitor
- Design
 - 38 coinfecting patients sequenced
 - 250 monoinfected sequences from GenBank analyzed
- A156G/T changes evaluated
- Results
 - Mutation found in 7.8% of coinfecting vs. 0.8% of monoinfected ($p < 0.02$)
 - All changes in coinfecting among those who received prior HIV protease inhibitors

Morsica et. al, AASLD 2006 Abs 436

LIVER TRANSPLANTATION

- VIABLE OPTION
- EARLY REFERRAL CRITICAL
- NIH SOT PROTOCOL

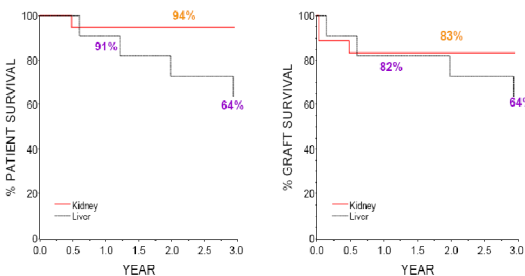
END STAGE LIVER DISEASE

- Ascites
- Encephalopathy
- PT > 3 seconds (INR > 1.3)
- Varices (bleeding or nonbleeding)

MELD

- Bilirubin
- PT (INR)
- Creatinine

NIH Pilot Study Outcomes



Roland et. al., Int. AIDS Conf, 2006, Updated 2007

...and miles to go before we sleep.

paraphrased from Robert Frost- 1923