

HCV/HIV Coinfection

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Disclosures
(Activity w/i 12 months)

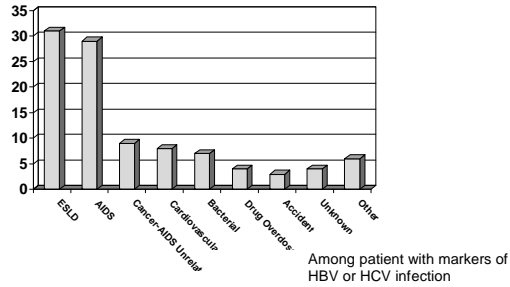
- Research Support (to institution):
 - Roche, Schering, SciClone, Vertex, GSK, HGS, Gilead, BMS
- Advisory Board/Consultation:
 - BMS, SciClone, Vertex, Merck, Valeant, Anadys

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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



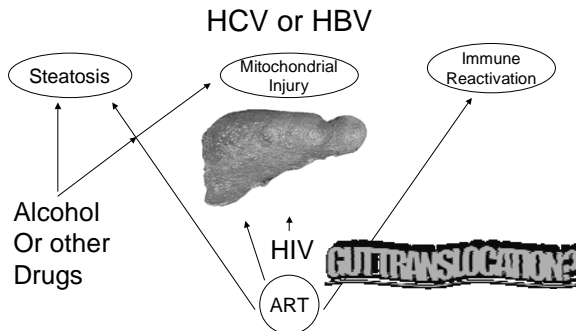
Salmon-Ceron et al., J HEPATOL 2005

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



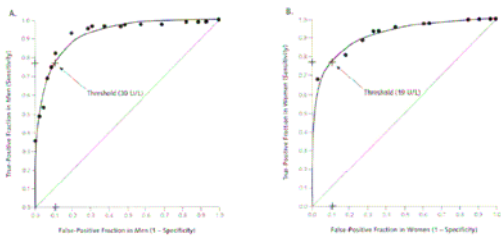
WHO SHOULD BE TESTED?

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

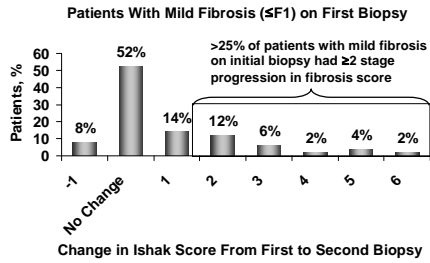
To confirm the presence of chronic infection, all HCV-seropositive persons should be tested for plasma HCV RNA using a qualitative or quantitative assay

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

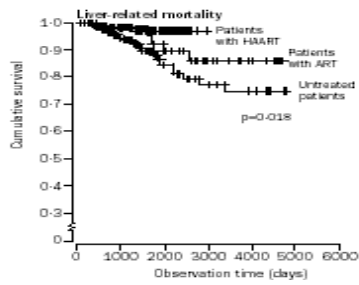
Rapid Progression of Liver Disease in HIV/HCV-Coinfected Patients Slide 10

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



Sulkowski M et al. AIDS, 2007

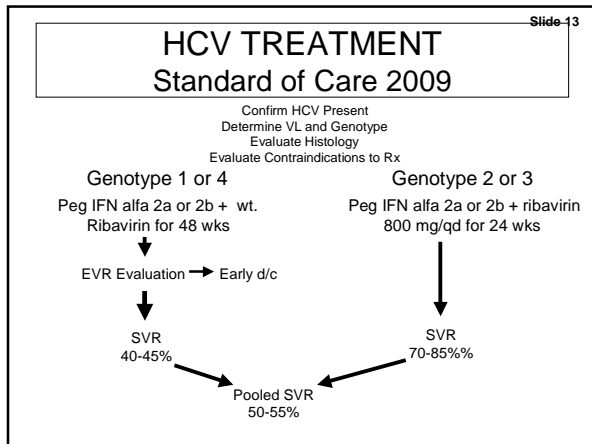
EFFECT OF HAART ON LIVER RELATED MORTALITY IN HCV/HIV INFECTED PATIENTS Slide 11

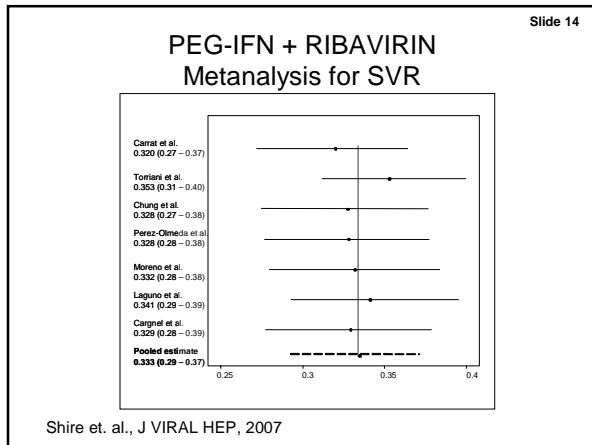


Qurishi N et al., LANCET, 2003

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TREATMENT & MANAGEMENT PRINCIPLES

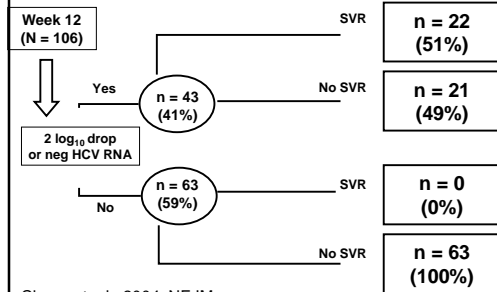




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- ## TREATMENT RECOMMENDATIONS in HIV
- PegIFN + Ribavirin is the recommended treatment (A1)
 - Genotype 1 SVR 14-29%
 - Genotype 2, 3 SVR 43-73%
 - Many experts recommend weight-based ribavirin (A2)
 - 48 Weeks of Therapy in All Patients (A1)
 - Acute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

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Early virologic response has 100% negative predictive value



Chung et. al., 2004, NEJM

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Issues Limiting Treatment of HCV

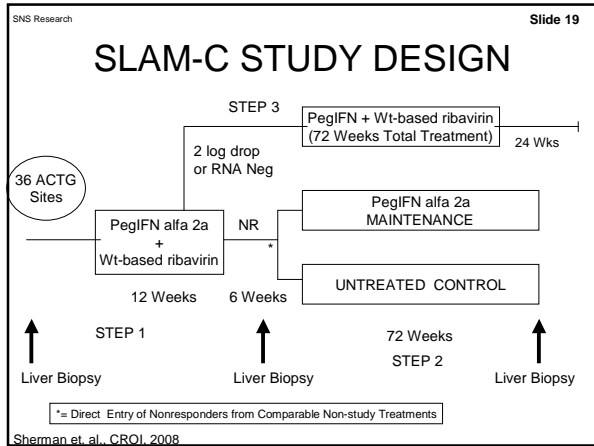
- Inexperience using agents
- Liver disease too advanced
- Psychiatric complications
- Anemia
- Neutropenia
- Weight loss
- Drug Interactions

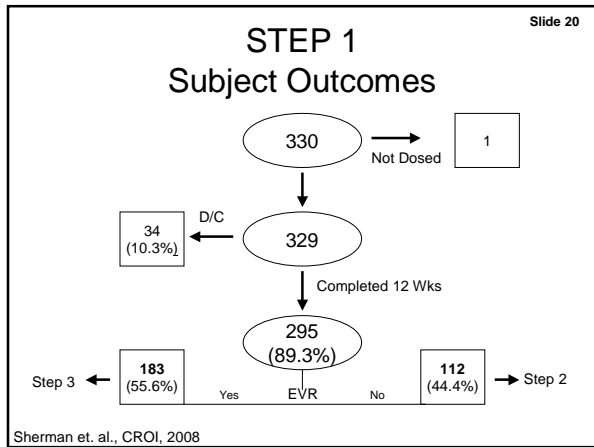
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MAINTENANCE THERAPY

- Treatment of NR with low dose PEGIFN to slow fibrotic progression
- SLAM-C protocol designed to study this
 - Lead in- All subjects treated with PegIFN alfa 2a 180 mcg + wt. based ribavirin
 - Subjects without 2 log drop in viral load or clearance of HCV randomized to maintenance vs. observation
 - Paired liver biopsy performed

Sherman et. al., CROI, 2008

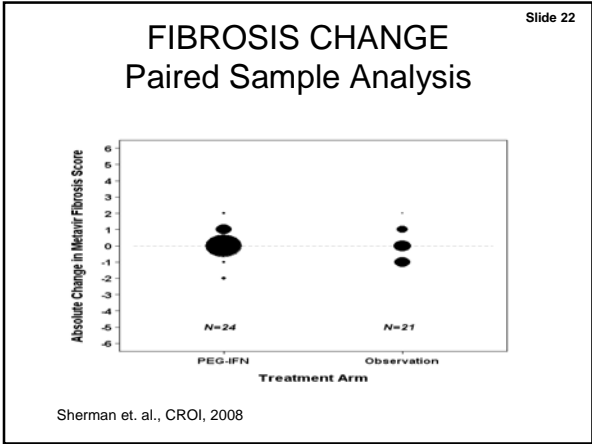


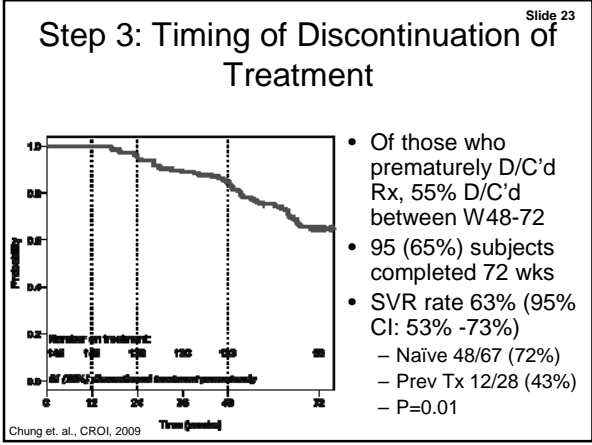


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STEP 1 EVR

ITT	55.62% (95% C.I. 50.1-61.1%)
Genotype	P= 0.0001
1,4	53.4%
2,3	90.3%
Race	P= 0.001
White, Non-Hispanic	64.8%
Black, Non-Hispanic	42.3%
Hispanic	56%
Gender	P= 0.02
Male	58.4%
Female	41.8%





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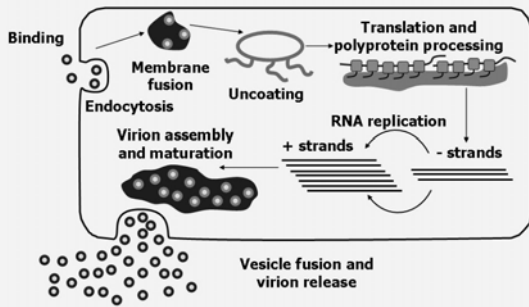
NEW TREATMENTS FOR HCV

FDA ANTIVIRAL ADVISORY COMMITTEE OCTOBER 2006

- Superiority should be required for first approval of small molecules
- Combination small molecule trials may be appropriate after Phase 2b evaluation of individual agents
- Prior to NDA studies must be initiated in special populations
 - HCV/HIV coinfection
 - Decompensated liver disease
 - Pediatric populations
- Appropriate representation of high prevalence minority groups is essential

Sherman et. al, HEPATOLOGY, 2007

HCV Life Cycle



Davis G et al. Semin Liver Dis. 1999(suppl 1):103-112.

Agents That Block Entry

- Antibodies
 - Monoclonal
 - Polyclonal
- Entry Inhibitors

Agents That Block HCV Translation

- Antisense
- Ribozymes
- Small-interfering (si) RNA
- Ribosomal Entry Site Inhibitors

Agents That Block Protease Function

- Protease Inhibitors
 - Blocks cleavage of structural proteins
 - Blocks cleavage of non-structural proteins from polyprotein
 - Blocks cleavage of non-structural proteins into individual proteins (NS3-NS4a serine protease inhibitors)

Agents That Block Transcription

- Polymerase Inhibitors
 - Nucleoside Analogues
 - Non-nucleoside Analogues
- Cyclophilin B Inhibitors
- Helicase Inhibitors

Inhibition of Viral Assembly and/or Release

- Alpha-glucosidase inhibitors
- Release Inhibitors

Innate Immune Response Modifiers

- Therapeutic Vaccines
- Immunomodulatory Agents
 - TLR Agonists
 - Peptides
- Interferon Sensitizers
 - Nitazoxanide

EXPERIMENTAL HCV AGENTS

- | | |
|--|---|
| <ul style="list-style-type: none"> • <u>Protease Inhibitors</u> – BILN-2061 – VX-950 (Telaprevir) – ITMN- 191 – SCH 503034 (Boceprevir) – ACH-806 – TMC435350 – MK-7009 – TMC-435 | <ul style="list-style-type: none"> • <u>Polymerase Inhibitors</u> – Nucleoside Analogues <ul style="list-style-type: none"> • NM-283 (Valopicitibine) • A-837093 • R1626 – <u>Non-nucleoside</u> <ul style="list-style-type: none"> • AG-021541 • HCV-796 • BIL-1941 • R-7128 • GS9190 • VCH-759 • BI-207127 • ANA-598 • PF-00868554 (Filibuvir) |
|--|---|

EXPERIMENTAL HCV AGENTS

- **Protease Inhibitors**
 - BILN-2061
 - VX-950 (Telaprevir)
 - ITMN- 191
 - SCH 503034 (Boceprevir)
 - ACH-806
 - TMC435350
 - MK-7009
 - TMC-435
- **Polymerase Inhibitors**
 - **Nucleoside Analogues**
 - NM-283 (Valopicitibine)
 - A-837093
 - R1626
 - Non-nucleoside
 - AG-021541
 - HCV796
 - BIL-1941
 - B-7128
 - GS-9190
 - VCH-759
 - BI-207127
 - ANA-598
 - PF-00868554 (Filibuvir)

LIMITATIONS OF SMALL MOLECULE BASED THERAPIES

- **Safety**
 - NM-283 (Valopicitibine) GI toxicity- No longer in development
 - BILN-2061 Animal cardiotoxicity- No longer in development
 - VX-950 (Telaprevir)- Rash and Anemia
 - R1626- Anemia- No longer in development
 - ACH861- Nephrotoxicity- No longer in development
 - HCV796- Hepatotoxicity- No longer in development
 - Debio 025- Hyperbilirubinemia
 - GS9190- QT Prolongation

LIMITATIONS OF SMALL MOLECULE THERAPIES (2)

- **Antiviral Activity**
 - Genotype specific to varying degrees
 - Unknown whether wide quasispecies variation in population will limit therapy
- **RESISTANCE**
 - Observed within 8 days with protease inhibitors
 - Higher barrier of resistance to polymerase inhibitors
 - Little resistance to cyclophilin inhibitors, but ?host effects

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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

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SUMMARY OF NEW TREATMENTS

- Many targets for directed HCV therapy are available
- Some agents show promise, but development is slow and should not delay treatment in individual patients now
 - New Agent Approval- ?2011
- Expect need for Pegylated Interferon and ribavirin for the foreseeable future

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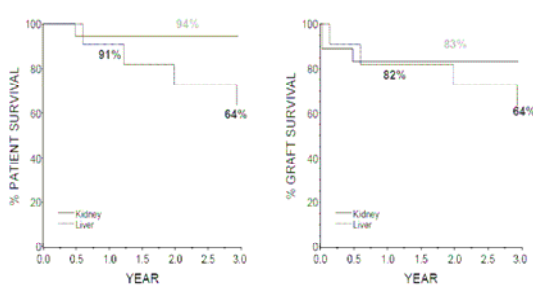
LIVER TRANSPLANTATION

- VIABLE OPTION
- EARLY REFERRAL CRITICAL
- NIH SOT PROTOCOL

END-STAGE LIVER DISEASE

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

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

Changes

- Increased font size, fixed formatting, and text alignment throughout
