Overview

- Influence of ART on Liver disease
  - Reduced morbidity/mortality
  - Increased hepatotoxicity?
- Case 1
  - HBV co infection
  - Viral factors, treatment options
- Case 2
  - HCV co infection
  - New treatment options
- Influence of Co infection on HIV outcomes
Impact of ART on Overall Liver Mortality in HIV/HCV-Coinfected Patients

- Bonn cohort (1990-2002)
  - 285 HIV/HCV coinfected patients

- Liver-related mortality rates per 100 person-years
  - HAART: 0.45
  - ART: 0.69
  - No therapy: 1.70

- Predictors for liver-related mortality
  - No HAART
  - Low CD4 cell count
  - Increasing age

HAART HEPATOTOXICITY

- Additional visits and admissions
- Drug D/C
- Increase pre-existing liver damage
  - Increased cost
  - Virological Failure
  - Disease Progression
  - Liver Failure

HCV and ART-associated Hepatotoxicity

Sulkowski MS et al. Hepatology 2002
Incidence of >/= Grade 2 Liver Enzyme Elevation

- LEE more frequent in HIV/HCV co infection 14.7% vs 12% in mono infection
- Baseline ALT
- Meta-analysis of 20 publications of HIV-infected patients ± HCV coinfection

Benhamou et al. Systemic overview of HAART-associated liver enzyme elevations in patients infected with HIV and co-infected with HCV. 13th CROI 2006; Abstract 88

Mechanism of HAART related Hepatotoxicity

<table>
<thead>
<tr>
<th>Direct Toxicity</th>
<th>HSR</th>
<th>Mitochondrial Toxicity</th>
<th>IRIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td>NNRTI/PI</td>
<td>Abacavir, NNRTIs, Fosamprenavir, Darunavir</td>
<td>NRTI (AZT, D4T, DDI)</td>
</tr>
<tr>
<td>Dose Dependence</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Onset</td>
<td>2-12m</td>
<td>&lt;6 weeks</td>
<td>Late</td>
</tr>
<tr>
<td>Other</td>
<td>Fever, Rash, Eosinophilia</td>
<td>AST&gt;ALT, Lactic Acidosis</td>
<td>HBV, HCV</td>
</tr>
</tbody>
</table>
Drugs available for HIV therapy

NRTIs
- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir
- Zidovudine

Mitochondrial Toxicity

Drugs available for HIV therapy

NNRTIs
- Efavirenz
- Nevirapine
- Etiravirine

2NN Study: Severe Hepatotoxicity in Patients Receiving NNRTI-Based Regimens

- Treatment-naïve patients
  - 1216 enrolled
  - HBV co infected: 5.2%
  - HCV co infected: 9.5%
- NNRTI + d4T + 3TC
  - Nevirapine qd (400 mg)
  - Nevirapine bid (200 mg)
  - Efavirenz qd (600 mg)
  - Nevirapine + efavirenz qd (400 + 600 mg)
- 2 Nevirapine-attributed deaths
  - Fulminant hepatitis, pancreatitis, renal failure
  - Stevens-Johnson syndrome (recovered)

Grade 3/4 Hepatotoxicity

Time to Onset of *Asymptomatic ALT or AST >5 x ULN* on NVP in *Controlled Trials*

**0-12 Months**

- **NVP (n = 1731)**
- **Control (n = 1912)**

**3-12 Months**

**Incidence of Severe Hepatotoxicity of NNRTIs in Hepatitis Co infection**

- Prospective study on the incidence of severe hepatotoxicity (grade 3 or 4 AST/ALT)
  - Johns Hopkins HIV cohort (n=568)
  - HCV (43%) and HBV (7.7%)

- Overall incidence of severe hepatotoxicity
  - Nevirapine: 15.6%
  - Efavirenz: 8.0%

- Hepatotoxicity risk was significantly greater in:
  - Hepatitis co infection
  - NNRTI + PI

Drugs available for HIV therapy

Protease Inhibitors
- Atazanavir
- Darunavir
- Fos-Amprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

Incidence of Severe Hepatotoxicity During Therapy With PI-Based Regimens

Hepatotoxicity with Newer PIs

New Classes
Fusion Inhibitors
- Enfuvirtide
R5 Inhibitors
- Maraviroc
Integrase Inhibitors
- Raltegravir

Drugs available for HIV therapy
Hepatotoxicity and New Agents

Rates of Grade 3/4 rises in ALT
Case 1

- 44 year old Vietnamese female
- 2005 diagnosed HIV antibody positive
- CD4 962 cells/ml
- HIV viral load 257 copies/ml

Hepatitis B Co infection

- Hepatitis B surface antigen positive
- Hepatitis B e antigen positive
- ALT 236 IU/ml
- Hepatitis B DNA 267,465,380 copies/ml

What other tests would you require?
Pre-existing Antiviral Resistance Mutations Among Treatment-naive HBV Patients Can Be Detected Using A Sensitive Line Probe Assay

Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>N = 146</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age ± SD (years)</td>
<td>39 ± 17</td>
</tr>
<tr>
<td>% Male</td>
<td>63</td>
</tr>
<tr>
<td>% Asian</td>
<td>89</td>
</tr>
<tr>
<td>% Cirrhosis</td>
<td>15</td>
</tr>
<tr>
<td>% HBeAg-positive</td>
<td>43</td>
</tr>
<tr>
<td>Mean HBV DNA ± SD (log IU/ml)</td>
<td>5.7 ± 2.2</td>
</tr>
<tr>
<td>Median (range) ALT (U/L)</td>
<td>41 (3-2212)</td>
</tr>
<tr>
<td>% Genotype A/B/C/D</td>
<td>6/33/51/10</td>
</tr>
</tbody>
</table>

rt Mutation | Prevalence (%) |
-------------|----------------|
L80V/I       | 7              |
V173L        | 1              |
L180M        | 7              |
M204V/I      | 13             |
A181V/T      | 0              |
I233V        | 0              |
N236T        | 0              |
A194T        | 0              |
T184G        | 3              |
S202I        | 5              |
M250V        | 5              |

Fung SK, et al., EASL 2008; Poster #649.

HBV Genotype in EuroSIDA Cohort

HBV Genotype

- Genotype A: better response to IFN
- Genotype B: mild hepatitis B, higher rate of seroconversion
- Genotype C: increased risk of HCC\(^1\)
- Genotype G: increased liver fibrosis\(^2,3\)

\(^1\)Chan HL, J Clin Oncol 2008. \(^2\)Lacombe K, AIDS 2006. \(^3\)Dao et al. CROI 2010

HepBsAg Loss by Genotype Entecavir vs. Lamividine

<table>
<thead>
<tr>
<th>Genotype</th>
<th>ETV (%)</th>
<th>LAM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>C</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>D</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>E</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>F</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>2</td>
</tr>
</tbody>
</table>

022 Study
**Does She Require Therapy?**

**Treatment Criteria for Chronic Hepatitis B**

- Recommended HBV DNA and ALT levels

<table>
<thead>
<tr>
<th>Liver Society Guidelines*</th>
<th>HBeAg Positive</th>
<th>HBeAg Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBV DNA, IU/mL</td>
<td>ALT</td>
</tr>
<tr>
<td>APASL 2008[2]</td>
<td>≥ 20,000</td>
<td>≥ 2 x ULN‡</td>
</tr>
<tr>
<td>AASLD 2009[3]</td>
<td>&gt; 20,000</td>
<td>&gt; 2 x ULN‡ or (+) biopsy</td>
</tr>
</tbody>
</table>

*Although ALT and HBV DNA are primary tests used to determine treatment candidacy, the levels of elevation that warrant consideration of treatment are not universally agreed upon.
†Laboratory normal.
‡30 U/L for men and 19 U/L for women.
**In patients older than 40 yrs of age, 2000 IU/mL should be considered as a cutoff for treatment.

BHIVA 2010

Brook et al. HIV Medicine (2010) 11, 1-30

Cumulative Risk of Cirrhosis in 3582 HBsAg+ patients (REVEAL-HBV)

<table>
<thead>
<tr>
<th>RR</th>
<th>1</th>
<th>1.4</th>
<th>2.5</th>
<th>5.9</th>
<th>9.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4.5</td>
<td>5.9</td>
<td>9.8</td>
<td>23.5</td>
<td>36.2</td>
</tr>
</tbody>
</table>

365 cases of cirrhosis over 11 years

Adjusted for gender, ALT, alcohol and smoking

Iloeje U et al. Gastroenterology 2006;130:679-86
Risk of HCC in HBsAg+ patients (REVEAL-HBV)

184 cases of HCC over 12 years
Adjusted for gender, ALT, alcohol and smoking

Does She Require Therapy?

- Hepatitis B surface antigen positive
- Hepatitis B e antigen positive
- ALT 236 iu/ml
- Hepatitis B DNA 267, 465, 380 copies/ml
What agent?

Immune modulators

IFN-alpha
Pegylated Interferon-alpha

Polymerase Inhibitors

Lamivudine
Adefovir
Entecavir
Telbivudine
Tenofovir
Emtricitabine

HIV/HBV response to Interferon

- **Peg-IFN + ADV**: 17 patients treated with ADV + PegIFNα2a for 48ws (pilot)
  - no HBe or HBs seroconversion
  - 100% HBVDNA rebound after end of treatment
  - effect on ALT/AST on treatment only

  Ingiliz M, Antivir Ther 2008

- **PegIFN + TDF**: 10 patients treated with TDF alone or PegIFNα2a for 24ws then TDF (randomized trial)
  - Non difference in seroconversion rates or HBVDNA levels at 48ws

  Johnson M, HIV Clin Trials 2007

A-B, A-C, A-D: p<0.05
B-C, B-D, C-D: NS

Di Martino V, Gastroenterol 2002
**Anti-HIV Activity of Entecavir**

17 HIV/HBV coinfected pts (10 naïve, 7 treatment-experienced from US and Australia) who received entecavir (ETV) monotherapy for HBV therapy. ETV monotherapy results in clinically significant reduction in HIV RNA in the majority but not all pts and can select for the M184V mutation even in naive pts. **HIV/HBV coinfected individuals should not receive ETV monotherapy**

- Median time to M184V: 148 days for ART naïve, 98 days for ART experienced.
- Selection of M184V following ETV treatment:
  - ART naïve: 3/7
  - ART experienced: 3/5
  - Total: 6/12

**Univariate analysis for selection of M184V**

- Risk factor                      | p value
  - Total duration on ETV          | 0.05
  - Magnitude of HBV DNA reduction on ETV | 0.04
  - HIV RNA pre-ETV therapy        | 0.87
  - HBV DNA pre-ETV therapy        | 0.69
  - Nadir CD4+ count               | 0.20

**Telbivudine – ?anti-HIV activity**

- **No in vitro activity against 8 wild-type HIV-1, 2 drug resistant HIV-1 isolates**

C Avila et al. CROI 2009;PB13b
Telbivudine – ?anti-HIV activity

HIV viral load over time

Undetectable* HBV DNA in HBV Patients After 1 Year of Treatment

Not head-to-head trials; different patient populations and trial designs

*By PCR-based assay (LLD ~ 50 IU/mL) except for some LAM studies.

Outcomes to Consider and Goals to Achieve

Ultimate goal

Cure

HBsAg clearance

Current goals

Viral suppression

HBeAg seroconversion*

ALT normalisation

Remission

Prevent cirrhosis/HCC

Survival

Cessation of therapy

Short term

Long term

*HBeAg positive patients only

Keeffe et al, 2006
Loe & McMahon, 2007

More Information......

• She has previously been seen for hepatitis B in a gastroenterology clinic

• She had been prescribed lamivudine for 18 months that she had taken intermittently

• She has stored blood that shows she was HIV antibody positive but HIV viral load and resistance testing fails?

• How does this alter your choice of therapy?
Incidence of LAM Resistance in HBV and HBV/HIV Patients

- HIV negative
- HIV positive

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>20%</td>
<td>38%</td>
<td>47%</td>
<td>49%</td>
</tr>
<tr>
<td>0%</td>
<td>20%</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>80%</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


LAM MonoTherapy: Major Issues

- M204V/I
- L180M
- A181T/V
- T184S
- T184G/S202I/M250V
- L80V/I
- A194T
- V214A/Q215S

- Adefovir
- Telbivudine/Clevudine
- Tenofovir
- Entecavir
Conclusion:
- TDF/3TC superior to 3TC alone but not TDF in HBV naïve
- No benefit continuing 3TC in experienced HBV viraemic patients
- No difference between adding or switching TDF

Nelson M et al. 13th CROI. Denver, CO, February 5-8, 2006; Abst. 831.

- Due to her excellent immunological function it is decided to commence her on Adefovir 10mg od

- Would you add lamivudine?
ADV vs ADV + LAM for HBeAg-Negative LAM-Resistant Patients

- Multicenter cohort study; retrospective/prospective
  - Mean follow-up: 33 months

Undetectable HBV DNA* (%)

<table>
<thead>
<tr>
<th>Month</th>
<th>Patients (%)</th>
<th>Adefovir (n = 303)</th>
<th>Adefovir + Lamivudine (n = 285)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td>12</td>
<td>40</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>18</td>
<td>60</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>24</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>30</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>36</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
</tbody>
</table>

*< 1000 copies/mL.

Year 3 Cumulative Adefovir Resistance

<table>
<thead>
<tr>
<th>Month</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADV</td>
<td>16</td>
</tr>
<tr>
<td>ADV + LAM</td>
<td>0</td>
</tr>
</tbody>
</table>

She commences Adefovir and Lamivudine

After 1 year

<table>
<thead>
<tr>
<th>Month</th>
<th>HBV DNA</th>
<th>ALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>267,456,376</td>
<td>234</td>
</tr>
<tr>
<td>3</td>
<td>4,876,487</td>
<td>112</td>
</tr>
<tr>
<td>6</td>
<td>1,284,356</td>
<td>67</td>
</tr>
<tr>
<td>9</td>
<td>1,534,643</td>
<td>54</td>
</tr>
<tr>
<td>12</td>
<td>1,263,456</td>
<td>58</td>
</tr>
</tbody>
</table>
**Patients’ perceptions of necessity and concerns**

- HAART patients received ‘Beliefs about Medicines Questionnaire’
- Statistical analysis determined associations between beliefs about HAART and reported adherence

<table>
<thead>
<tr>
<th>Adherence level</th>
<th>Perceived necessity</th>
<th>Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low adherence (n = 32)</td>
<td>3.78</td>
<td>3.11</td>
</tr>
<tr>
<td>High adherence (n = 91)</td>
<td>3.99</td>
<td>2.88</td>
</tr>
</tbody>
</table>


**At 1 Year….**

- CD4 373 cells/ml
- HIV Viral load 23,758 copies/ml
- Resistance Test M184V
- What treatment would you initiate?
### Most Common HBV Cross-Resistance Mutations

<table>
<thead>
<tr>
<th></th>
<th>Lamivudine</th>
<th>Telbivudine</th>
<th>Entecavir</th>
<th>Adefovir</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>M204I</td>
<td>R</td>
<td>R</td>
<td>I/R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>L180M + M204V</td>
<td>R</td>
<td>R</td>
<td>I</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>A181 T/V</td>
<td>I</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>N236T</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>R</td>
<td>I</td>
</tr>
<tr>
<td>I169T + V173L + M250V*</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>T184G + S202I/G*</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>


### TDF + ETV in Patients With Multidrug Resistance: Virologic Outcomes

- Median HBV DNA decrease: 4.5 log_{10} copies/mL
- Median ALT decrease: 28%

Starting HIV treatment 2006

- She commences Tenofovir, Didanosine, Efavirenz and Entecavir

- She is transferred to an immigrant centre in the north of England

Follow up....

- 3 years later she is admitted via A&E with haematemesis
- She remains on the same therapy
- She has hepatosplenomegaly
- What complication(s) may have developed?
Differential Diagnosis…

- Variceal Bleed
- Hepatitis B cirrhosis
- DDI induced non cirrhotic portal hypertension
- Untreated/untested Delta hepatitis

DDI induced non cirrhotic portal hypertension

<table>
<thead>
<tr>
<th>Finding</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gl bleeding</td>
<td>9</td>
<td>(60%)</td>
</tr>
<tr>
<td>Ascites</td>
<td>6</td>
<td>(40%)</td>
</tr>
<tr>
<td>Endoscopy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varices</td>
<td>12</td>
<td>(80%)</td>
</tr>
<tr>
<td>Ultrasound</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>11</td>
<td>(73%)</td>
</tr>
<tr>
<td>Portal venous thrombosis</td>
<td>3</td>
<td>(20%)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild portal or periportal fibrosis (&lt;F2)</td>
<td>13</td>
<td>(87%)</td>
</tr>
<tr>
<td>Nodular regenerative hyperplasia</td>
<td>2</td>
<td>(13%)</td>
</tr>
</tbody>
</table>

Scourfield et al BHIVA 2009
HIV/HBV patients on TDF

Tan et al J Viral Hepat 2009 Jul;16(7):471-8

5-Year Tenofovir Therapy Is Associated with Maintained HBV Response and Renal Toxicity in HIV/HBV Co-infected Patients

De Vries-Sluijs et al. CROI 2010

eGFR in mL/min/1.73 m2 was calculated using the (MDRD) equation, based on the serum creatinine, age, sex and race.
• She is admitted

• Varices are banded

• Overnight she has a catastrophic bleed and dies

Hepatitis B DNA is later reported as undetectable Delta AB/RNA positive
Case 2

- 37 year old man presents with acute hepatitis C

- He can pinpoint the date of infection to a sex party 3 weeks previously

- He had a negative hepatitis C test 8 weeks previously

- He is HIV antibody positive
- CD4 count 456 cells/ml
- HIV viral load undetectable
- HAART consists of Kivexa Saquinavir Ritonavir
- He has never failed therapy

- How soon can we predict spontaneous clearance?
Spontaneous Clearance of Acute HCV

<table>
<thead>
<tr>
<th>Clearance</th>
<th>Chronic HCV</th>
<th>Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral load &gt; 2 log fall at week 4</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Viral load &lt; 2 log fall at week 4</td>
<td>15</td>
<td>52</td>
</tr>
<tr>
<td>Viral load &lt; 600 copies at week 12</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Viral load &gt; 600 copies at week 12</td>
<td>5</td>
<td>51</td>
</tr>
</tbody>
</table>

Vogel M. NEAT Study Group. CROI 2010

Case 2

- **Genotype 1**

- **Hepatitis C RNA 2,764,500 IU/ml**

- **Hepatitis C RNA 1,345,876 IU/ml at week 4**
• It is decided to initiate treatment

• With what?

• What duration?

Treatment

• Most studies utilize (Pegylated) interferon alone

• Treatment periods 4-24 weeks

• EOTR 56-100%

• SVR 22-100%
Virological response: EOTR rates vs SVR rates

- All Patients: n=61, EOTR 72%, SVR 66%
- Genotype 1: n=50, EOTR 72%, SVR 65%
- Genotype non-1: n=8, EOTR 75%, SVR 75%

P = 0.703

Is 48 weeks better?
Response to treatment by genotype – intention to treat (ITT) analysis

- All Patients (n=31)
  - ETVR: 78%
  - SVR: 68%
- Genotype 1/4 (n=26)
  - ETVR: 77%
  - SVR: 65%
- Genotype 2/3 (n=5)
  - ETVR: 80%
  - SVR: 80%

Treated patients (ITT)

- GT 1 or 4 (n=27)
  - ETR: 80%
  - SVR: 65%
- GT 2 or 3 (n=7)
  - ETR: 80%
  - SVR: 68%
- PegIFN + RBV (n=21)
  - ETR: 80%
  - SVR: 77%
- PegIFN (n=15)
  - ETR: 78%
  - SVR: 68%

Graphs show the percentage of patients achieving ETR and SVR after 24 and 48 weeks of treatment for different genotypes and treatment regimens.
Case 2

- The patient is treated with Pegylated interferon sole therapy

- At week 4 the patient has a less than 1 log fall in hepatitis C viral load

- At week 8 there is no further fall and treatment is stopped

- The patient asks you is he now more at risk of any complications of HIV disease and its treatment?
Increased Risk of Cirrhosis and ESLD Due to HIV/HCV Coinfection

Histologic Cirrhosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Makris (UK)</td>
<td>2.57</td>
</tr>
<tr>
<td>Soto (Spain)</td>
<td>1.0</td>
</tr>
<tr>
<td>Pol (France)</td>
<td>1.0</td>
</tr>
<tr>
<td>Benhamou (France)</td>
<td>1.0</td>
</tr>
<tr>
<td>Combined</td>
<td>10.83</td>
</tr>
</tbody>
</table>

Decompensated Liver Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyster (USA)</td>
<td>2.07</td>
</tr>
<tr>
<td>Telfer (UK)</td>
<td>2.07</td>
</tr>
<tr>
<td>Makris (UK)</td>
<td>1.0</td>
</tr>
<tr>
<td>Lesens (Canada)</td>
<td>1.0</td>
</tr>
<tr>
<td>Combined</td>
<td>10.1</td>
</tr>
</tbody>
</table>


Rate ratio of Cirrhosis between HIV/HCV and HCV: HAART era

<table>
<thead>
<tr>
<th>Model</th>
<th>Study name</th>
<th>N</th>
<th>Statistics for each study</th>
<th>Risk ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Risk Lower Upper limit</td>
<td>Limit Z-Value p-Value</td>
</tr>
<tr>
<td>Fixed</td>
<td>Verma, 2006a</td>
<td>381</td>
<td>2.015 1.421 2.658 3.928</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Di Martino, 2001</td>
<td>160</td>
<td>2.245 0.581 8.683 1.172</td>
<td>0.241</td>
</tr>
<tr>
<td></td>
<td>Brau, 2006</td>
<td>656</td>
<td>1.404 1.010 1.951 2.019</td>
<td>0.044</td>
</tr>
<tr>
<td></td>
<td>Gaslightwala &amp; Bini, 2006</td>
<td>708</td>
<td>7.288 4.938 10.760 9.998</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Mouto, 2005</td>
<td>464</td>
<td>0.776 0.327 1.854 0.566</td>
<td>0.572</td>
</tr>
<tr>
<td></td>
<td>Mohsen, 2003</td>
<td>208</td>
<td>1.614 0.958 3.434 1.830</td>
<td>0.067</td>
</tr>
<tr>
<td></td>
<td>Martinez-Sierra, 2003</td>
<td>188</td>
<td>4.195 1.665 10.557 3.042</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Macias, 2005</td>
<td>234</td>
<td>1.896 0.911 3.165 1.668</td>
<td>0.096</td>
</tr>
<tr>
<td>Random</td>
<td>Fixed</td>
<td></td>
<td>2.500 1.191 2.732 5.157</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Random</td>
<td></td>
<td>2.181 1.285 3.703 2.887</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Meta-Analysis
Cumulative probability of cirrhosis

More rapid fibrosis progression in HIV/HCV

Changes in fibrosis stage between LB

- Regression 2 to 1 stage: 17%, n=23
- No Change: 30%, n=52
- Progression 1 stage: 29%, n=38
- Progression 2 stage: 16%, n=22

Median (Q1-Q3) time between LB: 3.3 (2-5.2) years
Risk Ratio
Lumbar spine [F]
Femoral neck [F]
Lumbar, femoral, both [F]
Lumbar spine [M]
Femoral neck [M]
Lumbar, femoral, both [M]

Favors HIV monoInfected
Favors HIV/Hepatitis Coinfected

Guaraldi et al. AIDS. 2009 Oct 23;23(16):2191-8

Top 12
Ways to Avoid a Heart Attack
Defrim Kërcagu, MD
### Risk of AMI and CVD Among HIV and HIV/HCV Patients in the HAART era

<table>
<thead>
<tr>
<th>Events</th>
<th>Acute Myocardial Infarction</th>
<th>Cerebrovascular Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV/HCV</td>
<td>HIV/HCV</td>
</tr>
<tr>
<td>Event Rate/1000 Patient-Years</td>
<td>3.36</td>
<td>4.19</td>
</tr>
<tr>
<td></td>
<td>11.12</td>
<td>12.47</td>
</tr>
<tr>
<td>Unadjusted Hazard Ratio (95% CI; P value)</td>
<td>1.25 (0.98-1.59) p=0.075</td>
<td>1.12 (0.98 - 1.29) p=0.105</td>
</tr>
<tr>
<td>Adjusted Hazard Ratio (95% CI; P value)</td>
<td>1.25 (0.98-1.61) P=0.072</td>
<td>1.20 (1.04 - 1.38) p=0.013</td>
</tr>
</tbody>
</table>

### Insulin Resistance and Diabetes Mellitus in HCV/HIV Coinfection

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hep C negative</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hep C positive</td>
<td>1.12</td>
<td>1.32</td>
</tr>
</tbody>
</table>

Adjusted for sex, age, risk, ethnicity, previous AIDS, smoking, family history, ART drug exposure, cohort, year

Merchante N, et al., Gut 2009

Rainer CROI 2008
April 2010

- The patient continues to be well on his current regimen (Kivexa, Saqunavir/r)

- He undergoes yearly fibroscan which shows <F2 disease

- The patient decides he wishes to be retreated
Would you

- Advise him to wait for new treatments (STAT-C)
- Retreat him with Pegylated interferon and weight based ribavirin?
- Switch his antiviral regimen?
- Test for IL28B genotype?

New HCV Treatments in Development

- Interferons
- Nucleosidic polymerase inhibitors
- Cyclophilin B inhibitors
- Oligonucleotides
- Immune modulators
- Therapeutic Vaccines
- Analogues of ribavirin
- Protease inhibitors
- Non-nucleosidic polymerase inhibitors
- Glucosidase α inhibitors
- RNA interference
- New HCV Treatments in Development

- Glucosidase α inhibitors
- RNA interference
Virologic response 12 or 24 weeks after treatment discontinuation (ITT)

![Graph showing virologic response](image)

**SPRINT-1: Boceprevir in genotype 1 naïve patients**

**Boceprevir Protocol in HIV/HCV Coinfection**

International trial (P05411) in Co infection: A Phase II Safety and Efficacy Study of Boceprevir in Subjects Coinfected with HIV and Hepatitis C
Ritonavir Boosting and STAT-C

In vivo: mean plasmatic level (5 mg/kg per os)

VX-950 (Telaprevir)
- AUC ↑ > 8-fold
- $C_{\text{max}}$ > 50-fold

VX-950 + ritonavir

SCH 503034 (Boceprevir)
- AUC ↑ > 20-fold
- $C_{\text{max}}$ > 100-fold

Hours after administration

www.hepatonews.com


EPIC3: SVR by Previous Treatment and Response

PegIFN alfa-2b 1.5 µg/kg/week + Weight-Based RBV 800-1400 mg/day for 48 Weeks

SVR (%)

<table>
<thead>
<tr>
<th>Previous Regimen</th>
<th>PegIFN alfa-2b + RBV (n = 488)</th>
<th>PegIFN alfa-2b + RBV (n = 375)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (N = 2293)</td>
<td>22 (100)</td>
<td>18 (94)</td>
</tr>
<tr>
<td>IFN/RBV (n = 1423)</td>
<td>14 (25)</td>
<td>6 (17)</td>
</tr>
<tr>
<td>PegIFN alfa-2b + RBV</td>
<td>25 (43)</td>
<td>32 (43)</td>
</tr>
<tr>
<td>PegIFN alfa-2a + RBV</td>
<td>18 (43)</td>
<td>18 (43)</td>
</tr>
</tbody>
</table>

Note: results from EPIC3 study led to expanded indication for nonresponders to non-pegylated interferon & ribavirin


44
PARADIGM: 800 vs 1000/1200mg RBV Plus PegIFN in HCV/HIV Coinfected Pts

- Double-blind, multicenter phase IV study of G1, treatment-naive pts

Risk Factors for Failure of HCV Tx in RIBAVIC

- Study of risk factors for failure to achieve EVR to PEG-IFN + RBV
  - 154 HIV/HCV-coinfected patients
  - EVR: ≥2 log_{10} c/mL HCV-RNA

- Increased risk of failure with:
  - Serum HIV-RNA
  - HCV genotypes 1/4
  - Abacavir use
  - Increased bilirubin levels

- Potential drug interaction between RBV and ABC may be impacting outcomes

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Univariate OR</th>
<th>Multivariate OR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum HCV-RNA</td>
<td>2.12</td>
<td>2.11</td>
<td>0.022</td>
</tr>
<tr>
<td>HCV GT 2/3</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV GT 1/4</td>
<td>9.82</td>
<td>12.13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>d4T</td>
<td>0.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABC</td>
<td>3.62</td>
<td>4.92</td>
<td>0.0083</td>
</tr>
<tr>
<td>GGT (x ULN)</td>
<td>1.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin (x ULN)</td>
<td>2.52</td>
<td>4.52</td>
<td>0.0064</td>
</tr>
</tbody>
</table>
Abacavir and SVR

Patients (n=256) taking 1 PI or 1 NNRTI and ABC plus LDV or TDF plus LDV or FTC as N(t)RTI backbone during HCV therapy

% patients achieving SVR

ITT RBV <13.2 mg/kg/day

RBV ≥13.2 mg/kg/day

p=0.02

p=0.03

p=0.4


Medscape® www.medscape.com

IL28B

Figure 2: Rate of SVR according to HCV and rs12979860 genotypes

Pineda et al CROI 2010
If he were to fail therapy would you consider...

- Long term interferon to prevent progression
- Transplantation if needed

HCV in the HIV-Infected Patient: ACTG 5178 No Benefit of Maintenance PEG-IFN

- No benefit of 18 months of maintenance
- DSMB stopped study
- Cirrhosis 18% and 21% of maintenance and observation arms

Adapted from David Thomas. ICAAC/IDSA 2008; abstract 849. Sherman and ACTG 5178 team, CROI 2008
Five-Year Graft Survival of OLT in HCV/HIV Coinfected Recipients Was Lower Than That Matched HCV-Monoinfected Patients

<table>
<thead>
<tr>
<th>Survival at</th>
<th>HIV + (N=84)</th>
<th>HIV - (N=252)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>77%</td>
<td>86%</td>
<td>NS</td>
</tr>
<tr>
<td>3 years</td>
<td>52%</td>
<td>76%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>5 years</td>
<td>37%</td>
<td>67%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Miro J. CROI 2009
Transplant in HIV/HBV Coinfection

- 1999-2007
- 75 HIV+ Liver transplants
- N=13 HIV/HBV+
  - 5 Delta+, 6 HCV+ (4 Both)
- 100% graft survival mean follow up 32 months
- HCV recurrence

Tateo et al. AIDS 2009, 23:1069–1076

So what can we all do…

- Early diagnosis and appropriate monitoring
- Vaccination
- Reduce toxicity to liver - ART, alcohol etc…
- Early and appropriate HAART
Liver in HIV-infected patients

- Opportunistic diseases
- HCV treatment
- HIV treatment NNRTIs, PIs, NRTIs
- Fatty liver disease
- Alcohol abuse/IVDU
- Hepatitis viruses
- Immune reconstitution
- Pre-existing diseases