HIV and Hep B and C co-infection

Dr. Mark Nelson

Chelsea & Westminster Hospital

Executive Committee of the British HIV Association (BHIVA)
“Support needing populations through medical assistance and the transfer of knowledge to local medical practitioners.”

Our vision for the Medical Assistance & Medical Education (MAME) Programs
Overlapping HBV & HIV Epidemics

- HIV
- Hep B

HBsAg+

5-15% of HIV

40 million

400 million

4 million
## Clinical-Epidemiologic Correlations

<table>
<thead>
<tr>
<th>HBV Endemicity</th>
<th>Location</th>
<th>Age of Infection</th>
<th>Mode of Transmission</th>
<th>Chronicity</th>
<th>HCC Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>High 10-15%</td>
<td>Asia Sub-Saharan Africa</td>
<td>Birth Toddler</td>
<td>Perinatal Horizontal</td>
<td>Likely</td>
<td>High</td>
</tr>
<tr>
<td>Low &lt; 2%</td>
<td>N. America W. Europe Scandinavia</td>
<td>Early Adulthood</td>
<td>Percutaneous Sexual</td>
<td>Rare</td>
<td>Low</td>
</tr>
</tbody>
</table>

Prevalence of Chronic Hepatitis B

HBsAg Prevalence
- > 8% - High
- 2-8% - Intermediate
- < 2% - Low

Immigration numbers summed by continent from 1996-2002
- ~ 2 million Asians
- ~ 400,000 South Americans
- ~ 930,000 Europeans
- ~ 350,000 Africans

# Anti-HBV Therapies

<table>
<thead>
<tr>
<th>Immune modulators</th>
<th>Polymerase Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-alpha</td>
<td>Lamivudine</td>
</tr>
<tr>
<td>Pegylated-Interferon-alpha</td>
<td>Adefovir</td>
</tr>
<tr>
<td></td>
<td>Entecavir</td>
</tr>
<tr>
<td></td>
<td>Telbivudine</td>
</tr>
<tr>
<td></td>
<td>Tenofovir</td>
</tr>
<tr>
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</tr>
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## Anti-HBV Therapies

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</tr>
</tbody>
</table>
Hepatitis B Therapy
Outcomes to Consider and Goals to Achieve

Ultimate goal:
- Cure
  - HBsAg clearance

Current goals:
- Viral suppression
  - ALT normalisation
- HBeAg seroconversion*
  - Remission
  - Cessation of therapy
  - Prevent cirrhosis HCC
- Short term
- Long term

Keeffe et al, 2006
Lok & McMahon, 2007

*HBeAg positive patients only
**HBV DNA Level and Risk of HCC**

<table>
<thead>
<tr>
<th>HBV DNA (copies/ml)</th>
<th>Cumulative incidence of HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;300</td>
<td>1.30</td>
</tr>
<tr>
<td>300-9999</td>
<td>1.37</td>
</tr>
<tr>
<td>10,000-99,999</td>
<td>3.57</td>
</tr>
<tr>
<td>100,000-999,999</td>
<td>12.17</td>
</tr>
<tr>
<td>&gt;1 million</td>
<td>14.89</td>
</tr>
</tbody>
</table>

IFN-α in HBV/HIV co-infection

16 RCT IFN-α vs placebo 837 HBsAg+ - 107 HIV+ included in 5 studies

<table>
<thead>
<tr>
<th>Author(Yr.)</th>
<th>n. Tx</th>
<th>n. Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoefnagle(88)</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Brook (89)</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Brook (89)</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Pol (92)</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Wong (95)</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>All</td>
<td>61</td>
<td>46</td>
</tr>
</tbody>
</table>

HBe seroconversion/negativation: HIV+ vs HIV: - 0.38 (CI 0.06-0.7 P = .02)

Puoti et al. personnal comm.
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 naïve pts
- HIV/HBV coinfected individuals should not receive ETV monotherapy

Selection of M184V following ETV treatment

Univariate analysis for selection of M184V

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total duration on ETV</td>
<td>0.05</td>
</tr>
<tr>
<td>Magnitude of HBV DNA reduction on ETV</td>
<td>0.04</td>
</tr>
<tr>
<td>HIV RNA pre-ETV therapy</td>
<td>0.87</td>
</tr>
<tr>
<td>HBV DNA pre-ETV therapy</td>
<td>0.69</td>
</tr>
<tr>
<td>Nadir CD4+ count</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Median time to M184V 148 days 98 days

Audsley J, et al. 15th CROI, Boston 2008, #63
Telbuvidine – ?anti-HIV activity

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

E Low, et al. CROI 2009;P813a

C Avila, et al. CROI 2009;P813b
Incidence of LAM Resistance in HBV and HBV/HIV Patients

Resistance to Lamivudine even at Very Low Viral Load

Hepatitis B Viral Load IU/ml

Perno International Drug Resistance Workshop 2009
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.
Study design

Primary objective
To compare the safety and efficacy of tenofovir (TDF) to lamivudine (LAM) and to combination TDF/LAM in treating HBV in ARV- naive patients with HIV/HBV co-infection over 48 weeks.

N=36

Week 12

AZT / LAM / EFV
VK

AZT / TDF / EFV
VK

LAM / TDF / EFV
VK

Week 48

Gp 1

Gp 2

Gp 3
Median HBV reduction 48 weeks
HBV DNA suppression at 48 w

On treatment

P=0.016
Kaplan Meier: HBV-free survival (MSM)

Numbers in Observation

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Observation Time (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Treatment</td>
<td>50 19 8</td>
</tr>
<tr>
<td>Treatment, No TDF</td>
<td>67 36 16</td>
</tr>
<tr>
<td>Treatment, with TDF</td>
<td>49 38 12</td>
</tr>
</tbody>
</table>

Brinkman K, et al. 20th CROI; Atlanta, GA; 2013. Abstract 33

- ESLD associated death: % total mortality
- ESLD associated death: % HBsAg+

Hepatitis and HIV testing

• Aim of study was to identify rates of HIV testing in patients with HBV and/or HCV and to assess HIV testing practice in a large UK teaching hospital

• Retrospective case note review of 185 individuals with known hepatitis infection

Which was discovered first?
The personal is political

Larry Eklund, 61, is currently serving his fifth term as a state legislator in Illinois. He is the state’s only HIV-positive legislator and jokes that he has tenure because of his term limits. Photograph by Aurora for TIME

Pioneer

Bill Roberts, 73, was diagnosed with HIV in 1985. Like many gay men of his generation, Bill buried his partner and then worked to denounce it. Photograph by Katja Hensmedium / AIDS for TIME
Available Treatments for Hepatitis C 2014 (UK)

- Interferon
- Ribavrin
- Protease Inhibitors
  - Telaprevir
  - Boceprevir
THE WINDS OF CHANGE

EARTH BOUNCE
Phase I
ABT-450/ABT-267 and/or ABT-333 (Abbott/Enanta)

Phase II
Telaprevir/VX-222 (Vertex)

Phase III
Boceprevir (Vertex)

Phase IV
Telaprevir (Vertex)

DAA combinations

NS5A inhibitors

Protease inhibitors

Polymerase inhibitors
HCV targets for therapy

“entry inhibitors”
- mAbs anti-E2/CD81
- PRO 206 Ezetimibe

miRNA
- ISIS 14803 (antisense)
- AVI-4066 (antisense)
- Heptazyme (ribozyme)
- VGX-410C (small molecules IRES inhibitor) TT 033 (siRNA)

Protease inhibitors

Drugs active on viral enzymes
Drugs active on host cell enzymes

Replication inhibitors:
- NS5b
- NNI
- NI
- NSa
- Ciclophyllin B

CRICKET
as explained to a foreign visitor

You have two sides, one out in the field and one in.

Each man that's in the side that's in goes out and when he's out he comes in and the next man goes in until he's out.

When they are all out the side that's out comes in and the side that's been in goes out and tries to get those coming in out.

Sometimes you get men still in and not out.

When both sides have been in and out including the not outs.

That's the end of the game

HOWZAT!
Direct Acting Antivirals against HCV
Hepatitis C (HCV) could be attacking your liver and you may not even know it. Without a liver, you can’t live. To find out more information about this deadly disease, visit www.cdc.gov/hepatitis.
Toxicity
Drug Resistance
IF HEP C WAS ATTACKING YOUR FACE
INSTEAD OF YOUR LIVER, YOU’D DO
SOMETHING ABOUT IT.

READY TO FIGHT BACK?
Why do you not want to have hepatitis C and HIV
Why do you not want to have hepatitis C and HIV

- Transmission

**Causes of Hepatitis C**

- Blood Transfusions
- Sharing of needles & other drug taking equipment
- Mother to baby transmission
- Body piercing
- Tattooing
- Unprotected sex with multiple partners
Acute HCV among HIV+ MSM

**USA**
- **55 cases**
- Prevalence chronic HCV/HIV: 15 – 30%: 180,000 – 360,000

**Lebanon**
- **1 case**
- Prevalence chronic HCV/HIV: 49%: 1,500

**Canada**
- **~30 cases**
- Prevalence chronic HCV/HIV: 19%: 11,200

**Europe**
- **1068 cases**
- Prevalence chronic HCV/HIV: 15 – 30%: 185,500
- **UK**
  - 552
- **Germany**
  - 157
- **France**
  - 126
- **Netherlands**
  - 97
- **Belgium**
  - 69
- **Swiss**
  - 23
- **Italy**
  - 21
- **Denmark**
  - 13
- **Spain**
  - ~8

**Taiwan**
- **28 cases**
- Prevalence chronic HCV/HIV: 55%: 8,800

**Australia**
- **47 cases**
- Prevalence chronic HCV/HIV: < 1%: 1,000

References:
Social sites and apps have made finding Chem-Sex easy and anonymous. IDU or 'slamming' has become more commonplace.
Summary

HCV transmission in HIV-positive MSM

Internet

Drug type (‘club drugs’)

High-risk sexual practices

STIs

Shared routes (intranasal)
Safety First!

www.PREVAIDS.org
Seminal Positivity for HCV

P=0.033

Briat AIDS 2005
Hepatitis C Genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>NEAT</th>
<th>EUROSIDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>29</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>15</td>
</tr>
</tbody>
</table>
Results: Genotype

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate (log10)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from baseline (years) [SLOPE]</td>
<td>0.024</td>
<td>(0.0042, 0.043)</td>
<td>0.017</td>
</tr>
<tr>
<td>HCV Genotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-0.10</td>
<td>(-0.35, 0.15)</td>
<td>0.42</td>
</tr>
<tr>
<td>3</td>
<td>-0.21</td>
<td>(-0.31, -0.12)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>4</td>
<td>-0.21</td>
<td>(-0.34, -0.084)</td>
<td>0.0012</td>
</tr>
</tbody>
</table>

*Adjusted for: age, gender, race, region, HIV-RNA, CD4, HCV genotype, HCV assay, HBsAg, HIV risk group, cART, HCV infection date.
Comparison of HCV blood viral load between patients presenting with HCV RNA positive seminal fluid (n=7) and patients presenting with HCV RNA-negative seminal fluid (n=11)

The bar indicates the median HCV viral load in blood (log/mL)

HCV RNA in seminal fluid

Briat AIDS 2005
Increased risk of MTC Transmission HCV with HIV.

Why do you not want to have hepatitis C and HIV

- Transmission
- Stigma
Why do you not want to have hepatitis C and HIV

- Transmission
- Stigma
- More Rapid Progression of disease
No Association of Hepatitis C with AIDS
Defining Events

Risk Ratio

Hung et al [11]
Klein et al [19]
Rockstroh et al [54]
Stebbing et al [59]
Sulkowski et al [55]
Sullivan et al [56]
Tedaldi et al [57]
Combined

Risk Ratio

[.25, .5, 1.12, 3, 6, 9]
Increased Risk of Cirrhosis and ESLD Due to HIV/HCV Coinfection

**Histologic Cirrhosis**

<table>
<thead>
<tr>
<th>Relative Risk</th>
<th>Makris (UK)</th>
<th>Soto (Spain)</th>
<th>Pol (France)</th>
<th>Benhamou (France)</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV Only</td>
<td>.76</td>
<td>1.0</td>
<td>2.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV/HCV</td>
<td>1.0</td>
<td>10.83</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

** Decompensated Liver Disease**

<table>
<thead>
<tr>
<th>Relative Risk</th>
<th>Eyster (USA)</th>
<th>Telfer (UK)</th>
<th>Makris (UK)</th>
<th>Lesens (Canada)</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV Only</td>
<td>.61</td>
<td>1.0</td>
<td>6.14</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>HIV/HCV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Why do you not want to have hepatitis C and HIV

- Transmission
- Stigma
- More Rapid Progression of disease
- Increase in now known HIV related comorbidities
HIV/HCV co-infection may result in multi-systemic disorders

- Global cognitive impairment
- Cognitive-motor impairment
- Dementia
- Peripheral neuropathy
- Cerebrovascular disease
- Acute myocardial infarction
- Opportunistic infections
- Wasting syndrome
- Proteinuria
- Acute renal failure
- Chronic kidney disease
- Osteonecrosis
- Osteoporosis
- Bone fracture
- CD4 apoptosis
- Abnormal T-cell responses and cytokine production
- Cytotoxic T-cell accumulation in liver
- CD4 recovery post-HAART
- Severe immunodeficiency
- Diabetes mellitus
- Insulin resistance
- Steatosis
- Fibrosis
- Cirrhosis
- End-stage liver disease
- Liver-related death
- Microbial translocation
- Global cognitive impairment
- Cognitive-motor impairment
- Dementia
- Peripheral neuropathy
- GI tract
- Neurologic disease
- Cardi-vascular
- Immune activation
- Immune dysregulation
- HIV disease progression
- Liver disease
- Bone disorders
- GI tract
- Metabolic disorders

GI: gastrointestinal; HAART: highly active antiretroviral therapy

Top 12 Ways to Avoid a Heart Attack

Defrim Kërçagu, MD
Figure 1. Kaplan-Meier curves showing the occurrence of overall deaths (A), liver-related deaths (B), non-liver related deaths (C), and non-liver-related, non-AIDS-related deaths (D) in 1599 patients coinfected with human immunodeficiency virus and hepatitis C virus, with or without sustained virological response after therapy with interferon plus ribavirin. Abbreviation: SVR, sustained virological response.
Why do you not want to have hepatitis C and HIV

- Transmission
- Stigma
- More Rapid Progression of disease
- Increase in now known HIV related comorbidities
- Increase in HAART toxicity
Incidence of Grade 2 or Above Liver Enzyme Elevation

Why do you not want to have hepatitis C and HIV

- Transmission
- Stigma
- More Rapid Progression of disease
- Increase in now known HIV related comorbidities
- Increase in HAART toxicity
Negative

Think
Positive
## HCV: Probability of the presence of viral variants

**Hepatitis C virus:**
- Error rate during replication: ~9600 nucleotides
- Viral turnover: ~$10^{-4} – 10^{-5}$ per copied nucleotide
- ~$10^{12}$ virions produced every day

<table>
<thead>
<tr>
<th>Number of nucleotide change</th>
<th>Probability of generation after one round of replication</th>
<th>Number of virions with nucleotide change(s) produced per day</th>
<th>Number of all possible nucleotide mutants</th>
<th>Fraction of all possible mutants created per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>91%</td>
<td>$9.1 \times 10^{11}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8.7%</td>
<td>$8.7 \times 10^{10}$</td>
<td>$2.9 \times 10^{4}$</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>0.4%</td>
<td>$4.2 \times 10^{9}$</td>
<td>$4.1 \times 10^{8}$</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>0.001%</td>
<td>$1.3 \times 10^{8}$</td>
<td>$4.0 \times 10^{12}$</td>
<td>$3.4 \times 10^{-5}$</td>
</tr>
</tbody>
</table>

- HCV genome ~ 9600 nucleotides; the average number of changes per genome is 0.096 per replication cycle
- Before treatment, a new virion has a probability of 91% to carry an unmutated genome and 8.7% to carry one substitution

### Not all variants survive
- Dead mutations (variants that can not replicate)
- Immune sensitive mutations (variants eliminated by the immune system)

---

Emergence of Pre-existing Resistant Variants During Treatment with DAA

- Baseline HCV RNA
- Drug Potency
- Viral breakthrough
- Resistance Barrier

Timeline:
- Before Treatment
- Time on Treatment with DAA Alone

Viral load changes over time during treatment with DAA alone, showing the emergence of resistant variants.
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 $\geq$ LLQ at TW 24 were offered open-label PEG2b/RBV+BOC via a cross-over arm
Virologic Response Over Time†

% HCV RNA Undetectable

† Three patients undetectable at FW4 have not yet reached FW12 and were not included in SVR12 analysis.

Sulkowski M et al., 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 47
Study Design

**Part A: no ART**

<table>
<thead>
<tr>
<th>Weeks</th>
<th>T/PR</th>
<th>PR</th>
<th>Follow-up</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>TVR + PR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>PR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>Pbo + PR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>PR</td>
<td></td>
<td>SVR</td>
<td></td>
</tr>
<tr>
<td>72</td>
<td></td>
<td></td>
<td>Follow-up</td>
<td>SVR</td>
</tr>
</tbody>
</table>

**Part B: ART (EFV/TDF/FTC or ATV/r + TDF + FTC or 3TC)**

<table>
<thead>
<tr>
<th>Weeks</th>
<th>T/PR</th>
<th>PR</th>
<th>Follow-up</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>TVR + PR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>PR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>Pbo + PR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>PR</td>
<td></td>
<td>SVR</td>
<td></td>
</tr>
<tr>
<td>72</td>
<td></td>
<td></td>
<td>Follow-up</td>
<td>SVR</td>
</tr>
</tbody>
</table>

(EFV)=efavirenz; (TDF)=tenofovir; (FTC)=emtricitabine; (ATV/r)=ritonavir-boosted atazanavir; (3TC)=lamivudine;
(T) TVR=telaprevir 750 mg q8h or 1125 mg q8h (with EFV); Pbo=Placebo; (P) Peg-IFN=pegylated interferon alfa-2a (40 kD) 180 µg/wk; (R)
RBV=ribavirin 800 mg/day or weight-based (1000 mg/day if weight <75 kg, 1200 mg/day for if weight ≥75 kg; France, Germany)
Roche COBAS® TaqMan® HCV test v2.0, LLOQ of 25 IU/mL (pts with values below 25IU/mL were reported as <25 detectable or undetectable)
Prior to Week 24 visit, 1 patient in this cohort was lost to follow up. SVR24 was imputed based on SVR12 for this patient.

### HIV/HCV coinfected patients: SVR at post-treatment week 24 (SVR$_{24}$)

<table>
<thead>
<tr>
<th></th>
<th>No ART</th>
<th>EFV/TDF/FTC</th>
<th>ATV/r/TDF/FTC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>T/PR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n/N</td>
<td>5/7</td>
<td>11/16</td>
<td>12/15*</td>
<td>28/38</td>
</tr>
<tr>
<td>HIV/HCV coinfected patients with SVR (%)</td>
<td>71</td>
<td>69</td>
<td>80</td>
<td>74</td>
</tr>
<tr>
<td>PR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n/N</td>
<td>2/6</td>
<td>4/8*</td>
<td>4/8</td>
<td>10/22</td>
</tr>
<tr>
<td>HIV/HCV coinfected patients with SVR (%)</td>
<td>33</td>
<td>50</td>
<td>50</td>
<td>45</td>
</tr>
</tbody>
</table>

T/PR, telaprevir in combination with peginterferon alfa-2a and ribavirin; PR, peginterferon alfa-2a and ribavirin

Boceprevir
Telaprevir
## DAA Classes and Subclasses

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Subclass</th>
<th>Potency</th>
<th>Resistance Barrier</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td>1st Generation first wave i.e. Telaprevir/Boceprevir</td>
<td>Medium-Low</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>1st Generation 2nd wave i.e. Faldaprevir/Simeprevir/Asunaprevir ABT450/r</td>
<td>Medium</td>
<td>Low</td>
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<tr>
<td></td>
<td>2nd Generation MK5172 ABT 493</td>
<td>High</td>
<td>High except HCVG3</td>
</tr>
<tr>
<td><strong>NS5a Inhibitor</strong></td>
<td>1st Generation Daclatasvir, Ledipasvi,r ABT 267</td>
<td>High</td>
<td>Medium- High except HCV G3 &amp; 1a</td>
</tr>
<tr>
<td></td>
<td>2nd Generation MK 8742 GS 5816 ABT530</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td><strong>NN Polymerase Inhibitors</strong></td>
<td>ABT 333 GS 9669 Deleobuvir BMS 791325</td>
<td>Low-Medium</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Nucleos/tides Poly</strong></td>
<td>1st Generation: Mericitabine</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Polymerase inhibitors</td>
<td>2nd Generation : Sofosbuvir</td>
<td>High Lower in HCV G1b and 3</td>
<td>High</td>
</tr>
</tbody>
</table>
# DAA Classes and Subclasses

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Subclass</th>
<th>Potency</th>
<th>Resistance Barrier</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td>1st Generation 1st wave i.e. Telaprevir/Boceprevir</td>
<td>Medium-Low</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>1st Generation 2nd wave i.e. Telaprevir/Boceprevir</td>
<td>Medium</td>
<td>Low</td>
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<td>1st Generation: Mericitabine</td>
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<td>High</td>
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<tr>
<td><strong>2nd Generation : Sofosbuvir</strong></td>
<td></td>
<td>High Lower in HCV G1b and 3</td>
<td>High</td>
</tr>
</tbody>
</table>
SOF + PegIFN + RBV in Treatment-Naïve HIV/HCV Co-infected Patients

Phase 2 Study 1910 Design

- Single-center, open-label, single-arm trial to assess the safety and efficacy of a 12-week course of SOF + PegIFN + RBV for the treatment of patients with chronic HCV, co-infected with HIV

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>12</th>
<th>16</th>
<th>24</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV GT 1–4 Treatment-naïve, on stable HIV ARV</td>
<td>N=23</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Primary endpoint: SVR12

No response guided therapy

Rodriguez-Torres M, et al. IDWeek 2013; San Francisco, CA. Poster #714
There was no on-treatment HCV or HIV virologic breakthrough.
Relapse occurred in 1 patient and accounted for all virologic failures.
Two patients discontinued treatment early due to adverse events, one of whom achieved SVR12 after receiving 8 weeks of SOF + PegIFN + RBV.

Rodriguez-Torres M, et al. IDWeek 2013; San Francisco, CA. Poster #714
SOF + PegIFN + RBV in HIV/HCV Coinfection

SVR12 According to HCV Genotype and HIV ARV Regimen

GT 1
GT 1a
GT 1b
GT 2
GT 3
GT 4

HCV RNA < LLOQ (%)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>89</th>
<th>87</th>
<th>100</th>
<th>100</th>
<th>100</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>17/19</td>
<td>13/15</td>
<td>4/4</td>
<td>1/1</td>
<td>2/2</td>
<td>1/1</td>
</tr>
</tbody>
</table>

SVR12 (%)

<table>
<thead>
<tr>
<th>Combination</th>
<th>89</th>
<th>88</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTC/TDF + Protease Inhibitor</td>
<td>8/9</td>
<td>7/8</td>
<td>6/6</td>
</tr>
<tr>
<td>FTC/TDF + NNRTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FTC/TDF + Raltegravir</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NNRTI, non-nucleoside reverse transcriptase inhibitor

Rodriguez-Torres M, et al. IDWeek 2013; San Francisco, CA. Poster #714
Genetic barrier to resistance can be increased in HCV G1 by combination drug regimens

No relationship with IFN sensitivity no IFN related side effects

Baseline

Anchor drug

Sensitive virus

Resistant virus

NN-NS5B in + NS5A + PI + RBV

Sofosbuvir + NS5A / PI + RBV
Summary of EASL 2014

100%
Sofosbuvir + Simeprevir + RBV for 12 weeks

Sofosbuvir + Daclatasvir + Ribavirin for 12-24 weeks in 167 HCV G1 (32 F4)
3D combo + R in HCV Genotype 1 (1a + 1b; experienced + naives) stratified according to the presence of cirrhosis

Kowdley et al. NEJM 2014; Lawitz et al AASLD 2013; Abbvie Press Release Jan 31st 2014
PEARL-III: Study Design

N = 210
ABT-450/r/ABT-267 + ABT-333 + RBV

N = 209
ABT-450/r/ABT-267 + ABT-333 + Placebo for RBV

Study drug dosing
Day 0

Assess for SVR\textsubscript{12}
Week 12

48-wk follow-up
Week 24

Week 60

ABT-450/r/ABT-267: 150 mg/100 mg/25 mg QD
ABT-333: 250 mg BID
RBV: 1000 mg if body weight was <75 kg, 1200 mg if body weight ≥75 kg, or matching placebo

Adapted from the K Rajender Reddy presentation at CRDI on March 4, 2014
SVR_{12} \geq 99\% \text{ Achieved After 12 Weeks with 3-DAA} \pm \text{RBV}

- 3-DAA + RBV: 99.5\% (209/210 patients)
- 3-DAA: 99.0\% (207/209 patients)

ITT population

Adapted from the K. Rajender Reddy presentation at CRDI on March 4, 2014
C-WORTHY: MK-5172 (PI)+ MK-8742(NS5a) ± RBV in Treatment-Naive GT1 HCV Pts

- Randomized phase II trial

Pts with GT1a randomized 1:1 to RBV arms only; patients with GT1b randomized 1:1:2 into all 3 arms

C-WORTHY: Virologic Response Rates With MK-5172 + MK-8742 ± RBV

- All treatment regimens safe and well tolerated
- No early discontinuations due to drug-related AEs

Study Design

GT 1-4 HIV-HCV (PHOTON-1 and 2)

- Broad inclusion criteria
  - Compensated cirrhosis permitted; no platelet cutoff
  - Hemoglobin: \( \geq 12 \text{ mg/dL} \) (males); \( \geq 11 \text{ mg/dL} \) (females)
- Wide range of ART regimens allowed
  - Undetectable HIV RNA for >8 weeks on stable ART regimen
- Baseline CD4 count
  - ART treated: >200 cells/\( \mu \text{L} \); ART untreated: > 500 cells/\( \mu \text{L} \)
Results: SVR12 for HCV genotype 1, 2 and 4

GT 1-4 HIV-HCV (PHOTON-1 and 2)

- **GT 1-TN 24 Weeks:** 182/226 (81%)
- **GT 2-TN 12 Weeks:** 40/45 (89%)
- **GT 2-TE 24 Weeks:** 27/30 (90%)
- **GT 4-TN 24 Weeks:** 26/31 (84%)

Relapse, n (%):
- GT 1: 39 (17%)
- GT 2: 1 (<1%)
- GT 4: 2 (<1%)

Breakthrough, n (%):
- GT 1: 1 (<1%)
- GT 2: 1 (2%)
- GT 4: 1 (3%)

Lost to follow-up, n (%):
- GT 1: 2 (<1%)
- GT 2: 1 (2%)
- GT 4: 0

Withdrawn consent, n (%):
- GT 1: 2 (<1%)
- GT 2: 2 (4%)
- GT 4: 1 (3%)

---

SVR12 (%)
Results: SVR12 for HCV genotype 3
GT 1-4 HIV-HCV (PHOTON-1 and 2)

<table>
<thead>
<tr>
<th></th>
<th>GT 3 TN 12 Weeks</th>
<th>GT 3 TN 24 Weeks</th>
<th>GT 3 TE 24 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse, n (%)</td>
<td>12 (29)</td>
<td>4 (7)</td>
<td>7 (11)</td>
</tr>
<tr>
<td>Breakthrough, n (%)</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Lost to follow-up, n (%)</td>
<td>2 (5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Withdrawn consent, n (%)</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
</tr>
</tbody>
</table>
TURQUOISE-I Methods: Part 1a Study Design (N = 63)

Phase 2/3* multicenter, randomized, open-label study; HCV/HIV-1 coinfected patients

Open-label treatment

3D + RBV (N = 31)

3D + RBV (N = 32)

Day 1  Week 12  Week 24  Week 36

SVR12  SVR12

All patients followed up for 48 weeks after end of HCV treatment

3D: coformulated ombitasvir/ABT-450/r, 25/150/100 mg once daily; dasabuvir, 250 mg twice daily

RBV: 1000 or 1200 mg daily according to body weight (<75 kg and ≥75 kg, respectively) in 2 divided doses

*Part 1: phase 2 pilot cohort (part 1a and part 1b); part 2: phase 3 cohort
TURQUOISE-I Results: Intent-to-Treat Virologic Response Rates

*2 patients in the 24-week group had recurrence of HCV viremia believed to be due to HCV re-infection.

EOTR, end of treatment response; RVR, rapid virologic response.
Study Design

Open label
- **LDV 90mg/ SOF 400 mg STR for 12 wks**
- Treatment-naive GT-1 patients without cirrhosis
- No ribavirin administered
- **ARVs: TDF/FTC, EFV, RILP and RALT**

**REFERENCES:**
1. Osinusi A et al; AASLD, 2014. Poster
Treatment Response
SVR12 in HCV Mono-infected and HCV/HIV Co-infected
SOF + RBV ± PegIFN x 12 or 24 weeks

Similar response rates in HCV/HIV co-infected patients
compared to HCV mono-infected patients

SVR12 from VALENCE includes pooled analysis from all patients (treatment-naïve and –experienced) by genotype and duration of therapy
*GT1 SVR24 of 75%; GT3 TE SVR24 of 88%

SVR 12 HIV/HCV vs HCV mono-infection

Trend for better virologic responses in co-infected patient is potentially explained by a selection bias

Martel V et al CID 2013
ELECTRON: Sofosbuvir/Ledipasvir FDC + RBV for 6 Wks in Naive GT1 HCV Pts

- Open-label phase II trial in GT1 HCV pts
- 68% SVR12 rate with 6 wks of SOF/LDV FDC + RBV lower\(^1\) than SVR rates previously achieved with 8 wks\(^2\) or 12 wks\(^3\) treatment with this regimen

Sofosbuvir 400 mg QD; ledipasvir 90 mg QD; weight-based RBV 1000-1200 mg/day

Duration of SOF/LDV + RBV in Tx-Naive Pts

Study Design

- **Sofosbuvir** (nucleotide NS5B inhibitor) 400 mg / **ledipasvir** (NS5A inhibitor) 90 mg once daily
- **GS-9669** (non-nucleoside NS5B inhibitor) 500 mg once daily
- **GS-9451** (a protease NS3/4 inhibitor) 80 mg once daily

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>6</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment naïve</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All stages fibrosis</td>
<td>Sofosbuvir + Ledipasvir (n=20)</td>
<td></td>
<td>SVR12</td>
</tr>
<tr>
<td>Treatment naïve</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis excluded</td>
<td>Sofosbuvir + Ledipasvir + GS-9669 (n=20)</td>
<td></td>
<td>SVR12</td>
</tr>
<tr>
<td>Treatment naïve</td>
<td></td>
<td></td>
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<tr>
<td>Cirrhosis excluded</td>
<td>Sofosbuvir + Ledipasvir + GS-9451 (n=20)</td>
<td></td>
<td>SVR12</td>
</tr>
</tbody>
</table>

**48 weeks**
Treatment Response (ITT)

- Sofosbuvir + Ledipasvir (n=20)
- Sofosbuvir + Ledipasvir + GS-9669 (n=20)
- Sofosbuvir + Ledipasvir + GS-9451 (n=20)

<table>
<thead>
<tr>
<th></th>
<th>Week 4</th>
<th>EOT</th>
<th>SVR 4</th>
<th>SVR 12</th>
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</thead>
<tbody>
<tr>
<td>% of patients with HCV RNA &lt; LLOQ (ITT)</td>
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<td></td>
<td></td>
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<tr>
<td>Sofosbuvir + Ledipasvir (n=20)</td>
<td>90</td>
<td>100</td>
<td>100</td>
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<tr>
<td>Sofosbuvir + Ledipasvir + GS-9669 (n=20)</td>
<td>100</td>
<td>100</td>
<td>95</td>
<td>100</td>
</tr>
<tr>
<td>Sofosbuvir + Ledipasvir + GS-9451 (n=20)</td>
<td>100</td>
<td>95</td>
<td>100</td>
<td>100</td>
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</tbody>
</table>
HIV TREATMENT AS PREVENTION...WHAT ABOUT HCV?
NEED DYNAMIC TRANSMISSION MODEL TO ASSESS IMPACT OF TREATMENT ON PREVALENCE/INCIDENCE

Figure 1. Model schematic. S: Susceptible individuals; A<sub>A</sub>: Acute asymptomatic cases; A<sub>S</sub>: Acute symptomatic cases; T<sub>A</sub>: Treated Acute symptomatic cases; R: Recovered infections; C: Chronic infections; T<sub>C</sub>: Treated Chronic infections.

doi:10.1371/journal.pone.0034548.g001
MODELLING PROJECTIONS: TOWARDS ELIMINATION IN EDINBURGH WITH DAA THERAPY

What could possibly go wrong?
<table>
<thead>
<tr>
<th></th>
<th>ATVr</th>
<th>DRVr</th>
<th>LPW</th>
<th>EFV</th>
<th>ETV</th>
<th>RPV</th>
<th>Ral</th>
<th>DTG</th>
<th>EVGc</th>
<th>MVC</th>
<th>TDF</th>
<th>ABC</th>
<th>3TC</th>
<th>FTC</th>
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<tr>
<td><strong>Teleprevir</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60%</td>
<td>65%</td>
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</tr>
<tr>
<td><strong>Boceprevir</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>65%</td>
<td>64%</td>
<td>45%</td>
<td>41%</td>
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<tr>
<td><strong>Simeprevir</strong></td>
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<td>72%</td>
<td>41%</td>
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<td>11%</td>
<td>12%</td>
<td></td>
<td></td>
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<tr>
<td><strong>Sofosbuvir</strong></td>
<td></td>
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<td></td>
<td>+15%</td>
<td>12%</td>
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<tr>
<td><strong>Ledipasvir</strong></td>
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<td>11%</td>
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<td>12%</td>
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<tr>
<td><strong>Faldeprevir</strong></td>
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<td><strong>Daclatasvir</strong></td>
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<td><strong>MK-5172</strong></td>
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</tr>
</tbody>
</table>

* Co-formulations  * Dose modification required

Data from USP1, CROI, EASL, AASLD, EACS, ICAAC, PK workshop, HepDART 2013-2014 www.hep-druginteractions.org

S.Khoo, 15th Intl. W’shop, 2014
Your EKG is showing a huge financial strain are you alright?

How shall we frighten them this year?
<table>
<thead>
<tr>
<th>Episode</th>
<th>Genotype</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>PEG/RBV</td>
<td>ETR</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>PEG/RBV</td>
<td>SVR</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>NIL</td>
<td>Clearance</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>NIL</td>
<td>Clearance (?)</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>PEG/RBV</td>
<td>SVR</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>PEG/RBV</td>
<td>SVR</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>PEG/RBV</td>
<td>Null Response(?)</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>PEG/RBV/PI</td>
<td>SVR</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>PEG/RBV/TPV</td>
<td>?</td>
</tr>
</tbody>
</table>
HCV Reinfection Incidence

Post-treatment: 9.6 per 100py (95%CI 6.6-14.1/100py)

Overall: 7.8 per 100 py (95%CI 5.8-10.5 per 100py)

Post-spontaneous clearance: 4.2 per 100py (95%CI 1.7-10/100py)

- Comparing reinfection post-treatment versus post-spontaneous clearance: p=0.15
Thank you

For further information please contact:

Jean-Marc Debricon
CEO
jm@greenshootsfoundation.org
Mobile: +44 7595 600 766

UK charity number 1138412 US 501(c)(3) registered

General enquiries: info@greenshootsfoundation.org
Website: www.greenshootsfoundation.org