When to treat HIV/HCV co-infection

Graham R Foster
Professor of Hepatology
QMUL
When to treat HIV/HCV
Twist or Stick?

• I have received consultancy fees from:-

• Roche, Gilead, AbbVie, BI, BMS, Idenix, Regulus, Novartis, Chughai, Merck, Janssen
Twist or Stick?

• Todays drugs

• What is emerging

• HIV studies

• My opinion
Twist or Stick?

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Genotype 1 – Good Drugs on the market PegIFN/Ribavirin and Protease inhibitors

SVR (%)

<table>
<thead>
<tr>
<th></th>
<th>PR48</th>
<th>T12PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N</td>
<td>158/361</td>
<td>659/903</td>
</tr>
<tr>
<td>SVR (%)</td>
<td>44</td>
<td>72–75*</td>
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* p<0.001 vs PR48 in ADVANCE (75% versus 44%)

Sherman KE, et al. Hepatology 2010;52(Suppl.):401A
Genotype 1 – Good Drugs on the market PegIFN/Ribavirin and Protease inhibitors

WORK WELL IN CO-INFECTION

Beware DDIs

SVR (%)

n/N = 158/361

PR48

72–75*

T12PR

659/903

* p<0.001 vs PR48 in ADVANCE (75% versus 44%)

Sherman KE, et al. Hepatology 2010;52(Suppl.):401A
Telaprevir SVR rates by fibrosis stage in treatment-naïve patients

SVR, considered virologic cure, was defined as HCV RNA undetectable 24 weeks after last planned dose.

Response of HCV G3 patient subgroups to PegIFN/RBV

Current Drugs - not perfect

• For G1 – reasonable efficacy, high side effects
• For G2/3 – good efficacy, moderate side effects

• In cirrhosis efficacy falls, side effects rise

DO NOT LET YOUR PATIENT GET CIRRHOSIS
Twist or Stick?

- Todays drugs
- What is emerging
- HIV studies
- My opinion
Specific targets for HCV treatment: protease, polymerase and NS5A inhibition

New Protease Inhibitors
New Protease Inhibitors
(With Peg + Riba)

Results are for separate trials for each compound, not head-to-head studies, in treatment-naïve patients also receiving PegIFN/RBV.

Hatched regions indicate ranges of results.

QD, once daily; RGT, response-guided therapy; SVR, sustained virological response; TID, three times daily.

1. Incivo EU SmPC 2011; 2. Victrelis EU SmPC 2011;
New protease inhibitors

Restricted to the US viral strains

Early data in HIV encouraging

Fewer DDIs

(Not as good as they pretend they are)
NS5A Inhibitors
Daclatasvir + PR

DCV arms RGT criterion

SVR: 75-87%

PDR <LLOQ Wk4 + <LOD Wk 12

G1a

G1b

SVR:

PR48 DCV 20/PR DCV 60/PR

Hézode et al, AASLD 2012 (SVR 12 analysis), abstract 755; TVR EU SmPC

PDR: protocol defined response
NS5A Inhibitors

- Quirky
- Large variation in efficacy
- Good to work with
NS5B – Non Nucleotides
NS5B – Non Nucleotides

Very unpredictable

Generally G1 specific
Nucleotides
Sofosbuvir with PEG-IFN + RBV

- NEUTRINO Phase III trial
  - Sofosbuvir plus PEG-IFN + RBV* for 12 weeks
  - Treatment naïve, GT1 (89%), 4, 5 or 6 (N=327)
    - 17% had compensated cirrhosis
  - Primary endpoint: SVR12

![Bar chart showing patients achieving SVR (%)](chart)

*Dose administered according to body weight
†Last observed measurement

Nucleotides

- Fast
- Effective
- Cures all strains
- Side effect free

(Too good to be true)
What about interferon free?

• Interferon is horrid - can we go to interferon free?
Playing Tag (I)

Protease Inhibitor + Non – Nuc/NS5A
BI 201335 + BI207127 ± R (SOUND-C2)

- Non cirrhotics TN
- 16-40 week
- SVR12 (with RBV):
  - G1a: 38-47%
  - G1b: 63-83%

SVR12 (with RBV):
Daclatasvir + Asunaprevir (AI-447-017)

- G1b Null R and IFN ineligible/intolerant
- non cirrhotic, japanese
- 24W
- SVR24:
  - 91% in Null R (N=21)
  - 64% in IFN inel/intol (N=22)

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Two drugs

• Great for G1b

• Lots of combinations emerging

• May be very cost effective
Two drugs (PI + X) is good

• But not good enough – send in the boys!
AVIATOR: SVR12 Rates With ABT-450/RTV, ABT-267, ABT-333, and RBV

- SVR12 rates higher in pts with HCV GT1b, but also high in pts with HCV GT1a
  - 12-wk regimen with all 3 DAAs + RBV produced highest SVR12 rates
- No drug-related SAEs reported; 2 pts discontinued tx due to drug-related AEs

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What about the alternatives?

Sofosbuvir + Ribavirin 24 weeks

Cures 68% of tough patients

(Kotttilil – JAMA 2013)
Does Superman need a friend
GS-7977+DCV for 24 weeks

*1 patient required addition of peg-IFN/RBV, 1 patient with relapse at Week 4
**2 patients lost to follow-up (following Week 12 and 24 visits)

GS-7977+DCV for 24 weeks

<table>
<thead>
<tr>
<th></th>
<th>GT1 TN</th>
<th>GT2/3 TN</th>
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<tbody>
<tr>
<td>N=15</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>N=14</td>
<td>100</td>
<td>88*</td>
</tr>
<tr>
<td>N=16</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>N=14</td>
<td>86**</td>
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= < LLOQ and detectable

Sofosbuvir +

- Sofosbuvir + ‘anything potent’ looks wonderful
- Sofosbuvir + Ledipasvir (NS5A) = ~100%
- Sofosbuvir + Simeprevir (NS3) = ~100%
G2
-Current Therapy

• Interferon therapy for G2 is over

• FISSION trial – SVR >90% for Sofos+Ribavirin
  (Lawitz NEJM 2013)

• PHOTON trial (HIV co-infected) – SVR 81%
## Genotype 3

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<th>G3 16 WEEKS</th>
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<td>21%</td>
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Jacobson NEJM 2013
### IFN Intolerant and IFN treated G3

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Jacobson NEJM 2013
### IFN Intolerant and IFN treated G2 and G3

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Jacobson NEJM 2013
Genotype 3

- PHOTON trial (G3 + HIV)
- Sofosbuvir + Ribavirin – SVR = 67% (N=42)

- Breaking news suggests 24 weeks of Sofosbuvir+ Ribavirin may cure G3
Nucleotide struggles with G3
We are nearly there...
We are nearly there...

Genotype 1

• Powerful drugs with Peg+ Riba (PIs, Nucs)

• Multiple PI drug regimes without Peg
  G1b = PI + 1, G1a = PI + 2 (Abbott, Nuc+NS5A)

• Sofosbuvir + AN Other – almost perfect!
We are nearly there....

Genotype 2
• Nuc + Ribavirin – Game over

Genotype 3
• Struggling
• We need a partner for the nuc
Twist or Stick?

• Todays drugs

• What is emerging

• HIV studies

• My opinion
So What About Co-Infection

• Too little data to know!

• Trials for some combinations are under way but there is inadequate data to comment

• Early data suggests excellent results

• So lets speculate.........
Co-infection
Crystal Ball

G1

• IFN + regimes will work
  (Drug- drug interactions/side-effects)

• IFN Free regimes will work very well
  (Much better tolerated)
Co-infection
Crystal Ball

G2

- New regimes will be spectacular
Co-infection
Crystal Ball

G2

• New regimes will be spectacular

G3

• New regimes will be pants
Twist or Stick?

- Todays drugs
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Co-Infection
What do I do

• All patients with cirrhosis who are ‘edgy’ but treatable – offer therapy

• For G1 ‘peri-transplant’ BEG for all oral combo

• For G1 early disease - wait
Co-Infection
What do I do

• G2 mild – wait

• G3 – Try current therapy
Co-Infection
A word to the wise
Co-Infection
A word to the wise

• There is no money (there really isn’t)

• The days of protection for HIV are gone

• The new drugs may be available but not funded for early, treatment naive patients
Co-Infection
A word to the wise

• There is no money (there really isn’t)

• The days of protection for HIV are gone

• The new drugs may be available but not funded for early, treatment naive patients

• I tell my patients you may have to wait 5 years
New Therapies for HCV/HIV co-infection

- The superheroes are in play
- The optimal combinations are emerging
- The costs remain to be seen
The Future

• Oral combination therapy for everyone is very close

• It will be here in 5 years
The Future

• Oral combination therapy for everyone is very close

• It will be here in 5 years

• For NOW
  • Sick patients need Peg+Riba+/-PI
  • Mild patients should wait