Debate: Do We Need More HCV Drugs

Con Standpoint

18th Antivirals PK Workshop,
Friday 16th June 2017, Chicago

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University Hospital Bonn, Bonn, Germany
Conflict of Interest: JKR

- Honoraria for lectures and/or consultancies from Abbott, AbbVie, Bionor, BMS, Cipla, Gilead, Janssen, Merck, Roche, ViiV.
- Research grants from Dt. Leberstiftung, DZIF, NEAT ID.
This debate is not about who is more beautiful but really do we need even more HCV DAAs than we already have....
HCV DAAs

5’ UTR → Core → E1 → E2 → p7 → NS2 → NS3 → NS4B → NS5A → NS5B → 3’ UTR

Protease

Ribavirin

NS3 Protease Inhibitors

Telaprevir
Beceprevir
Simeprevir
Paritaprevir
Asunaprevir
Grazoprevir
Glecaprevir
Voxilaprevir

-previr

NS5A Replication Complex Inhibitors

Daclatasvir
Ledipasvir
Ombitasvir
Velpatasvir
Elbasvir
Pibrentasvir
GS-5816
Ruzasvir

-asvir

NS5B NUC Inhibitors

Sofosbuvir
VX-135
Uprifosbuvir
ACh-3422

NS5B Non-NUC Inhibitors

Dasabuvir
Beclabuvir

-buvir
FEBRUARY 2, 2017

U.S. FDA Grants Priority Review to AbbVie for its Investigational Regimen of Glecaprevir/Pibrentasvir (G/P) for the Treatment of Chronic Hepatitis C in All Major Genotypes (GT1-6)

- If approved, G/P will provide an eight week, once-daily, ribavirin-free cure* for HCV patients without cirrhosis across all major genotypes
- The priority designation shortens the regulatory review period from the standard 10 months to six months from the acceptance of the NDA [1]

NORTH CHICAGO, ILL., Feb. 2, 2017 /PRNewswire/ — AbbVie (NYSE: ABBV), a global biopharmaceutical company, today announced that the U.S. Food and Drug Administration (FDA) has accepted its New Drug Application (NDA) and granted priority review for its investigational, pan-genotypic regimen of glecaprevir/pibrentasvir (G/P), being evaluated for the treatment of all major genotypes (GT1-6) of chronic hepatitis C virus (HCV). The FDA grants priority review designation to medicines that it determines have the potential to provide significant improvements in the safety and effectiveness of the treatment of a serious disease. The NDA is supported by data from eight registrational studies in AbbVie’s G/P program.
<table>
<thead>
<tr>
<th>Combination regimen</th>
<th>Genotype 1</th>
<th>Genotype 2</th>
<th>Genotype 3</th>
<th>Genotype 4</th>
<th>Genotypes 5 and 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir + ribavirin</td>
<td>No</td>
<td>Suboptimal</td>
<td>Suboptimal</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Sofosbuvir/ledipasvir ± ribavirin</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sofosbuvir/velpatasvir ± ribavirin</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/ritonavir ± ribavirin</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Grazoprevir/elbasvir ± ribavirin</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sofosbuvir + dadatasvir ± ribavirin</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sofosbuvir + simeprevir ± ribavirin</td>
<td>Suboptimal</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

G/P Summer 2017 for all genotypes

Summary of EASL 2014

100%

SVR24 rate (%)
HCV therapy: Game over!

Treatment of chronic hepatitis C virus (HCV) infection has improved considerably in the last 5 years with the introduction of direct-acting antiviral (DAA) agents that target key steps of the HCV replication cycle.1 DAAs are able to halt HCV replication by inhibiting the activity of 3 nonstructural (NS) viral proteins: the NS3 protease, the NS5B polymerase, and the NS5A protein. Combinations of 2 or 3 DAAs have been shown to be highly effective and safe in phase III clinical trials and large real life cohorts, providing sustained virologic response (SVR) rates of >90%.2,3

Although the greatest challenge that clinicians, stakeholders, and patients with HCV are facing currently is how to expand access to treatment to all HCV patients, there are therapeutic areas where gaps in knowledge remain, and areas where treatment optimization is required.4 With respect to previously untreated patients, shortening the duration of treatment below the standard of care 12 weeks is a relevant aim because it provides clinical and public health benefits. Shorter treatment durations could be particularly useful for large-scale strategies aimed at eliminating HCV in marginalized HCV populations, that not only are at the core of new incident HCV cases, but also might suffer from reduced adherence to medications.5 Last, a shorter course of therapy would likely decrease the direct health care costs of treatment, thus positively impacting on access to DAAs.5 Current HCV treatment guidelines support 8 weeks of treatment only in HCV-1 treatment-naïve patients receiving sofosbuvir/ledipasvir who do not have cirrhosis and have a baseline HCV-RNA of <6,000,000 IU/mL.6,7

In the current issue of Gastroenterology, and Lawitz et al8 and Gane et al9 provide evidence that by combining 3 classes of DAAs, the NS5B polymerase inhibitor sofosbuvir,
Debate: Do we need more HCV drugs?

» More drugs, more competition and eventually lower prices….

» Any special patient populations left?

» Need for shorter treatment durations?

» Need for better tolerated drugs?

» Need for drugs with less drug-drug interactions?

» How about treatment of DAA failures?
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» Need for drugs with less drug-drug interactions?

» How about treatment of DAA failures?
Box price of DAA in current use in Egypt as of April 2017

<table>
<thead>
<tr>
<th>DAA</th>
<th>Manufacturerg</th>
<th>NCCVH Pharmacies</th>
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<tbody>
<tr>
<td>Sofosbuvir</td>
<td>Generic</td>
<td>450 LE (25$)</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>Brand</td>
<td>1315 (73$)</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>Brand</td>
<td>1315 (73$)</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>Generic</td>
<td>60 LE (3$)</td>
</tr>
<tr>
<td>OMB/PAR</td>
<td>Brand</td>
<td>3050 LE (170$)</td>
</tr>
<tr>
<td>SOF/LDV</td>
<td>Brand</td>
<td>3050 LE (170$)</td>
</tr>
<tr>
<td>SOF/LDV</td>
<td>Generic</td>
<td>Not available</td>
</tr>
</tbody>
</table>

Price of ribavirin 1200mg/d for a month is 125 LE (7$) in NCCVH
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High SVR in adult patients with HIV/HCV co-infection treated with DAAs

- **ALLY-2:**
  - GT 1–4, TN & TE
  - SOF + DCV
  - SVR12 (%): 97, 98

- **ION-4:**
  - GT 1 or 4, TE & TN
  - LDV/SOF
  - SVR12 (%): 96

- **TURQUOISE-1, part 2:**
  - GT 1 or 4, TN and TE
  - OMV/PTV/RTV + DSV ± RBV
  - SVR12 (%): 97

- **C-EDGE:**
  - GT 1, 4 or 6, TN
  - GRZ/EBV
  - SVR12 (%): 96

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3. Rockstroh JK, et al. IAS 2016; Abstract # 10333;

*Studies included non-cirrhotic and cirrhotic patients.*

*TE: treatment-experienced*

NOT HEAD-TO-HEAD COMPARISONS
EXPEDITION-I Study: 
Next Generation Direct-Acting Antivirals

Glecaprevir (formerly ABT-493) 
pangenotypic NS3/4A protease inhibitor

Pibrentasvir (formerly ABT-530) 
pangenotypic NS5A inhibitor

In vitro:¹,²
- High barrier to resistance
- Potent against common NS3 polymorphisms (e.g., positions 80, 155, and 168) and NS5A polymorphisms (e.g., positions 28, 30, 31 and 93)

Clinical PK & metabolism:
- Synergistic antiviral activity
- Once-daily oral dosing with food
- Minimal metabolism and primary biliary excretion
- Negligible renal excretion (<1%)

G/P is co-formulated and dosed once daily as three 100 mg/40 mg pills for a total dose of 300 mg/120 mg
Glecaprevir was identified by AbbVie and Enanta.

EXPEDITION-1 Study: Objective and Study Design

Objective

» Evaluate the efficacy and safety of G/P for 12 weeks in patients with HCV GT1, 2, 4, 5 or 6 infection and compensated cirrhosis

Open-label Treatment

G/P is coformulated and dosed once daily as three 100 mg/40 mg pills for a total dose of 300 mg/120 mg.

Forns X, et al. 52nd EASL; Amsterdam, Netherlands; April 19-23, 2017. Abst. GS-006.
EXPEDITION-1 Study: SVR12 by Intent-to-Treat (ITT) Analysis

*Patient with HCV GT1a infection relapsed at PTW8  -  No treatment-emergent substitutions were present in NS3
* In NS5A, Y93N was present at baseline; Y93N, Q30R and H58D were present at the time of failure

Forms X, et al. 52nd EASL; Amsterdam, Netherlands; April 19-23, 2017. Abst. GS-006.
98% of patients had HCV RNA <LLOQ by treatment week 4
**SVR12 (mFAS)**

- **EBR/GZR + SOF + RBV** (8 weeks) | 91 (21/23)
- **EBR/GZR + SOF** (12 weeks) | 100 (22/22)
- **EBR/GZR + SOF** (12 weeks) | 100 (17/17)
- **EBR/GZR + SOF + RBV** (12 weeks) | 100 (17/17)
- **EBR/GZR + SOF** (16 weeks) | 100 (17/17)

**Relapse**

<table>
<thead>
<tr>
<th></th>
<th>Treatment-naive</th>
<th>Treatment-experienced</th>
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<tr>
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<td>0</td>
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</table>

mFAS excluded patients who discontinued treatment for reasons unrelated to study medication.
Any special patient populations left?

» HIV coinfected (SVR >95%)
» Renal insufficiency (SVR up to 99%)
» Cirrhotics (SVR up to 99%)
» GT3 treatment experienced with cirrhosis (SVR 96%)
» Inherited blood disorders (SVR 94%)
» Transplant patients (SVR >95%)
» ...you name it......
So what does Nancy really think and that already in 2014.....

Nancy Reau, MD
Associate Professor of Medicine
University of Chicago
Management of Hepatitis C:
New Drugs and New Paradigms

Summary
- Dual and triple DAA regimens yield the highest SVR rates (90+%) ever described
- Treatment duration of 12 weeks (maybe shorter)
- Well-tolerated across all populations
- Baseline characteristics are becoming irrelevant
- Special populations have equal efficacy
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» Need for drugs with less drug-drug interactions?

» How about treatment of DAA failures?
8-week LDV/SOF in non-cirrhotic, treatment naïve GT 1 patients: real-world confirmation of clinical data

*Two patients received LDV/SOF + RBV. LDV/SOF + RBV for 8 weeks is not licensed in the EU.

ITT: intention-to-treat

Real world virological response (>4000 patients)
Post hoc analysis; per protocol; ITT analysis

<table>
<thead>
<tr>
<th>SVR12 (%)</th>
<th>ION-3</th>
<th>ifi</th>
<th>DHC-R</th>
<th>Burman's pharmacy</th>
<th>US Com. Centers</th>
<th>Kaiser LA</th>
<th>HCV Target</th>
<th>TRIO Cohort</th>
<th>VA</th>
<th>HEPA-C Registry</th>
<th>GECCO</th>
<th>Kaiser Permanente</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>94</td>
<td>99</td>
<td>98</td>
<td>98</td>
<td>98</td>
<td>97</td>
<td>95</td>
<td>95</td>
<td>94</td>
<td>93</td>
<td>92</td>
<td></td>
</tr>
</tbody>
</table>

GARNET: Efficacy

Sustained Virologic Response

<table>
<thead>
<tr>
<th></th>
<th>% Patients with SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>98</td>
</tr>
<tr>
<td>mITT-GT</td>
<td>98</td>
</tr>
<tr>
<td>mITT-GT-VF</td>
<td>99</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>N/S</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>162/166</td>
</tr>
<tr>
<td>mITT-GT</td>
<td>160/163*</td>
</tr>
<tr>
<td>mITT-GT-VF</td>
<td>160/162†</td>
</tr>
</tbody>
</table>

**ITT:** All enrolled patients who received at least 1 dose of study drug

**mITT-GT:** ITT modified to exclude 3 patients without GT1b infection

**mITT-GT-VF:** mITT-GT population excluding non-virologic failures

Virologic failure in three patients, including one who failed to suppress on treatment

- This patient was later determined to have GT6 infection

*One patient each was infected with HCV GT1a, GT1d, and GT6
†One patient discontinued treatment prematurely

Adapted from Asselah et al; AFEF 2016, Sept 28-Oct 1, Bordeaux, France
ENDURANCE-3 Study: Objective and Study Design

- Arm C: 8-week treatment duration
- Per discussion with regulatory authorities after phase 2 treatment data became available, an 8 week treatment Arm of G/P was added to the study design
  - SVR12: Non-inferiority of 8 weeks of G/P compared to 12 weeks of G/P*

*Endpoint was tested only after 12 weeks of G/P was determined non-inferior to 12 weeks of SOF + DCV

Foster G, et al. 52nd EASL; Amsterdam, Netherlands; April 19-23, 2017. Abst. GS-007.
### ENDURANCE-3 Study: Baseline Demographics and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>2:1 randomized</th>
<th>Non-randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G/P 12 weeks N = 233</td>
<td>SOF + DCV 12 weeks N = 115</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>121 (52)</td>
<td>52 (45)</td>
</tr>
<tr>
<td>White race, n (%)</td>
<td>205 (88)</td>
<td>103 (90)</td>
</tr>
<tr>
<td>Age, median years (range)</td>
<td>48 (22 – 71)</td>
<td>49 (20 – 70)</td>
</tr>
<tr>
<td>BMI, median kg/m² (range)</td>
<td>25 (17 – 49)</td>
<td>25 (18 – 42)</td>
</tr>
<tr>
<td>HCV RNA, median log_{10} IU/mL (range)</td>
<td>6.1 (3.5 – 7.5)</td>
<td>6.0 (3.8 – 7.4)</td>
</tr>
<tr>
<td>History of injection drug use, n (%)</td>
<td>149 (64)</td>
<td>73 (63)</td>
</tr>
<tr>
<td>Baseline fibrosis stage, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F0 – F1</td>
<td>201 (86)</td>
<td>97 (84)</td>
</tr>
<tr>
<td>F2</td>
<td>12 (5)</td>
<td>8 (7)</td>
</tr>
<tr>
<td>F3</td>
<td>20 (9)</td>
<td>10 (9)</td>
</tr>
<tr>
<td>Subtype GT3a, n/N (%)*</td>
<td>226/229 (99)</td>
<td>113/113 (100)</td>
</tr>
</tbody>
</table>

BMI, body mass index; DCV, daclatasvir; G/P, coformulated glecaprevir/pibrentasvir; GT, genotype; HCV, hepatitis C virus; SOF, sofosbuvir

*HCV subtype determined by phylogenetic analysis; N = total number of patients with sequence data available.

Foster G, et al. 52nd EASL; Amsterdam, Netherlands; April 19-23, 2017. Abst. GS-007.
ENDURANCE-3 Study: Results SVR12 by Intent-to-Treat (ITT) Analysis

Non-inferiority:

- Lower bound of the confidence interval (CI) of the difference in SVR12 must be above -6%*
  - (1) -1.2% (95% CI -5.6 – 3.1)
  - (2) -0.4% (97.5% CI -5.4 – 4.6)
- Both G/P treatments met non-inferiority criteria for the primary endpoint

*Conventional statistical methods were used in multiplicity comparison for determining non-inferiority

Foster G, et al. 52nd EASL; Amsterdam, Netherlands; April 19-23, 2017. Abst. GS-007.
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- How about treatment of DAA failures?
DAAs were well-tolerated in clinical trials of HIV/HCV co-infected patients

Adverse events common across all DAA regimens in HIV/HCV co-infection trials

<table>
<thead>
<tr>
<th></th>
<th>ALLY-2</th>
<th>ION-4</th>
<th>TURQUOISE-I Part 2</th>
<th>C-EDGE CO-INFECTION</th>
<th>ASTRAL-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCV + SOF N=203</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Fatigue</td>
<td>17%</td>
<td>21%</td>
<td>23%</td>
<td>13%</td>
<td>25%</td>
</tr>
<tr>
<td>Headache</td>
<td>11%</td>
<td>25%</td>
<td>14%</td>
<td>12%</td>
<td>13%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>7%</td>
<td>11%</td>
<td>14%</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>Nausea</td>
<td>13%</td>
<td>10%</td>
<td>20%</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>D/C due to AE</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>


This table illustrate adverse events obtained between different regimens from different studies and are therefore not directly comparable as study populations are NOT matched
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» How about treatment of DAA failures?
Drug-drug Interactions between DAAs and ARVs

Don`t undermine your own existence as a clinical pharmacologist....

<table>
<thead>
<tr>
<th>HCV drugs</th>
<th>ATV/r</th>
<th>DRV/c</th>
<th>DRV/r</th>
<th>LPV/r</th>
<th>EFV</th>
<th>ETV</th>
<th>NVP</th>
<th>RPV</th>
<th>MVC</th>
<th>DTG</th>
<th>EVG/c</th>
<th>RAL</th>
<th>ABC</th>
<th>FTC</th>
<th>3TC</th>
<th>TAF</th>
<th>TDF</th>
<th>ZDV</th>
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</thead>
<tbody>
<tr>
<td>boceprevir</td>
<td>D35%</td>
<td>↓D</td>
<td>↓D</td>
<td>D44%</td>
<td>↓E</td>
<td>132%</td>
<td>14%</td>
<td>19%</td>
<td>10%</td>
<td>↓E</td>
<td>15%</td>
<td>D34%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>daclatasvir</td>
<td>↑110%</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>D</td>
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<tr>
<td>elbasvir/</td>
<td>↑</td>
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<td>grazoprevir</td>
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<tr>
<td>pantasvir/</td>
<td>↑8/13%</td>
<td>↑</td>
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<tr>
<td>dasabuvir</td>
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<td>paritaprevir</td>
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Legend:
- ↑↑ potential elevated exposure of DAA
- ↑↑ potential decreased exposure of DAA
- ↑↑ no significant effect
- D potential decreased exposure of ARV drug
- E potential elevated exposure of ARV drug

Numbers refer to decreased/increased AUC of DAAs and ARVs as observed in drug interactions studies. Sofosbuvir/ledipasvir: first/second numbers refer to changes AUC sofosbuvir/ledipasvir.

Colour legend:
- Light blue: no clinically significant interaction expected
- Red: these drugs should not be co-administered.
- Yellow: potential interaction which may require a dosage adjustment or close monitoring.

Note: the symbol (green, amber, red) used to rank the clinical significance of the drug interaction is based on http://www.hep-druginteractions.org.
Debate: Do we need more HCV drugs?

» More drugs, more competition and eventually lower prices….

» Any special patient populations left?

» Need for shorter treatment durations?

» Need for better tolerated drugs?

» Need for drugs with less drug-drug interactions?

» How about treatment of DAA failures?
Re-treatment after failure to LDV/SOF

9 patients without SVR in ION-4 after 12 weeks of LDV/SOF

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» SVR in 8/9

» 1 relapse 4 weeks after EOT: GT1a, no cirrhosis

C-SWIFT: Retreatment for 12 Weeks with EBR/GZR + SOF + RBV in GT1-infected Patients Who Relapsed on Short-duration DAA Therapy

PURPOSE: Evaluate 12 weeks of EBR/GZR + SOF + RBV for HCV GT1-infected patients who failed prior treatment with EBR/GZR + SOF; shorter durations of 4, 6, or 8 weeks.

RESULTS:

• SVR12 = 100% for retreatment of 12 weeks, regardless of cirrhosis, subgenotype, or baseline RAVs
• No discontinuations due to AEs or laboratory abnormalities
• The only AE occurring in > 10% of patients was fatigue (12%)

KEY MESSAGES: Addition of RBV, and lengthened treatment duration to 12 weeks improves SVR rates in patients who failed prior short-duration DAA therapy. If patients fail short-term treatment, other options are available.

†Excludes two patients lost to follow-up at Day 3 and treatment Week 4.

Debate: Do we need more HCV drugs?

» More drugs, more competition and eventually lower prices…. Price already down to 28$

» Any special patient populations left? no

» Need for shorter treatment durations? Already down to 8 weeks

» Need for better tolerated drugs? DC in trials for adverse events < 1%

» Need for drugs with less drug-drug interactions? All solvable with the help of a clinical pharmacologist

» How about treatment of DAA failures? 3-drug combinations from 3 drug classes already available as salvage therapy