Hepatitis C: The Easy and the Not so Easy

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Disclosures

- Research: Abbvie, Abbott, Gilead, Janssen, Wako/Fujifilm
- Scientific Consulting: Abbvie, Abbott, Enanta, Gilead, Janssen, Roche
Eye on the prize: Viral hepatitis elimination

- Eliminate viral hepatitis as a major public health threat by 2030
- Calling on all countries to develop national action plans

![Graph showing new infections and mortality reduction from 2016 to 2030](image)
What do we mean by elimination?
What do we mean by elimination?

**Eradication**
- Decrease *global* prevalence to 0 cases
- No ongoing surveillance or control efforts required

**Elimination**
- Decrease in *regional/national* prevalence to below a threshold to *limit impact as a public health problem*
- Ongoing surveillance and control required

Likely impossible without a vaccine (among other things!)

Challenging but feasible with the right tools

To get to any of these endpoints → we need to treat a lot of people
Outline

• How easy can it be?
  – Simplified therapy
    • Pretreatment assessment and regimen selection
    • On-treatment monitoring
    • Post-treatment follow-up

• The not so easy
  – Difficult patients
    • The liver
    • The virus
Outline

• How easy can it be?
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Recommended Treatment Regimens

- **Genotype-specific**
  - Elbasvir/Grazoprevir: GT 1, 4
  - Ledipasvir/Sofosbuvir: GT 1, 4, 5, 6

- **Pangenotypic**
  - Sofosbuvir/Velpatasvir – GT 1-6
  - Glecaprevir/Pibrentasvir – GT 1-6
  - Sofosbuvir/Velpatasvir/Voxilaprevir – GT 1-6 (reserved for salvage therapy)
Lots of Options…
How Do You Choose the Right One?

• The good news is they all work very well!
• SVR rates consistently > 95% in clinical trials and real-world studies
• Safety/tolerability excellent
• For most patients, any of the recommended options are fine
• You can make this difficult…but you need not (most of the time!)
  – 3 pills once a day for 8 weeks
  – 1 pill once a day for 12 weeks
Checklist for Choosing a Regimen: A Few Things to Know

• **Fibrosis assessment**
  – Cirrhosis?
  – If yes – any history or signs of decompensation

• **Genotype & subtype for GT 1**
  – Still necessary?

• **Treatment history**
  – Regimen + duration

• **Comorbidities**
  – CKD, coinfection (HIV/HBV)
  – Drug-drug interactions
  – Ongoing risk exposures: drug use, sex, alcohol
Fibrosis Assessment is Essential

• Don’t miss cirrhosis!!
  – Must assess fibrosis in ALL patients
  – May affect regimen
  – Need for post-SVR follow up

• Fibroscan is great
  – If you have access…
  – Remember the caveats
    • If the value is a surprise…make sure it’s a good reading and not due to inflammation, fat, big meal…
Fibrosis Assessment

• Serum tests
  – APRI or FIB-4 – very attractive, can be done anywhere by any provider
    • Very good negative predictive value – rule out cirrhosis
    • Can even get this after the fact with old records…more on this later
    • If high – PPV is not great…get another test to confirm (especially if a surprise)
      – FibroTest (0.75 = cirrhosis)

• Transient elastography
  – > 12.5 KPa = cirrhosis

• What about ultrasound – needed in all patients?
  – Insensitive for cirrhosis – only needed if cirrhotic to exclude HCC before treatment
If Cirrhosis is Present

• Need to exclude current or past decompensation
  – Affects choice of regimen – No PIs, add RBV
  – Affects safety – warn patient & monitor closely

• Calculate Child Pugh Score – if > 5 pay attention!
  – Bilirubin - Ascites
  – Albumin - Hepatic encephalopathy
  – INR

• Calculate MELD – if > 15 pay attention!
  – Bilirubin - Creatinine
  – INR
Be careful...nothing very new but a good reminder

Most cases in CP-B/C (a few CP-A but A-6)
- Issues in first 4 weeks
- If bili rising (or new ascites/HE) – stop treatment!
Checklist for Choosing a Regimen: A Few Things to Know

• Fibrosis assessment
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  – Drug-drug interactions
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What about SOF/VEL?

SOF + Velpatasvir (NS5A) x 12 wks in G1, 2, 4, 5, 6 – Naïve/Experienced +/- cirrhosis

<table>
<thead>
<tr>
<th>Genotype</th>
<th>SVR12 (%)</th>
<th></th>
<th>Genotype</th>
<th>SVR12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>99 ± 0</td>
<td>98 ± 0</td>
<td>99 ± 0</td>
<td>100 ± 0</td>
</tr>
<tr>
<td>1a</td>
<td>618</td>
<td>206</td>
<td>117</td>
<td>104</td>
</tr>
<tr>
<td>1b</td>
<td>624</td>
<td>210</td>
<td>118</td>
<td>104</td>
</tr>
<tr>
<td>2</td>
<td>100 ± 0</td>
<td>97</td>
<td>118</td>
<td>104</td>
</tr>
<tr>
<td>4</td>
<td>100 ± 0</td>
<td>97</td>
<td>118</td>
<td>104</td>
</tr>
<tr>
<td>5</td>
<td>100 ± 0</td>
<td>97</td>
<td>118</td>
<td>104</td>
</tr>
<tr>
<td>6</td>
<td>100 ± 0</td>
<td>97</td>
<td>118</td>
<td>104</td>
</tr>
</tbody>
</table>

G3: SOF/RBV x 24 vs SOF/VEL x 12

<table>
<thead>
<tr>
<th>Genotype</th>
<th>SVR12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0-3</td>
<td>97</td>
</tr>
<tr>
<td>F4</td>
<td>91</td>
</tr>
</tbody>
</table>

Clearly not an issue without cirrhosis...what about with cirrhosis?

Feld NEJM 2015, Foster NEJM 2015
Why is genotyping useful with cirrhosis?

**G3 cirrhosis – SOF/VEL vs SOF/VEL + RBV x 12 weeks**

**Overall**
- SOF/VEL: 91/101
- SOF/VEL + RBV: 96/103

**Effect of Resistance (RAS) – 21%**

- No RAS: SOF/VEL 96/103, SOF/VEL + RBV 99/103
- RAS: SOF/VEL 76/79, SOF/VEL + RBV 81/34
But does it really matter? Can’t we just retreat?

SOF/VEL/VOX in 573 Veteran’s after DAA failure

High overall efficacy
- G1-4 >93% SVR
- Lower SVR with SOF/VEL/VOX after SOF/VEL → small numbers but important to clarify if this is an issue

Belperio et al AASLD 2018, Abstract 227
Looks similar in Canada…

Patients retreated with SOF/VEL/VOX after DAA failure in the CANUHC cohort

- Small numbers but SOF/VEL/VOX may not be as effective for retreatment after SOF/VEL failure
- **Message:** Get it right the first time!

Onofrio AASLD 2019
And with GLE/PIB?
8 Wks in Patients **Without** Cirrhosis

![Graph showing SVR12 percentages for different HCV genotypes.](image)

- **GT 1**: 99.1%
- **GT 2, 4, 5, 6**: 98%, 93%, 100%, 90%
- **GT 3**: 95%

Clearly no relevance without cirrhosis – same 8 week treatment for everyone...but if cirrhotic?
EXPEDEITIION 8: GP for 8 weeks with cirrhosis

FDA NEWS RELEASE

FDA approves treatment for adults and children with all genotypes of hepatitis C and compensated cirrhosis that shortens duration of treatment to eight weeks

Brown et al. AASLD 2018, LB-7
And the genotype 3 cirrhotic data?

- 3 (5%) A30K
- 4 (6.5%) Y93H
- All SVR

Overall GLE/PIB looks promising for 8 weeks for compensated cirrhosis in all genotypes.

This approach would avoid the need to genotype – 8 weeks for all with or without cirrhosis.

But would be nice to have bigger numbers, especially with RAS for G3.
Can We Avoid Genotyping?

Maximizing SVR in Individual Patient
- Genotyping may be helpful
- Helpful in cirrhosis, particularly GT3
- ?add RBV to SOF/VEL
- ?Extend G/P to 12w...or not

A Reasonable Compromise
Genotype only for: Cirrhosis DAA-experienced

Maximize SVR in the Population
- Simplicity is key
- Genotyping adds some: cost, delay, and complexity
Other Labs?

• Work-up for other liver diseases?
  – Could do pretreatment or else wait for post-SVR if ALT still high
  – Iron saturation
  – Maybe nothing else (don’t need the full CLD w/u on everyone!)
• Renal function
  – Still relevant although SOF/VEL shown to be safe down to GFR<30, most would still prefer to avoid
  – GLE/PIB safe in CKD including dialysis
• HBV
  – HBsAg is important
  – Anti-HBc not very important (but very common!)
• HIV
  – Important due to common risk factors and importance of diagnosis
Drug-Drug Interactions

http://www.hep-druginteractions.org/
(or just google Hep C drug interactions)

This is often a decider for me on which regimen to use
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Simplifying Monitoring: Do we need visits?

Non-cirrhotic all genotypes randomized – **standard vs simplified (no visits)** monitoring

<table>
<thead>
<tr>
<th>Treatment-Emergent AEs, n (%)</th>
<th>Standard (n = 127)</th>
<th>Simplified (n = 253)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unscheduled visits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On treatment</td>
<td>3 (2)</td>
<td>11 (4)</td>
</tr>
<tr>
<td>Total</td>
<td>8 (6)</td>
<td>20 (8)</td>
</tr>
</tbody>
</table>

- Overall performed very well but did not quite reach noninferiority
- Highlights need for good patient selection for this approach

- VF: 2 (1.6%) standard vs 6 (2.4%) simplified
- Adherence > 95%: 98% standard vs 96% simplified

Dore J Hep *In Press*
AASLD/IDSA guidance – down to 1 page!

2015 → 22 pages

2019 → 1 page
Eligible for simplified assessment – No cirrhosis, no prior DAAs, no HIV/HBV

Pretreatment Assessment
- **Exclude cirrhosis** – any of the following suggests cirrhosis
  - FIB4>3.25  - Fibroscan>12.5 KPa
  - APRI>2.0  - Plt< 150,000
- **Other labs**
  - Liver panel – ALT/AST, INR, Bili, Albumin + Creatinine
  - HCV RNA
  - HIV, HBsAg
  - Pregnancy test
- **Drug interactions** → look them up

Treatment
- **GLE/PIB x 8 weeks** or **SOF/VEL x 12 weeks** *(no genotyping required)*
- No monitoring required (Blood sugar if DM, INR if on warfarin)

Post–treatment follow-up
- SVR12 HCV RNA – if no SVR, retreat
- HCV RNA serially if ongoing risk exposures
Time to give up some turf: Treatment should move out of specialty clinics

So my how many years of training and research are reduced to 3 hours???
If it’s so easy to treat...maybe we can give it to people on purpose...
Increasing HCV-infected donors

Most are young and often otherwise healthy donors
Using HCV+ donors in HCV- recipients

- 36 lung + 8 heart transplants from HCV NAT+ donors
- SOF/VEL first dose given a few hours post-transplant then x 4w

- Viremia
  - 42 of 44 recipients
  - Median VL 3.26 (0 to 4.6 log IU/mL) correlated with donor VL
  - Rapidly cleared – negative by week 2

- Genotype
  - G1 61%
  - G2 17%
  - G3 17%
  - Indet 5%
Using HCV+ donors in HCV- recipients

- 20 HCV –ve recipients received HCV +ve kidneys
- All viremic post-transplant
- Treated elbasvir/grazoprevir (Genotype 1 or 4)
  - **100% SVR**

Goldberg NEJM 2017, Woolley NEJM 2019
Prevention is better than treatment

25 recipients from 14 donors → **GLE/PIB + Ezetimibe before and x 7 days after transplant**

**Ezetimibe + Glecaprevir/Pibrentasvir**

- **n=25**
  - No virological failures
  - SVR12 – 22
  - SVR8 - 3

"It can’t get much easier..."
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Issues after treatment

1. Consequences of liver disease
   - Only an issue with cirrhosis (fibrosis assessment pre-treatment!)
   - HCC risk
   - Liver function – MELD purgatory (later to come)

2. Reinfection risk
   - Ongoing exposures – HCV RNA testing q6-12 m
   - No ongoing exposures – annual ALT, promote liver health (diet & ETOH) and *nothing else!*

- Communicate information well - people don’t know what SVR means
- Templated notes with key features
  e.g. anti-HCV Ab remains positive → don’t check it!
What About Post-SVR HCC Surveillance?

- AASLD/IDSA and EASL guideline recommendation: US surveillance every 6 mos after SVR in patients with “advanced fibrosis” or cirrhosis (ie, F3/F4)\[^{[1,2]}\]

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HCC Incidence per 100 Person-Yrs[^{[3]}]</th>
<th>ICER for Surveillance (Ultrasound Every 6 Mos) vs No Surveillance, per QALY[^{[4]}]</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without</td>
<td>3.45</td>
<td>--</td>
</tr>
<tr>
<td>With</td>
<td>0.90</td>
<td>--</td>
</tr>
<tr>
<td>Cirrhosis status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With</td>
<td>1.82</td>
<td>$40,803</td>
</tr>
<tr>
<td>Without</td>
<td>0.34</td>
<td>187,000</td>
</tr>
<tr>
<td>FIB-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 3.25</td>
<td>2.16</td>
<td>$32,016</td>
</tr>
<tr>
<td>1.45-3.25</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>&lt; 1.45</td>
<td>0.30</td>
<td>$133,977</td>
</tr>
</tbody>
</table>

Can we limit surveillance post-SVR to those with cirrhosis or FIB-4 > 3.25?
Using FIB4 to guide post-SVR HCC surveillance

HCC incidence during follow-up after SVR in 9,784 with cirrhosis and 38,351 without cirrhosis

- HCC risk remains stable out to 10 years...cannot stop surveillance
- Surveillance cost-effective if FIB4>3.25 and probably in all with cirrhosis
Can we improve on FIB4?

1,131 F3/F4 patients followed after SVR → 50 HCCs & validated in 2 Scottish cohorts n=1,176

Model developed using:
- Age
- Sex
- Platelets
- Albumin

C-index
- FIB4 – 0.66
- ASPA - 0.80

Predicted HCC risk at 1, 2, and 5 years
Can we improve on FIB4?

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A. Age = 50, female, albumin = 40, platelets = 150; PI = 1.10

Predicted HCC risk at 1, 2, and 5 years

Lau AASLD 2019
Can we improve on FIB4?

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Model developed using
- Age
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C-index
- FIB4 – 0.66
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A. Age = 50, female, albumin = 40, platelets = 150; PI = 1.10
B. Age = 60, male, albumin = 40, platelets = 150; PI = 2.54

- Improved prediction over FIB4
- Surprisingly – post-treatment variables of minimal impact

Patient A
Risk: 1y – 0.3%, 5y – 1.9%

Patient B
Risk: 1y – 1.3%, 5y – 7.8%

Lau AASLD 2019
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Safety first

433 patients with cirrhosis treated with DAAs at 4 centers

Child Pugh A vs Child Pugh B/C

First event: p=0.002
Subsequent event: p=0.321

Treatment very safe in CP-A

Maan Clin Gastro Hep 2017
If CP-B or C...who is at risk?

Factors associated with decompensation during treatment

MELD <15 vs ≥15

G3 vs non-G3

Albumin<3.5 vs >3.5

First event: p<0.001
Subsequent event: p=0.007

But even if you cure them...do they get better?
Case 1

- 54 yo Pakistani F G4 cirrhosis, NR to Peg/RBV
- Complications:
  - Variceal bleed x 2 - banded
  - Mild encephalopathy
  - Diuretic controlled ascites
  - MELD – 18-20
- Treated SOF/SIM + RBV x 24w
- SVR in July 2015

Case 2

- 72 yo Caucasian M G1b
- Past treatment Peg/RBV x 2, P/R + TVR → NR
- Complications:
  - Encephalopathy – lactulose
  - Ascites – Furos 120, Spir 300
  - MELD 18-22
- Treated SOF/SIM + RBV x 24w
- SVR in Nov 2015

Who will do better?
Same, same…but different

Case 1 – 54F G4

• Post SVR course
  – Persistent ascites
  – Persistent encephalopathy (lactulose/rifaximin)
  – Umbilical hernia repair (2 mild incarcerations)
  – MELD 16-18

• June 2018 – listed for transplant
• Apr 2019 – finally transplanted (took a long time due to low MELD)

Case 2 – 72M G1b

• Post SVR course
  – Resolution of ascites – off diuretics since mid-2016
  – Resolution of encephalopathy
  – No other complications
  – MELD 6-8

• Sep 2019 – highly functional 76 yo man
How do we avoid MELD purgatory?

Jaundiced with ascites (and mildly encephalopathic) with no prospect of a transplant....
Can we predict MELD purgatory?

Follow-up SOF trials for decompensated cirrhosis (CP-B n=502, CP-C n=120) chance of improvement to CP-A or MELD purgatory = CPT-B/C with MELD<15

- Improvement in some but definitely not all (or even most)
- SVR associated with improvement but short-term follow-up (36w)

El-Sherif, Jiang Gastro 2018
A simple pre-treatment score

Assign 1 point to each of the following:

- no Enceph
- BMI < 25
- no Ascites
- ALT > 60 IU/L
- Albumin > 3.5 g/dL

El-Sherif, Jiang Gastro 2018
Same, same…but different

Case 1

- 54 yo Pakistani F G4 cirrhosis, NR to Peg/RBV
- Complications:
  - Variceal bleed x 2 - banded
  - Mild encephalopathy
  - Diuretic controlled ascites
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- SVR in July 2015

BE3A score = 2

Case 2

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- Past treatment Peg/RBV x 2, P/R + TVR → NR
- Complications:
  - Encephalopathy – lactulose
  - Ascites – Furos 120, Spir 300
  - MELD 18-22
- Treated SOF/SIM + RBV x 24w
- SVR in Nov 2015

BE3A score = 2
So where are we with treating decompensated patients?

• Fortunately there are fewer…but not none - late diagnosis still an issue
  – 28% of those of those with decompensation/HCC diagnosed within 6 m of complication!!
• Don’t miss it
• If low BE3A score (0/1) – transplant first…(<25% chance of improving to CP-A with SVR)
• If not low…
  – Careful discussion with patients about pros and cons to treatment
  – Careful discussion with transplant program about pros and cons to treatment
• If you treat – be careful
Important Points in Decompensated Cirrhosis

• Be careful!!
  – Sick patients may worsen at any time: make sure patient is aware of risks
  – Treat in experienced centers and see patient frequently
  – Drugs can be toxic
    • ALL protease inhibitors contraindicated!
    • Even LDV/SOL, SOF/VEL can cause liver injury in this setting

• Add ribavirin
  – Unclear why but seems to be helpful
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POLARIS 1 - Prior NS5A Failures

SOF/VEL + VOX (PI) x 12 weeks → G1-6 prior NS5A, 41% cirrhosis

- 7 virologic failures
- 6 relapse
- 1 breakthrough
- All cirrhotic – G1a or 3 (1 GT4)
- No treatment emergent RAS!

• Based on this...no reason to do resistance testing...right?
• *But we won’t know unless we test*...
• With enough data, almost certainly relevant...

Bourliere NEJM 2017
Retreatment with GLE/PIB

G1 with past failure with NS5A + SOF → No cirrhosis 12w vs 16 w, compensated cirrhosis 12w + RBV vs 16w

- **G1b** (n=34) – no virological failures
- **G1a** failures
  - Breakthrough (n=6)
    - Complicated NS5A RAS at BL
    - Emergent NS3 & NS5A RAS
  - Relapse (n=7)
    - NS5A RAS at BL
    - Emergent (4/7) & NS5A RAS

- **Effective for G1b (12 or 16w)**
- **G1a** requires 16w with no benefit from RBV but failures may be challenging

Sulkowski et al. AASLD 2018, Abstract 226
And after G/P (and likely SVV) failure?

**SOF + glecaprevir/pibrentasvir + RBV x 12 vs 16w after G/P failure (8, 12 or 16w)**

- 1 relapse G1a – prior SOF/LDV then G/P before G/P + RBV
- Overall reassuring
- Unclear if RBV is necessary
- Duration unclear
- Need more data with SOF + G/P

**SVR12 (%)**

<table>
<thead>
<tr>
<th></th>
<th>12w</th>
<th>16w</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2/2</td>
<td>20/21</td>
</tr>
<tr>
<td>n/N</td>
<td>2</td>
<td>21</td>
</tr>
</tbody>
</table>

Wyles J Hep 2019
Bottom line on retreatment

• Fortunately a rare event
• Check a few things:
  1. Adherence
  2. DDIs
  3. Spontaneous clearance after relapse (~15%, especially if low VL)

Kuriry EASL 2018, EASL Guidelines J Hep 2018
Confirm relapse before retreatment

**Pre-treatment**
- HCV RNA (IU/mL)
  - Relapse
  - Spontaneous clearance
  - SVR
  - $p = 0.26$

**SVR12**
- HCV RNA (IU/mL)
  - Relapse
  - Spontaneous clearance
  - SVR
  - $p = 0.03$

**6 months post-relapse**
- HCV RNA (IU/mL)
  - Relapse
  - Spontaneous clearance
  - SVR

Kuriry EASL 2018
Bottom line on retreatment

- Fortunately a rare event
- Check a few things:
  1. Adherence
  2. DDIs
  3. Spontaneous clearance after relapse (~15%, especially if low VL)
  4. Reinfection – discuss with everyone
- Do resistance testing – even if it does not change your plan…it may one day!

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### Scenario

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Previous Experience</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-free DAA Combo</td>
<td></td>
</tr>
<tr>
<td>Genotype 1-6</td>
<td>SOF/VEL/VOX</td>
</tr>
<tr>
<td>High risk for failure</td>
<td>Consider SOF + G/P x 12w</td>
</tr>
<tr>
<td>(Cirrhosis, complex RAS, multiple courses)</td>
<td></td>
</tr>
<tr>
<td>Very difficult-to-cure</td>
<td>Consider SOF/VEL/VOX or SOF + G/P + RBV x 12-24w</td>
</tr>
<tr>
<td>(NS5A RAS and &gt;1 failure)</td>
<td></td>
</tr>
</tbody>
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EASL Guidelines J Hep 2018
Summary

• Most HCV treatment is now VERY easy
• Fibrosis assessment still important
• Post-SVR surveillance for cirrhotics only → FIB4 or ASPA useful guide
• Decompensated cirrhosis still challenging – don’t be afraid to transplant first
• Retreatment after DAA failure usually easy…but please do resistance testing to help the few cases that are not!
• Our biggest challenge is still finding and engaging the undiagnosed & untreated…we still have lots of work to do!
Was he talking about HCV in the era of DAAs?