# Cases: Management of HCV in Prior Treatment Failure

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IAS–USA
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## Learning Objectives

After attending this presentation, learners will be able to:

- List treatment options for treatment experienced patients
- Describe the relevance of resistance-associated substitutions



## Considerations for treatment failures after DAAs

- Was initial therapy appropriate?
- Was staging accurate? Is it needed again?
- Was adherence adequate?
- Were drug interactions present?
- What medication classes were used?

## Case

- 69 y/o African-American gentleman with HIV / HCV co-infection
  - HIV suppressed, CD4 568 cells/mm$^3$, TDF/FTC/rilpivirine
  - Plt=135K, Cirrhosis by ultrasound, no decompensation, no varices, albumin 3.6
  - BMI 33, Cr 1.1, IL-28B T-T, No prior treatment, genotype 1a
  - 12 weeks of ledipasvir/sofosbuvir, week 4 HCV RNA is target detected but not quantifiable
  - Reports good adherence, takes pills with HIV medication upon awakening, missed 2 doses (took 84 pills over 86 days). HIV RNA remains suppressed on treatment
  - HCV RNA positive at week 4 post-treatment
  - He was eating more tomatoes during the last two months of treatment that caused heartburn, was taking TUMS at night

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| | Simeprevir | Sofosbuvir | Ledipasvir | Daclatasvir | P/r/O + D |
|---|---|---|---|---|---|
| **DDI** | **Substrate of CYP3A4, OATP1B1/3** | **Substrate of P-gp and BCRP** | **Inhibitor/ Substrate of P-gp and BCRP** | **Inhibitor of OATP1B1/3, BCRP, Substrate of P-gp and CYP3A4** | **Inhibit/Sub of UGT1A1,OATP1B1/3 , BCRP, CYP3A4, CYP2C8, P-gp** |
| **ATV/r** | No data | No data | LDV ↑; ATV ↑ | DCV ↑* | ATV ↑; PAR ↑ |
| **DRV/r** | SIM ↑; DRV ↔ | SOF ↑; DRV ↔ | LDV ↑; DRV ↔ | ALLY-2 ↔ | DRV ↓; PAR ↓ |
| **LPV/r** | No data | No data | No data | ALLY-2 ↔ | LPV ↔; PAR ↑ |
| **TPV/r** | No data | No data | No data | No data | No data |
| **EFV** | SIM ↓; EFV ↔ | SOF ↔; EFV ↔ | ION-4 ↔ | DCV ↓* | No PK data** |
| **RPV** | SIM ↔; RPV ↔ | SOF ↔; RPV ↔ | LDV ↔; RPV ↔ | ALLY-2 ↔ | PAR ↑; RPV ↑ |
| **ETV** | No data | No data | No data | No data* | No data |
| **RAL** | SIM ↔; RAL ↔ | SOF ↔; RAL ↔ | LDV ↔; RAL ↔ | ALLY-2 ↔ | PrOD ↔; ↑ RAL |
| **ELV/cobi** | No data | Cobi ↑; SOF ↑ | LDV ↑; SOF ↑ | No data | No data |
| **DLG** | No data | No data | LDV ↔; DOL ↔ | ALLY-2 ↔ | PAR ↓; DOL ↑ |
| **MVC** | No data | No data | No data | No data | No data |
| **TDF** | SIM ↔; TFV ↔ | SOF ↔; TFV ↔ | LDV ↔; ↑TFV | DCV ↔; TFV ↔ | PrOD ↔; TFV ↔ |

## ARS Question 1: What type of HCV resistance testing would you perform at this time?

1. NS3
2. NS5A
3. NS5B
4. Both NS3 and NS5A testing
5. None

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## Case part 2

- NS5A resistance testing:
  - Mutation: Q30R

| Agent | Result |
|---|---|
| Daclatasvir | Resistance Probable |
| Ledipasvir | Resistance Probable |
| Ombitasvir | Resistance Probable |
| Elbasvir | Resistance Probable |

- NS3/4A resistance (2 years earlier):
  - Mutation: I37V

| Agent | Result |
|---|---|
| Boceprevir | Sensitive |
| Simeprevir | Sensitive |
| Telaprevir | Sensitive |
| | |

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## Was resistance testing helpful?




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## Key principles of HCV resistance-associated substitutions (RASs)

- **Viruses with RASs may exhibit variable "fitness" compared to wildtype**
  - Higher fitness last longer (e.g.NS5A), lower fitness may be transient (e.g. NS5B)
- **RAS are present at baseline in the absence of drug exposure, but may or may not be detected. RASs that are selected during treatment tend to confer more resistance.**
  - The longer on treatment the more likely to have RASs at time of virologic failure.
- **RASs may impact treatment responses in select situations**
  - Situation is often worse in presence of other treatment characteristics
- **Resistance is NOT futile**
  - May be overcome by longer durations, addition of ribavirin, or later-generation agents
- **For newly approved regimens detection of RASs is most often NOT necessary**

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## Resistance Testing Assays

- Traditional approach is population sequencing, newer assays use "ultras-deep sequencing (next-generation sequencing, or NGS)
- Available:
  - HCV NS5A drug resistance assay (LabCorp / Monogram Biosciences)
    - NGS - 10% threshold for reporting
  - HCV NS3 and NS5 HCV RNA genotype + resistance (Quest)
    - RT-PCR with DNA sequencing
  - For GT1 and GT3
    - GT1 assays are subtype specific

Adapted from David Wyles

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## Differences in the barrier to resistance by drug class

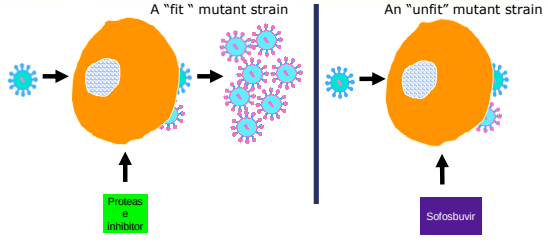
- RAVs to one drug are generally cross resistant to other drugs within a class (but not always)
- Viral fitness of RAVs effects their persistence after discontinuation of therapy

| | NS3/4A Protease Inhibitors | NS5B Nucleos(t)ide Polymerase Inhibitors | NS5B Nonnucleoside Polymerase Inhibitors | NS5A Inhibitors |
|---|---|---|---|---|
| **Drugs in Class** | Simeprevir<br>Paritaprevir<br>Grazoprevir<br>Voxilaprevir<br>Glecaprevir | Sofosbuvir | Dasabuvir | Ledipasvir<br>Ombitasvir<br>Daclatasvir<br>Elbasvir<br>Pibrentasvir |
| **Barrier to resistance** | Variable<br>(1a lower barrier than 1b) | Extremely High<br>(1a=1b) | Very low<br>(1a lower barrier than 1b) | Variable<br>(1a lower barrier than 1b) |
| **Comments** | 2nd and 3rd generation PIs have higher barrier, pangenotypic | Single target<br>Active site | Allosteric<br>Many targets | Multiple antiviral<br>Mechanism of Action |

Modified from Schaefer EA, et al. Gastroenterology. 201

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## What do we mean by barrier to resistance? Mutations may produce strains of varying fitness to replicate




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**ARS Question #2: How would you treat a patient with SOF/LDV experience and documented NS5A resistance?**

1. SOF/VEL + RBV x 24 weeks
2. SOF + PrOD + RBV x 12 weeks
3. Glecaprevir/pibrentasvir x 16 weeks
4. SOF/VEL/VOX x 12 weeks
5. SOF/VEL/VOX + RBV x 12 weeks

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## Broad Cross-resistance With "Early Generation" NS5As

| Fold-change | 1a | | | | 1b | |
|---|---|---|---|---|---|---|
| | M28T | Q30R | L31M/V | Y93H/N | L31V | Y93H/N |
| Ledipasvir | 20x | >100x | >100x/ >100x | >1,000x/ >10,000 | | >100x/-- |
| Ombitasvir | >1000x | >100x | <3x >100x | >10,000x/ >10,000x | <10x | 20x/50x |
| Daclatasvir | >100x | >1000x | >100x/ >1000x | >1,000x/ >10,000x | <10x | 20x/50x |
| Elbasvir | 20x | >100x | >10x >100x | >1,000x/ >1,000x | <10x | >100x/-- |
| Velpatasvir | <10x | <3x | 20x/50x | >100x/ >1000x | | <3x/-- |
| ACH-3102 | 30x | 20x | <10x | >100x/>100x | | <3x/<3x |
| Pibrentasvir | <3x | <3x | <3x | <10x/<10x | <3x | <3x/<3x |
| MK-8408 | <10x | <10x | <10x | <10x | <10x | <10x |

Wang C. AAC 2012. Cheng G. #1172. EASL 2012; Zhao Y. #A845 EASL 2012. Yang G. EASL 2013; Ng T. #639 CROI 2014. Asante-Appiah E. AASLD 2014.

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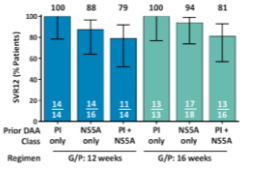
## Glecaprevir / pibrentasvir for re-treatment of NS5A failures - MAGELLAN 1

GLE
PIB




- 12 versus 16 weeks, GT1,4-6
- 34% / 26% cirrhosis per grou
- Baseline RAS
  - NS5A only: 55% / 52%
  - NS3+NS5A: 11% / 9%
- Overall SVR 89% vs 91%
- 12wks higher relapse w/ NS RAS
- Dual NS3/NS5A - 55% relap

**SVR12 by DAA Class in Prior Therapy**




Poordad et al. EASL 2017

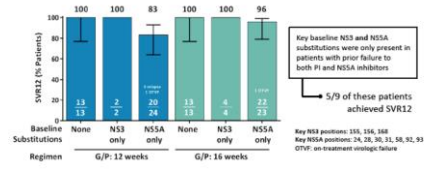
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## Glecaprevir / pibrentasvir for re-treatment of NS5A failures - MAGELLAN 1

GLE
PIB




### SVR12 by Key NS3 and NS5A Baseline Substitutions




**Y93H/N at baseline:** 100% (13/13) SVR12 in patients with NS5A inhibitor experience (PI-naïve)

Poordad et al. EASL 2017



## Glecaprevir / pibrentasvir for re-treatment of NS5A failures - MAGELLAN 1

GLE
PIB




### Adverse Events (AE) and Laboratory Abnormalities

| Event, n (%) | G/P 12 weeks N = 44 | G/P 16 weeks N = 47 |
|---|---|---|
| Any AE | 33 (75) | 32 (68) |
| Serious AE | 1 (2) | 2 (4) |
| Serious AE potentially related to DAA | 0 | 0 |
| AE leading to study drug d/c | 0 | 0 |
| AEs occurring in ≥10% of patients | | |
| Headache | 6 (14) | 11 (23) |
| **Post-baseline laboratory abnormalities** | | |
| Alanine aminotransferase*, Grade ≥3 (>5 × ULN) | 0 | 0 |
| Total bilirubin, Grade ≥3 (>3 × ULN) | 0 | 0 |
| Hemoglobin, Grade ≥3 (<8 g/dL) | 0 | 0 |

Serious AEs: gastrointestinal viral infection, back pain, and wound infection
*Post-rx≥ increase in grade to Grade ≥3

Poordad et al. EASL 2017

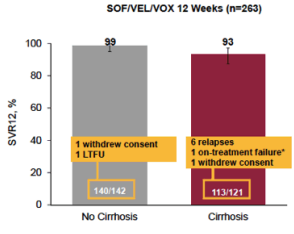


## SOF/VEL/VOX for re-treatment of NS5A failures

VOX
VEL
SOF



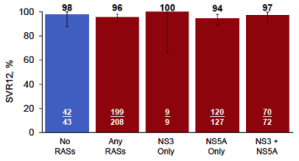
- POLARIS 1
  - GT 1-6 (30% GT3)
- 12 weeks of therapy
  - vs placebo
- Including compensated cirrhosis (46%)
- 2.2% relapse
- 4 GT 3 relapse – all 3a and ¾ had BL NS5A RAS
- No treatment emergent RAS
- all VF had cirrhosis (6 R, 1 VBT)




Bourliere et al. NEJM 2017

## POLARIS-1






- 83% of patients had baseline RASs; 79% had baseline NS5A RASs
- Two patients had S282T at baseline, both achieved SVR12
- None of the patients who relapsed had treatment-emergent RASs

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## Recommendations for Testing, Managing, and Treating Hepatitis C

AASLD IDSA

Recommended and alternative regimens for:

NS5A Inhibitor DAA-Experienced, Genotype 1 Patients With or Without Compensated Cirrhosis[a]

| RECOMMENDED | DURATION | RATING |
|---|---|---|
| Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) | 12 weeks | I, A |
| **ALTERNATIVE** | **DURATION** | **RATING** |
| Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b] except NS3/4 protease inhibitor inclusive DAA combination regimens | 16 weeks | IIa, B |

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.

- Resistance testing is generally not recommended for these regimens

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Taken from http://hcvguidelines.org, September 26, 2017

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## Case 2

- A 55 year old woman with GT 3 HCV has failed SOF + DCV x 12
- She is HIV pos on elvitegravir, cobi, FTC, TAF
- Other Meds: HCTZ 25mg; Vit D
- Exam: normal
- HCV 6.2 log IU/ml; alb 3.6; TB 1.2; creat 1.1; INR 1; AST 62 U/L; ALT 47; PLTs 120K; FibroSure 0.8; elastography 15.6 kPa; Fib-4 4.14

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## ARS Question 3: What is the next step?

1. Test for resistance
2. SOF/VEL/VOX x 12 wks
3. SOF/VEL/VOX + RBV x 12 wks
4. GP x 16 wks
5. SOF/DCV/RBV x 24

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## Retreatment of GT 3 failure with cirrhosis

Recommended regimen for:
DAA-Experienced (Including NS5A Inhibitors), Genotype 3 Patients With or Without Compensated Cirrhosis[a]

| RECOMMENDED | DURATION | RATING |
|---|---|---|
| Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/ voxilaprevir (100 mg) | 12 weeks | I, A |
| For patients with prior NS5A inhibitor failure and cirrhosis, weight-based ribavirin is recommended. | 12 weeks | IIa, C |

[a] For decompensated cirrhosis, please refer to the appropriate section.

No alternative recommendation for this situation

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Bourliere M NEJM 2017

## ARS Question #4: What is the next step before that step?

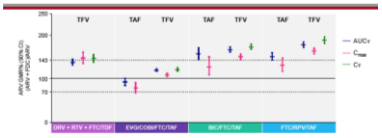
1. No changes needed
2. Switch ART

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## Sofosbuvir/velpatasvir/voxilaprevir: ARV DDI

- Healthy volunteer study included
  - DRV/r + TDF/FTC, EVG/cobi/TAF/FTC, BIC/TAF/FTC, RPV/TAF/FTC
  - Remember no EFV/ETR allowed due to VEL

**Effect of SOF/VEL/VOX on HIV ARV PK**



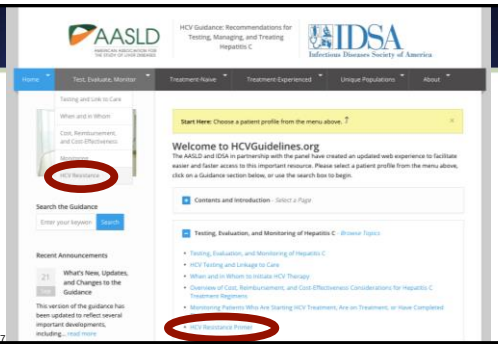

Garrison et al. Clin Pharm 2017



## ART HCV drug interactions – Kiser HCV guidance

| | Ledipasvir/ Sofosbuvir (LDV/SOF) | Sofosbuvir/ Velpatasvir (SOF/VEL) | Elbasvir/ Grazoprevir (ELB/GRZ) | Glecaprevir/ Pibrentasvir (GLE/PIB) | Sofosbuvir/ Velpatasvir/ Voxilaprevir (SOF/VEL/VOX) |
|---|---|---|---|---|---|
| Raltegravir (RAL) | ⇔ LDV<br>⇔ RAL | ⇔ VEL<br>⇔ RAL | ⇔ ELB<br>⇔ GRZ<br>▲ RAL | ⇔ GLE<br>⇔ PIB<br>▲ RAL | ND |
| Cobicistat-boosted elvitegravir (COB) | ▲ LDV<br>▲ COB[J] | ▲ VEL<br>▲ COB[J] | ▲ ELB<br>▲ GRZ<br>▲ COB | ▲ GLE<br>▲ PIB<br>▲ COB | ▲ VOX<br>▲ COB[J] |
| Dolutegravir (DTG) | ⇔ LDV<br>⇔ DTG | ⇔ VEL<br>⇔ DTG | ⇔ ELB<br>⇔ GRZ<br>▲ DTG | ▼ GLE<br>▼ PIB<br>▲ DTG | ND |
| Maraviroc (MVC) | ND | ND | ND | ND | ND |
| Tenofovir (TFV) disoproxil fumarate | ⇔ LDV<br>▲ TFV[C] | ⇔ VEL<br>▲ TFV | ⇔ ELB<br>⇔ GRZ<br>▲ TFV | ND | ▲ TFV[D] |
| Tenofovir (TFV) alafenamide | ⇔ LDV<br>▲ TFV[E] | ⇔ VEL<br>▲ TFV[E] | ND | ⇔ GLE<br>⇔ PIB<br>⇔ TFV | ▲ TFV[D] |
| | | | ⇔ RPV | ▲ RPV | ⇔ RPV |
| Etravirine (ETV)[I] | ND | ND | ND | ND | ND |





## When should one test for RASs?

Regimen-Specific Recommendations for Use of RAS Testing in Clinical Practice

| RECOMMENDED | RATING |
|---|---|
| **Elbasvir/grazoprevir**<br>NS5A RAS testing is recommended for genotype 1a-infected, treatment-naive or -experienced patients being considered for elbasvir/grazoprevir. If present, a different regimen should be considered. | I, A |
| **Ledipasvir/sofosbuvir**<br>NS5A RAS testing can be considered for genotype 1a-infected, treatment-experienced patients without cirrhosis being considered for ledipasvir/sofosbuvir. If clinically important[a] resistance is present, a different recommended therapy should be used.<br>NS5A RAS testing can be considered for genotype 1a-infected, treatment-experienced patients with cirrhosis being considered for ledipasvir/sofosbuvir. If clinically important[a] resistance is present, a different recommended therapy should be used. | I, A |
| **Sofosbuvir/velpatasvir**<br>NS5A RAS testing is recommended for genotype 3-infected, treatment-naive patients with cirrhosis and treatment-experienced patients (with or without cirrhosis) being considered for 12 weeks of sofosbuvir/velpatasvir. If Y93H is present, weight-based ribavirin should be added or sofosbuvir/velpatasvir/voxilaprevir should be used. | I, A |
| **Daclatasvir plus sofosbuvir**<br>NS5A RAS testing is recommended for genotype 3-infected, treatment-experienced patients without cirrhosis being considered for 12 weeks of daclatasvir plus sofosbuvir. If Y93H is present, weight-based ribavirin should be added.<br>NS5A RAS testing is recommended for genotype 3-infected, treatment-naive patients with cirrhosis being considered for 24 weeks of daclatasvir plus sofosbuvir. If Y93H is present, treatment should include weight-based ribavirin, or a different recommended therapy used. | I, B |

[a] Clinically important = greater than 100-fold resistance

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September 26, 2018

## When should one NOT test for RASs?

| NOT RECOMMENDED | RATING |
|---|---|
| **Elbasvir/grazoprevir**<br>RAS testing is not recommended for any genotype 1b-infected patients being considered for elbasvir/grazoprevir therapy. | I, A |
| **Glecaprevir/pibrentasvir**<br>RAS testing is not recommended for patients with genotype 1, 2, 3, 4, 5, or 6 infection being considered for glecaprevir/pibrentasvir for 8, 12, or 16 weeks. | I, A |
| **Ledipasvir/sofosbuvir**<br>NS5A RAS testing is not recommended for any genotype 1b-infected patients being considered for ledipasvir/sofosbuvir therapy. | I, A |
| NS5A RAS testing is not recommended for genotype 1a-infected, treatment-naive patients being considered for ledipasvir/sofosbuvir therapy. | I, A |
| NS5A RAS testing is not recommended for genotype 1a- or 1b-infected, treatment-naive patients without cirrhosis and with a viral load <6 million IU/mL being considered for an 8-week course of ledipasvir/sofosbuvir therapy. | I, A |
| **Paritaprevir/ritonavir/ombitasvir with dasabuvir ± weight-based ribavirin, or paritaprevir/ritonavir/ombitasvir + weight-based ribavirin**<br>RAS testing is not recommended for genotype 1- or 4-infected, treatment-naive or -experienced patients being considered for therapy with paritaprevir/ritonavir/ombitasvir with dasabuvir ± weight-based ribavirin or paritaprevir/ritonavir/ombitasvir + weight-based ribavirin, respectively. | I, A |
| **Sofosbuvir/velpatasvir**<br>RAS testing is not recommended for patients with genotype 1, 2, 4, 5, or 6 infection being considered for 12 weeks of sofosbuvir/velpatasvir therapy. | I, A |
| **Sofosbuvir/velpatasvir/voxilaprevir**<br>RAS testing is not recommended for patients with genotype 1, 2, 3, 4, 5, or 6 infection being considered for 12 weeks of sofosbuvir/velpatasvir/voxilaprevir therapy. | I, A |

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## Prevention and surveillance for hepatocellular carcinoma

- HCV: F3/F4
  - Older age, black race, lower platelet count
  - Increased with dual infection HBV, possibly HIV and other liver diseases (eg alcohol, fatty liver)
  - SVR reduces risk substantially
  - Coffee consumption protective
- Imaging every 6 months
  - Preferred modalities vary - but 6 months superior to 12 months
- Alfa-fetoprotein
  - Has poor specificity and poor sensitivity, perhaps most useful when

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## Controversy regarding HCC after DAA therapy

*"Unexpected high rate and pattern of tumor recurrence coinciding with HCV clearance"* Reig J Hepatol 2016

versus

"*We did not observe an increased risk of HCC recurrence after DAA treatment*"
Pol et al. J Hepatol 2016

Difference between IFN-induced and DAA-induced SVR?

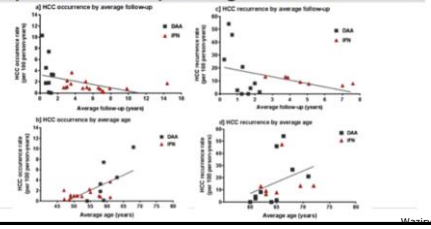
Some speculated an effect of DAAs

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## Controversy regarding HCC after DAA therapy

Meta-analysis of available studies

**Impact of Follow-up and Age on HCC incidence**



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Waziry R FASL 2017

## Controversy regarding HCC after DAA therapy

**HCC occurrence**

| | Unadjusted RR | Adjusted RR | 95% CI | P value |
|---|---|---|---|---|
| Average follow-up | 0.88 | 0.77 | 0.62, 0.97 | 0.03 |
| Average age | 1.11 | 1.06 | 0.99, 1.14 | 0.08 |
| Treatment | 2.77 | 0.75 | 0.22, 2.52 | 0.62 |

**HCC recurrence**

| | Unadjusted RR | Adjusted RR | 95% CI | P value |
|---|---|---|---|---|
| Average follow-up | 0.86 | 0.79 | 0.55, 1.15 | 0.19 |
| Average age | 1.11 | 1.11 | 0.96, 1.27 | 0.14 |
| Treatment | 1.36 | 0.62 | 0.11, 3.45 | 0.56 |

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## Key principles of HCV resistance-associated substitutions (RASs)

- **Viruses with RASs may exhibit variable "fitness" compared to wildtype**
  - Higher fitness last longer, lower fitness may be transient
- **RAS are present at baseline in the absence of drug exposure, but may or may not be detected**
  - Possibility of transmission
- **RASs may impact treatment responses in select situations**
  - Situation is often worse in presence of other treatment characteristics
- **Resistance is NOT futile**
  - May be overcome by longer durations, addition of ribavirin, or later-generation agents
- **For newly approved regimens detection of RASs is most often NOT necessary**

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## Take home points regarding case

- The most important factor in deciding upon re-treatment regimens is the prior DAA failure
- Resistance-associated substitutions are NOT futile
  - May impact select situations
  - Certain mutations may require longer treatment courses, ribavirin
- Ribavirin-free regimens are newly available approved for many re-treatment considerations
- Continue surveillance for those with hepatocellular carcinoma
  - Referral to liver transplant center if possible
  - When controlling for age and length of follow-up, no apparent increase of HCC occurrence or recurrence in DAA era

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## Question-and-Answer

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