HCV Infection in 2019: Are we on the path to elimination?

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Disclosures

• Dr Naggie has received research support from AbbVie, Gilead Sciences, Inc, Tacere; serves as scientific advisor for Vir and BioMarin; serves on event adjudication committee for PRA and FHI360. (Updated 10/01/2019)

• Discussion of off label use
Objectives

• Discuss HCV epidemiology and WHO elimination goals
• Discuss HCV treatment including in unique populations
• Discuss challenges to elimination and how to address them
• Discuss SVR benefits
A Case

- A new referral- from hematology
- 81 y/o man with long-standing chronic HCV infection, diagnosed in 2000
- Followed by PCP with labs and ultrasound of liver
- Hypertension (controlled), CKD III
- ? HCV genotype, HIV, HBV
- Over 5+ years decline in platelet count, decline in WBC
His Questions

• Can this issue with my bone marrow be from my HCV?
• How can this happen when I feel fine?
• Can I afford treatment?
• Will you offer me treatment?
• What does this all mean?
DISCUSS HCV EPIDEMIOLOGY AND ELIMINATION GOALS
Incident HCV Infection

1.75 million – 23.7/100,000

WHO Global Hepatitis Report 2017
Acute HCV Infection in US

CDC, National Notifiable Diseases Surveillance System
FIGURE 1. Incidence of acute hepatitis C among persons aged ≤30 years, by urbanicity and year — Kentucky, Tennessee, Virginia, and West Virginia, 2006–2012

FIGURE 1. Hepatitis C virus (HCV) detection rate among females aged 15–44 years and HCV testing rate among children aged ≤2 years — United States and Kentucky, 2011–2014.*

### WHO Goals by 2030

<table>
<thead>
<tr>
<th>2030 WHO Targets</th>
<th>Incidence Reduction</th>
<th>Mortality Reduction</th>
<th>Diagnosis Coverage</th>
<th>Treatment Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>80%</td>
<td>65%</td>
<td>90%</td>
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#### Incidence

<table>
<thead>
<tr>
<th>Year</th>
<th>Rate per 100,000</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
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<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
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<td>2010</td>
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<td>0.29</td>
<td>0.42</td>
<td>0.60</td>
<td>0.72</td>
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<td>0.98</td>
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#### Liver-related Death

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<tr>
<th>Year</th>
<th>Age-adjusted rate per 100,000</th>
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<th>2011</th>
<th>2012</th>
<th>2013</th>
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<th>2015</th>
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<tbody>
<tr>
<td>2010</td>
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<td>4.64</td>
<td>4.82</td>
<td>4.94</td>
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Will the US make it?

2030 WHO Targets

US

2022 2025 2026

Source: Razavia et al. EASL 2019, Vienna
How do we address this?

- Testing=Diagnosis
- Access=Treatment
- Harm reduction
- Vaccine?
How do we address this? Testing!

Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945–1965

Draft: Recommendation Summary

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Grade (What’s This?)</th>
</tr>
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<tbody>
<tr>
<td>Adults ages 18 to 79 years</td>
<td>The USPSTF recommends screening for hepatitis C virus (HCV) infection in adults ages 18 to 79 years.</td>
<td>B</td>
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</table>
DISCUSS HCV TREATMENT INCLUDING IN UNIQUE POPULATIONS
The initial challenges to DAA development

HIV = 4 x 10^8 – 3 x 10^{10} virions/day

HCV = 4 x 10^{10} – 1 x 10^{13} virions/day

100 to 3000 fold more HCV produced/day
Hepatitis C Virus: Life Cycle

(a) Entry
(b) Endocytosis and uncoating
(c) Translation and cleavage
(d) Replication
(e) Assembly
(f) Release

Adapted from Naggie et al. J Antimicrob Chemother 2010
Hepatitis C Virus

5′ UTR region

HCV Genome

9.6 kb RNA

3′ UTR region

IRES-mediated translation

Polyprotein

C E1 E2 NS2 NS3 A NS4B A NS5 B

Polyprotein Processing

C E1 E2 p7 NS2 NS3 4A NS4B NS5A NS5B

Core Envelope glycoproteins Serine Protease Serine Protease Cofactor RNA dependent RNA polymerase

NS3-4A Protease Inhibitors:
Grazoprevir*
Paritaprevir*
Simeprevir

NS5A Inhibitors:
Daclatasvir
Elbasvir*
Ledipasvir*
Ombitasvir*
Velpatasvir*

Adapted from Naggie et al. J Antimicrob Chemother 2010
HCV Therapeutic Timeline

- **1991**: Interferon 48W
- **1996**: Interferon + RBV
- **2001**: Telaprevir & Boceprevir
- **2011**: Sofosbuvir & Simeprevir
- **2013**: Ledipasvir* Paritaprevir/ Ombitasvir/ Dasabuvir Daclatasvir
- **2014**: First all oral GT 2 & 3
  - First in liver transplant & decompensation
- **2016**: Telaprevir & Boceprevir
- **2017**: Telaprevir & Boceprevir

Adapted from Naggie and Wyles. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, ed 9, 2019.
Goal of Treatment

- The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by a sustained virologic response.
  Rating: Class I, Level A

Recommendations for When and in Whom to Initiate Treatment

- Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Patients with short life expectancies owing to liver disease should be managed in consultation with an expert.
  Rating: Class I, Level A
### Initial Treatment of HCV in 2019

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Mechanism of Action</th>
<th>Genotype Coverage</th>
<th>Weeks of Therapy; Wholesale Acquisition Cost</th>
<th>Adverse Effects ≥5%</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elbasvir/ grazoprevir</td>
<td>NS5A/NS3</td>
<td>1, 4</td>
<td>12; $54,600</td>
<td>Fatigue, 11%; headache, 10%</td>
<td>Sustained virologic response lower for genotype 1a when baseline NS5A RAS is present (70% vs 98%); approval is for 16 weeks with ribavirin when genotype 1a and baseline RAS is present but is not recommended because of other treatment options; approved for CKD and ESRD</td>
</tr>
<tr>
<td>Gilead/velpatasvir</td>
<td>NS5B/NS5A</td>
<td>1-6</td>
<td>8 or 12 if cirrhosis; $26,400 or $39,600</td>
<td>Headache, 13%; fatigue, 11%; nausea, 8%</td>
<td>Approval is for 8 weeks in patients without cirrhosis and 12 weeks in patients with cirrhosis; approved for CKD and ESRD and liver and kidney transplant recipients</td>
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<tr>
<td>Ledipasvir/ sofosbuvir</td>
<td>NS5A/NS5B</td>
<td>1, 4, 5, 6</td>
<td>12; $94,500</td>
<td>Fatigue, 16%; headache, 14%; nausea, 7%; insomnia, 5%</td>
<td>Therapy can be shortened to 8 weeks for genotype 1, no cirrhosis, no prior treatment, HCV RNA &lt; 6 million IU/mL; approved for decompensated cirrhosis, liver transplant, and children aged &gt; 12 years</td>
</tr>
<tr>
<td>Sofosbuvir/ velpatasvir</td>
<td>NS5B/NS5A</td>
<td>1-6</td>
<td>12; $74,760</td>
<td>Headache, 22%; fatigue, 15%; nausea, 9%; asthenia, 5%; insomnia, 5%</td>
<td>For genotype 3 with cirrhosis, baseline NS5A RAS testing is recommended and if Y93H RAS is present, a different regimen is recommended; approved for decompensated cirrhosis</td>
</tr>
</tbody>
</table>

Generic $24K/12 weeks

Generic $24K/12 weeks
• Randomized, open-label
• Genotype 1
• Treatment duration and RBV use per clinician
• PrOD use discontinued 12/2017

Sulkowski et al, EASL 2019. Abstract THU-182
### SVR Comparison

<table>
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<tr>
<th></th>
<th>EBR/GZV+/−RBV</th>
<th></th>
<th>SOF/LDV+/−RBV</th>
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<th>Difference in SVR rate</th>
<th>95% CI</th>
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<tbody>
<tr>
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<td>n/N</td>
<td>SVR%</td>
<td>95% CI</td>
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<td>SVR%</td>
<td>95% CI</td>
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<td><strong>As randomized population</strong></td>
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<tr>
<td></td>
<td>551/581</td>
<td>94.8</td>
<td>92.7, 96.5</td>
<td>347/358</td>
<td>96.9</td>
<td>94.6, 98.5</td>
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<td>With RBV</td>
<td>39/46</td>
<td>84.8</td>
<td>71.1, 93.7</td>
<td>14/15</td>
<td>93.3</td>
<td>68.1, 99.8</td>
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<td>Without RBV</td>
<td>512/535</td>
<td>95.7</td>
<td>93.6, 97.3</td>
<td>333/343</td>
<td>97.1</td>
<td>94.7, 98.6</td>
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<td>Black</td>
<td>253/265</td>
<td>95.5</td>
<td>92.2, 97.6</td>
<td>153/159</td>
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<td>92.0, 98.6</td>
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<td>94.3</td>
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<td>94.2, 99.2</td>
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<td>Experienced</td>
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<td>80.4, 96.4</td>
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<td>Naive</td>
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<td>Cirrhosis</td>
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<td>96.8</td>
<td>91.0, 99.3</td>
<td>62/66</td>
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<td>85.2, 98.3</td>
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<td>No Cirrhosis</td>
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<td>Ras</td>
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<td>75.1, 94.6</td>
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<td>74.3, 95.2</td>
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<td>No Ras</td>
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<td>93.7, 97.4</td>
<td>285/289</td>
<td>98.6</td>
<td>96.5, 99.6</td>
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<td><strong>As treated population</strong></td>
<td>569/599</td>
<td>95.0</td>
<td>92.9, 96.6</td>
<td>330/341</td>
<td>96.8</td>
<td>94.3, 98.4</td>
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</table>
Closing the Gap in Persons with HIV
Pregnant women- are we ready to treat?

• NEED to ADD SLIDE
Barriers – Perceived and Real

- Cost=Access/Restrictions
- Engagement in care
- Prioritization by patients and providers
- Concern for re-infection
- Reaching the highest risk populations

VA has cured 100,000 Veterans of Hepatitis C

New drugs and outreach campaign helped VA to rapidly deploy and treat Veterans
DISCUSS CHALLENGES TO ELIMINATION AND HOW TO ADDRESS
Acute HCV Infection in US

CDC, National Notifiable Diseases Surveillance System
HCV Reinfection: high in HIV-infected persons and/or PWID

Ingiliz et al, J Hep 2016
Carollo et al. CROI 2019 Abstract #86
HCV Treatment as Prevention (TasP)

Patients at risk of transmitting HCV

- Cost-saving
- Cost-effective (ICER>$0/QALY and <$100,000/QALY)
- Not cost-effective (ICER>$100,000/QALY)

Spontaneous clearance rate vs. SVR rate of treatment of acute HCV

Number of acute HCV infections

Declining HCV incidence in Dutch HIV+ MSM after unrestricted access to HCV therapy – Boerekamps et al. Clin Inf Dis, 2018

Acute Infection - Treat early or treat as chronic?

Rockstroh et al: N=26, HIV infected, later treatment, asymptomatic

Deterding et al: N=20, not HIV infected, immediate treatment, primarily symptomatic
How low can you go for acute HCV treatment?

N=27 men with HIV/HCV including high viral load, 8 weeks of LDV/SOF sufficient for cure.

N=30 men mostly with HIV/HCV, 6 weeks of G/P sufficient for cure.
High-Risk Patients

Strategies Needed to Minimize Onward Transmission

• Education
  – HCV awareness
  – Safe injection practices
  – Sexual risk reduction

• Harm-reduction interventions
  – Opioid substitution therapy
  – Needle and syringe exchange

• Access to HCV treatment (TasP)
  – New pangenotypic DAA regimens

Cost Benefits of Test-and-Treat in Prisons  
*Can Correctional Systems Afford to NOT Treat HCV?*

**Infections Averted by In-prison HCV Management**

- **In-prison Management of Released Inmates, Number**
  - 1-Year Risk
  - 1-Year All
  - 5-Years All
  - 10-Years All

**Costs of Advanced HCV Disease Averted**

- **Cost of Advanced Disease Averted, $ (Millions)**
  - 1-Year Risk
  - 1-Year All
  - 5-Years All
  - 10-Years All


*Duke Clinical Research Institute*
DISCUSS SVR BENEFITS
Benefits of SVR are well accepted.
Kaplan-Meier curves Incident DM
Can we predict ESLD complications?

N=126, case:control of patients with HIV/HCV and available sample >1 year prior to ESLD event=ascites, SBP, EV bleed, HCC, HE, death.
Back to the case

• No risk for onward transmission/re-infection
• High risk for developing ESLD
• Treatment will impact his risk of liver-related mortality
• GT1a, fibroscan result consistent with cirrhosis and portal HTN
• Treatment started
Thank You

Mentors
John McHutchison
Chuck Hicks
Andrew Muir
Keyur Patel

Collaborators
Arthur Mosely
Jennifer Kiser
Svati Shah
Anna Mae Diehl, Guido Ferrari
Larry Parks, Sam Lusk, Joe Lucas

Leadership
John Perfect
Chris Woods
Mary Klotman

Research Team
Audrey Lan, Tammy Wong, Rachel
Safeek, Meredith Mock, Usha Kadiyala

Funding: NIDDK-R01DK112295; NIAID-1R61AI140485, HHSN272201300017I; NHLBI-1R56HL129880; Duke CFAR, AIDS Clinical Trials Group
Questions
Pharmacologic Prophylaxis
Not Recommended

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<th>RATING</th>
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<tr>
<td>Pre-exposure or post-exposure prophylaxis with antiviral therapy is not recommended.</td>
<td>III, C</td>
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