Southern African HIV Clinicians Society

3rd Biennial Conference

13 - 16 April 2016
Sandton Convention Centre
Johannesburg

Our Issues, Our Drugs, Our Patients

www.sahivsoc.org
www.sahivsoc2016.co.za
Impact of Viral Hepatitis on Mortality

N= 822 HIV +

HBV and HCV
N = 35

HCV
N = 235

HBV
N = 64

No HCV/HBV
N = 437

0%  20%  40%  60%  80%  100%

*50% who died of ESLD had CD4 > 200

Salmon-Ceron et al  J Hep 2005;42:799-805
Accelerated Fibrosis in HIV-HCV co-infected patients

Liver-Related Deaths in HIV

1246 deaths in 23,441 HIV+ pts followed for 3.5 yrs
22% HCV, 8% HBV

D:A:D Study Arch Int Med 2006
Causes of Death in a HIV/HCV Coinfected Population

- AIDS: 9 (13%)
- Liver disease: 30 (43%)
- Neoplasm: 4 (6%)
- Cardiovascular disease: 8 (12%)
- Traffic accident: 3 (4%)
- Other: 15 (22%)

n/N = 69/1011

Twice as likely to die from liver disease than HIV

ALIVE Study: HIV, Age, and Severity of HCV-Related Liver Diseases

- Prospective cohort of HCV-infected IDUs (2006-2011) (n=1176)
  - HIV co-infected (n=394)
  - Baseline and semi-annual elastography
- Fibrosis was significantly greater in HCV/HIV co-infected versus HCV monoinfection ($P<0.001$)
  - No cirrhosis (12.9% versus 9.5%)
  - With cirrhosis (19.5% versus 11.0%)
  - Independently associated with increasing age and HIV infection
- HCV/HIV patients have liver fibrosis similar to HCV mono-infected patients who are nearly 10 years older

HCV Coinfection vs Monoinfection: Cumulative Incidence of Decompensation

- 10-year hepatic decompensation risk 83% higher in coinfected patients
  - Adjusted HR 1.83 (95% CI: 1.54-2.18)

Summary of HIV/HCV- co-infection

- Accelerated rate of HCV-related liver fibrosis progression in co-infected patients
  - Progression to cirrhosis risk 3-fold higher in co-infected vs HCV-mono-infected patients
  - Relative risk of decompensated liver disease 6-fold higher in co-infected vs HCV-monoinfected patients
  - HCC occurs earlier and more aggressive
- Increased risk of PMTCT of HCV
- Conflicting evidence on whether HCV influences HIV
- HIV confers greater risk of acute HCV infection and reduced rate of spontaneous clearance

HCV transmission – risk factors

<table>
<thead>
<tr>
<th>Parenteral</th>
<th>Sexual</th>
<th>Perinatal</th>
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</thead>
<tbody>
<tr>
<td>IDU</td>
<td>Multiple partners</td>
<td>High viral load</td>
</tr>
<tr>
<td>Nasal cocaine</td>
<td>Traumatic</td>
<td>HIV (+)</td>
</tr>
<tr>
<td>Transfusions</td>
<td>HIV (+)</td>
<td></td>
</tr>
<tr>
<td>Needle stick injury</td>
<td>Use of a CSW</td>
<td></td>
</tr>
<tr>
<td>Tattoos</td>
<td>Rectal contact</td>
<td></td>
</tr>
<tr>
<td>Body piercing</td>
<td>MSM</td>
<td></td>
</tr>
<tr>
<td>Manicures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Household items</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toothbrush, razor,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nail clipper</td>
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<tr>
<td>? Scarification</td>
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</tr>
</tbody>
</table>
High Prevalence of HCV Among Injection Drug Users Worldwide

HCV prevalence in low/middle income countries – selected MSF data

• HCV prevalence in blood donors 2012: Centre African Republic: 7.1%, DRC: 8.5%, Nigeria: 7.2% (MSF Operational Center Amsterdam)

• Manipur India: prospective cohort analysis among 468 people infected with HIV, 50.6% are co-infected with HCV. (MSF Operational Center Amsterdam)

• HCV screening in Ukraine: 74% of prisoners in MDRTB project are HCV positive. (MSF Ops Brussels)
Aim of treatment:
Sustained Virological Response = SVR

= Negative HCV RNA 12 (24) weeks after EOT

= CURE
Aim of Hepatitis C treatment = cure

HCV life Cycle favors resistance development not persistence

<table>
<thead>
<tr>
<th></th>
<th>HIV</th>
<th>HBV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable genome</td>
<td>Provirus</td>
<td>cccDNA</td>
<td>(none)</td>
</tr>
<tr>
<td>Virion NA polymerase</td>
<td>Host RNAPol</td>
<td>HBV RT</td>
<td>HCV NS5B</td>
</tr>
<tr>
<td>Error-prone replications per cell</td>
<td>One</td>
<td>Multiple</td>
<td>Multiple</td>
</tr>
<tr>
<td>Plasticity of genome</td>
<td>High</td>
<td>Constrained</td>
<td>Very high</td>
</tr>
<tr>
<td>Recombination</td>
<td>Common</td>
<td>Common</td>
<td>Rare</td>
</tr>
</tbody>
</table>
5-year risk of death (all-cause) by SVR

- **General**: 18 studies
  - n=29,269
  - Avg. FU=4.6 years
  - SVR: 10.5%
  - No SVR: 4.5%

- **Cirrhotic**: 9 studies
  - n=2,734
  - Avg. FU=6.6 years
  - SVR: 11.3%
  - No SVR: 3.6%

- **HIV/HCV**: 5 studies
  - n=2,560
  - Avg. FU=5.1 years
  - SVR: 10.0%
  - No SVR: 1.3%

A Hill et al AASLD 2014
Does SVR improve outcomes?

711 HIV-HCV Pts treated 2000-2005
31% had SVR

Scorecard:
- Deaths-ALL: P=0.001
- Liver Death: P=0.029
- AIDS Deaths: P<0.001
- Other Deaths: P=0.05
- Decompensation: P=0.05
- HCC: P=0.05
- Liver Transplant: P=0.05

HCV Treatment Improves Health

- **Advanced fibrosis**
  - Multicenter study\[1\]
    - 5 hospitals (Europe, Canada)
  - 530 pts with HCV
    - IFN regimens 1990-2003
    - Advanced fibrosis or cirrhosis
    - Median follow-up: 8.4 yrs

- **Early-stage disease**
  - Extra-hepatic manifestations\[2\]
  - Health-related quality of life\[3\]

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Treatment past and treatment present....
Treatment Past: PEG-Interferon and RIBAVIRIN

MONO- vs. CO-INFECTION outcomes

SVR (%)

800 mg

GT 1

GT 2/3

1000-1200 mg

GT 1

GT 2/3

Hadziyannis et al, Ann Int Med 2004
Torriani et al. NEJM 2004
Fried et al. NEJM 2002
HCV life cycle – the **Direct Acting Antivirals**

*Allows for IFN-free all oral therapy*

## DAAs in 2015/16

<table>
<thead>
<tr>
<th>Protease Inhibitors</th>
<th>Polymerase inhibitors</th>
<th>NS5A inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telaprevir/Boceprevir</td>
<td>Sofosbuvir</td>
<td>Dasabuvir</td>
</tr>
<tr>
<td>Simeprevir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paritaprevir/Ritonavir</td>
<td></td>
<td>Ombitasvir</td>
</tr>
<tr>
<td>Asunaprevir</td>
<td></td>
<td>Elbasvir</td>
</tr>
<tr>
<td>Grazoprevir</td>
<td></td>
<td>Velpatasvir</td>
</tr>
</tbody>
</table>
Guiding principles for all oral DAA regimens

• Combine drugs from different classes
  - Protease (NS3/4A) inhibitors
  - Polymerase (NS5B) inhibitors
  - NS5A inhibitors

• Multiple drugs combined to produce greater efficacy and reduce risk of viral resistance (not unlike HAART)
## Indications for treatment

- Essentially everyone should be treated
- Treatment prioritization needs to be applied in resource limited settings

<table>
<thead>
<tr>
<th>Treatment priority</th>
<th>Patient group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment should be prioritized</td>
<td>. Patients with significant fibrosis (F3) or cirrhosis (F4), including decompensated cirrhosis</td>
</tr>
<tr>
<td></td>
<td>. Patients with HIV coinfection</td>
</tr>
<tr>
<td></td>
<td>. Patients with HBV coinfection</td>
</tr>
<tr>
<td></td>
<td>. Patients with an indication for liver transplantation</td>
</tr>
<tr>
<td></td>
<td>. Patients with HCV recurrence after liver transplantation</td>
</tr>
<tr>
<td></td>
<td>. Patients with clinically significant extra-hepatic manifestations</td>
</tr>
<tr>
<td></td>
<td>. Patients with debilitating fatigue</td>
</tr>
<tr>
<td></td>
<td>. Individuals at risk of transmitting HCV</td>
</tr>
<tr>
<td>Treatment is justified</td>
<td>. Patients with moderate fibrosis (F2)</td>
</tr>
<tr>
<td>Treatment can be deferred</td>
<td>. Patients with no or mild disease (F0-F1) and none of the above-mentioned extra-hepatic manifestations</td>
</tr>
<tr>
<td>Treatment is not recommended</td>
<td>. Patients with limited life expectancy due to non-liver related comorbidities</td>
</tr>
</tbody>
</table>

Adapted from EASL Treatment Recommendations HCV, April 2015
**ION-4: LDV/SOF for 12 weeks in GT1/4 HCV/ HIV–coinfected**

- Permitted ARTs: TDF/FTC plus efavirenz, raltegravir, or rilpivirine
- Effective across subgroups, but with lowered SVR in black pts
- LDV: LEDIPASVIR
- SOF: Sofosbuvir *(HARVONI)*

Naggie S, et al. CROI 2015
ALLY-2: DCV + SOF for 12 weeks in GT1-4 HCV/HIV–coinfected

- Permitted ARTs: atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir, efavirenz, nevirapine, rilpivirine, dolutegravir, raltegravir, enfuvirtide, maraviroc, zidovudine, lamivudine, abacavir, tenofovir DF, emtricitabine
- Cirrhosis: 8.9% of naive pts, 28.8% of experienced pts
- No significant difference in SVR12 rates among black vs nonblack pts (92% vs 97%, respectively)
- 8 week arms in ALLY-2 inferior

DCV: DACLATASVIR
SOF: SOFOSBUVIR

Ombitasvir/Paritaprevir/RTV + Dasabuvir + Ribavirin for 12 vs 24 weeks in GT1 HCV/HIV co-infection

- 65% HCV treatment-naive pts in 12-wk arm, 69% in 24-wk arm
- 19% pts with METAVIR F4 fibrosis

**C-EDGE**: Grazoprevir/Elbasvir for 12 weeks in GT1-4 HCV/HIV–coinfection

- SVR rates similar across pt subgroups, including in black pts and pts with cirrhosis
- Tx failure in 2 pts attributable to posttreatment reinfection with GT3 HCV

# Summary – Treatment response

## SVR Responses in Treatment naïve GT 1 HCV-HIV Coinfection and HCV Mono-infection

<table>
<thead>
<tr>
<th>Regimen</th>
<th>HCV and HIV Coinfection</th>
<th>HCV Monoinfection</th>
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<tbody>
<tr>
<td></td>
<td>Study</td>
<td>n</td>
</tr>
<tr>
<td>Daclatasvir + Sofosbuvir</td>
<td>ALLY-2</td>
<td>83</td>
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<tr>
<td>Ledipasvir-sofosbuvir</td>
<td>ION-4</td>
<td>327</td>
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<tr>
<td>Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir + Ribavirin</td>
<td>TURQUOISE-I</td>
<td>31</td>
</tr>
<tr>
<td>Simeprevir + PR</td>
<td>C-212</td>
<td>53</td>
</tr>
<tr>
<td>Sofosbuvir + PR</td>
<td>PS7977-1910</td>
<td>19</td>
</tr>
<tr>
<td>Sofosbuvir + Ribavirin</td>
<td>PHOTON-1</td>
<td>114</td>
</tr>
</tbody>
</table>

PR= Peginterferon + Ribavirin
## Drug-Drug-interactions: Antiretrovirals

[http://www.hep-druginteractions.org](http://www.hep-druginteractions.org)

University of Liverpool *HEP i-chart* (Android/Apple)

<table>
<thead>
<tr>
<th></th>
<th>SIM</th>
<th>DCV</th>
<th>SOF</th>
<th>LDV/SOF</th>
<th>3D</th>
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<tr>
<td><strong>NRTIs</strong></td>
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<td>Abacavir</td>
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<tr>
<td>Emtricitabine</td>
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<tr>
<td>Lamivudine</td>
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<tr>
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<td><strong>NNRTIs</strong></td>
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<tr>
<td>Efavirenz</td>
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<td>▢</td>
<td>✓</td>
<td>✓*</td>
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<td>Etravirine</td>
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<td>▢</td>
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<td>Nevirapine</td>
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<td>✓</td>
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<td>Rilpivirine</td>
<td>●</td>
<td>▢</td>
<td>✓</td>
<td>✓</td>
<td>●</td>
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<td><strong>Protease inhibitors</strong></td>
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<tr>
<td>Atazanavir; Atazanavir/Ritonavir</td>
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<td>▢</td>
<td>✓</td>
<td>✓*</td>
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<tr>
<td>Darunavir/Ritonavir; Darunavir/Cobicistat</td>
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<td>✓</td>
<td>✓</td>
<td>✓*</td>
<td>▢</td>
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<td>▢</td>
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<td>Lopinavir</td>
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<td><strong>Entry/integrase inhibitors</strong></td>
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<tr>
<td>Dolutegravir</td>
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<td>◇</td>
<td>✓</td>
<td>✓</td>
<td>●</td>
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<tr>
<td>Elvitegravir/Cobicistat</td>
<td>●</td>
<td>▢</td>
<td>✓</td>
<td>✓*</td>
<td>●</td>
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<tr>
<td>Maraviroc</td>
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<td>◇</td>
<td>✓</td>
<td>✓</td>
<td>▢</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>●</td>
<td>◇</td>
<td>✓</td>
<td>✓</td>
<td>▢</td>
</tr>
</tbody>
</table>
HCV/HIV co-infection

• No longer considered difficult to cure
• Same recommendations as in HCV mono-infected
• Co-infected patients are a treatment priority
• Consider drug–drug interactions
• DCV + SOF ± RBV is recommended when ART regimen changes cannot be made to accommodate other DAAs

AASLD/IDSA. HCV guidelines.