Overview

- Epidemiology
  - Prevalence of HCV co-infection
  - Incidence and Recent Trends
- Consequences of Co-infection
  - Higher level of HCV RNA
  - Accelerated natural history
  - Beneficial effect of antiretroviral therapy
- Treatment
Worldwide Prevalence of HCV in Patient with HIV Infection Can Be Very High

The Prevalence of HCV in HIV Infected Individuals Differs by Risk Groups

Recent Epidemic of HCV Among HIV+ MSM: An Emerging Population

- Reports of epidemic of sexually transmitted HCV among HIV+ MSM
  - Amsterdam, Netherlands: HIV/HCV coinfection prevalence increased from 14.6% to 20.9% from 2000-2007
  - United States: 6-fold higher incidence rate in HIV+ vs HIV- MSM
  - Swiss HIV Cohort Study: HCV incidence increased 18-fold from 1998 to 2010
  - Sydney, Australia: 9% of HIV+ MSM coinfected with HCV vs 1.9% HIV- MSM

- Phylogenic analysis indicates HCV transmission clusters in some areas

MMWR. 2011;60:945-950.

Risk Factors for Sexual HCV Transmission Among HIV+ MSM

- Multiple factors associated with HCV transmission
  - Unprotected receptive anal intercourse
  - Online casual sexual partners
  - Sex at sex venues
  - Older age
  - Syphilis
  - Recreational drug use
  - Drinking > 13 alcoholic drinks per week

Outbreak of Acute HCV CASCADE Cohorts

- Data from 12 cohorts within the Concerted Action on SeroConversion to AIDS and Death in Europe (CASCADE) Collaboration
- Of 4724 MSM, 3014 had HCV testing at the time of HIV seroconversion
  - 124 (4%) were repeatedly HCV positive
  - 92 (3%) had one negative and subsequent positive HCV test (new HCV infections)
  - 2798 (93%) were HCV negative and remained negative
- HCV incidence:
  - 1990: 0.9-2.2 per 1000 person-years
  - 1995: 5.5-8.1 per 1000 person-years
  - 2005: 16.8-30.0 per 1000 person-years
  - 2007: 23.4-51.1 per 1000 person-years

HCV is a Sexually Transmitted Disease Among HIV-infected MSMs: NYC 2005-2010

- HIV-positive MSM diagnosed with HCV reported from Mount Sinai Hospital: (N=74)
  - No IVDU
  - Newly elevated ALT levels and a positive HCV antibody test result
  - Median age 39 years
- Case Control study was carried out:
  - Cases: HIV-infected MSM with HCV infection
  - Controls: HIV-infected MSM without HCV infection
- Independent risk factors associated with HCV
  - Receptive anal intercourse (AOR = 23, p=0.009)
  - Sex while on methamphetamine (AOR 28.56, p=0.02)
HIV-HCV Coninfection

Consequences of HIV-HCV Co-infection

HIV Co-infection Leads to Higher HCV RNA

HIV Co-infection Leads to Accelerated Liver Disease


Risk of Hepatic Decompensation in HIV-HCV

Adjusted HR 1.83 (95% CI: 1.54-2.18)

**HIV-HCV Co-infection Leads to Higher Incidence of Hepatocellular Carcinoma in Spain**

- HIV-HCC (N=82) in 18 hospitals in Spain
  - HCV: 81%
  - HCV/HBV: 12%
  - HBV: 7%
- In patients with HIV/HCV, incidence of HCC increased
- Death occurred in 79% of patients with HCC
- Median survival: 91 days (IR: 31–227 days)


**Due to Increased Rates for Adverse Outcomes, Liver Deaths is One of the Leading Causes of Death Among HIV-HCV Infected Patients**

- Cirrhotic Patients: > 50% deaths related to HCV
- Non cirrhotic patients: 60% deaths non related to HCV nor HIV

Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D study

- D:A:D Cohort study of 33,308 individuals [180,176 person-years (PY)]
- Patient Death N=2482 [Death rate/1000 PY = 13.8 (95% CI 13.2–14.3)].
  - Causes of death: AIDS, Liver and CVD
  - Smoking was associated with CVD and non-AIDS cancers
  - HBV and HCV co-infection with liver-related deaths

Liver Disease is the Second Leading Cause of Death in Swiss HIV-Cohort Study (1988-2010)

- SHCS Cohort 1998-2010 N=16,134
  - 5023 (31%) died
  - AIDS mortality peaked in 1992 11 per 100 person year and declined to 0.211 per 100 PY
  - Cause of death: AIDS 78% (1988-1995) liver was not reported
- Recent SHCS 2005-2009 (N=9053)
  - 459 (5.1%) died
  - Causes of death: 19% non-AIDS malignancy, 18% liver including HCC and 16% AIDS


Consequences of Treatment

- Treatment of HIV
- Treatment of HCV

Treatment of HIV with Antiretroviral Agents is Associated With a Reduction Risk of Liver-related Complications

<table>
<thead>
<tr>
<th>HIV/AIDS stage</th>
<th>No. of Events</th>
<th>Person-Years</th>
<th>Crude</th>
<th>Adjusted²</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>33</td>
<td>1383</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>33</td>
<td>1383</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>C</td>
<td>33</td>
<td>1383</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>D</td>
<td>33</td>
<td>1383</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Successful Treatment of HCV (SVR) is Associated With Improved Survival

![Graph showing survival over time for SVR vs. No SVR](Limketkai et al. JAMA. July 25, 2012;308(4):370-378)

Treatment of HCV in HIV-HCV Co-infected

- IFN-based Treatment
- First Generation DAAs
- Second Generation DAAs
Presence of Comorbidities Negatively Impact Candidacy and Tolerance of HIV-HCV Co-infected Patients to IFN-based Therapy

<table>
<thead>
<tr>
<th></th>
<th>HCV (n = 114,005)</th>
<th>HIV/HCV (n = 6,502)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug use</td>
<td>39%</td>
<td>56%</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>44%</td>
<td>48%</td>
</tr>
<tr>
<td>Depression (major)</td>
<td>18%</td>
<td>23%</td>
</tr>
<tr>
<td>Bipolar</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Anemia</td>
<td>12%</td>
<td>24%</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td>Received HCV treatment</td>
<td>12%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Low Efficacy of PEG-IFN and RBV Based Regimen

SVR %

HIV/HCV 16%
HCV alone 39%

Treatment of HIV and HCV

First Generation DAAs

Telaprevir/PR for HCV GT 1 Treatment Naïve
HIV Negative and Positive Patients

Boceprevir/PR for HCV GT 1 Treatment Naïve HIV Negative and Positive Patients

These regimens have significant side effects and are no longer recommended

Treatment of HIV and HCV

Second Generation DAAs

Simeprevir + PEG/RBV for HCV GT 1 infection in HIV-Infected patients: SVR12

85% of treatment-naïve and prior PR relapsers without cirrhosis met response-guided therapy criteria and were eligible for shortened therapy to 24 weeks, with 87% achieving SVR12.

**Study Design (PHOTON-1)**

- **GT 1 TN**
  - SOF + RBV, n=114

- **GT 2 or GT 3 TN**
  - SOF + RBV, n=68

- **GT 2 or GT 3 TE**
  - SOF + RBV, n=41

**Broad inclusion criteria**
- Cirrhosis permitted with no platelet cutoff
- Hemoglobin: \( \geq 12 \text{ mg/dL} \) (males); \( \geq 11 \text{ mg/dL} \) (females)

**Wide range of ART regimens allowed**
- Undetectable HIV RNA for >8 weeks on stable ART regimen

**Baseline CD4 count**
- ART treated: CD4 T-cell count >200 cells/mm\(^3\) and HIV RNA < 50 c/mL
- ART untreated: CD4 T-cell count >500 cells/mm\(^3\)

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**Virologic Response with SOF/RBV for 24 Weeks: Genotype 1**

<table>
<thead>
<tr>
<th>Week 4</th>
<th>EOT</th>
<th>SVR12</th>
<th>SVR24</th>
</tr>
</thead>
<tbody>
<tr>
<td>110/114</td>
<td>103/103</td>
<td>87/114</td>
<td>86/114</td>
</tr>
</tbody>
</table>

86% 98% 100%

HCV RNA < LL0Q (%)

---

### Virologic Response: Genotype 2

<table>
<thead>
<tr>
<th>Patients with HCV RNA &lt; LLOQ (%)</th>
<th>Week 4</th>
<th>EOT</th>
<th>SVR12</th>
<th>SVR24</th>
<th>Treatment Naïve 12 Weeks SOF + RBV</th>
<th>Treatment Experienced 24 Weeks SOF + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25/26</td>
<td>22/23</td>
<td>23/26</td>
<td>23/26</td>
<td>24/24</td>
<td>23/23</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>100</td>
<td>92</td>
<td>92</td>
<td>22/24</td>
<td>22/24</td>
</tr>
</tbody>
</table>


### Virologic Response: Genotype 3

<table>
<thead>
<tr>
<th>Patients with HCV RNA &lt; LLOQ (%)</th>
<th>Week 4</th>
<th>EOT</th>
<th>SVR12</th>
<th>SVR24</th>
<th>Treatment Naïve 12 Weeks SOF + RBV</th>
<th>Treatment Experienced 24 Weeks SOF + RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>41/41</td>
<td>39/40</td>
<td>28/42</td>
<td>28/42</td>
<td>17/17</td>
<td>16/17</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>100</td>
<td>94</td>
<td>88</td>
<td>15/17</td>
<td>15/17</td>
</tr>
</tbody>
</table>

**PHOTON-2: Study Design**

- **GT 1, 3, 4**: Naive
  - SOF + RBV (n = 200) → SVR12

- **GT 2**: Naive
  - SOF + RBV (n = 19) → SVR12

- **GT 2, 3**: Experienced
  - SOF + RBV (n = 55) → SVR12

Molina et al., IAS 2014, Melbourne, Australia

**PHOTON-2 SVR12 Results: SOF + RBV**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>GT 1</th>
<th>GT 2</th>
<th>GT 3</th>
<th>GT 4</th>
<th>GT 2</th>
<th>GT 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naive</td>
<td>95/112</td>
<td>17/19</td>
<td>52/57</td>
<td>26/31</td>
<td>5/6</td>
<td>42/49</td>
</tr>
<tr>
<td>Experienced</td>
<td>85</td>
<td>89</td>
<td>91</td>
<td>84</td>
<td>83</td>
<td>86</td>
</tr>
</tbody>
</table>

Molina et al., IAS 2014, Melbourne, Australia
PHOTON-2: SVR12 in GT 1 Treatment-Naïve (Cirrhosis vs No Cirrhosis)

Molina et al., IAS 2014, Melbourne, Australia

AASLD/IDSA GUIDANCE
### AASLD and IDSA HCV Guidance: Regimens for Patients with HCV/HIV Coinfection

#### Genotype 1
- **HCV treatment-naive and prior PR relapsers**
  - IFN eligible: Sofosbuvir + PR 12 weeks
  - IFN ineligible: Sofosbuvir + RBV 24 weeks
  - HCV treatment experienced*
    - IFN eligible: Sofosbuvir + simeprevir† + RBV 12 weeks
    - IFN ineligible: Sofosbuvir + simeprevir† + RBV 12 weeks

#### Genotype 2
- Regardless of HCV treatment history: Sofosbuvir + RBV 12 weeks

#### Genotype 3
- Regardless of HCV treatment history: Sofosbuvir + RBV 24 weeks

#### Genotype 4
- Regardless of HCV treatment history: Sofosbuvir + PR 12 weeks
- IFN eligible: Sofosbuvir + RBV 24 weeks

#### Genotype 5 or 6
- Regardless of HCV treatment history: Sofosbuvir + PR 12 weeks

*Prior PR non-responders regardless of IFN eligibility.
†For genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if present.

Allowable ART: Sofosbuvir: all except the NRTIs didanosine and zidovudine.
Simeprevir: INSTI (raltegravir); NNRTI (rilpivirine); Entry/Fusion Inhibitor (maraviroc, enfuvirtide);
NRTIs (tenofovir, emtricitabine, lamivudine, abacavir).


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### Treatment of HIV and HCV

**Second Generation DAAs**

**Future Treatment**
**SOF+LDV (Interim Analysis 2014)**

- Fifty HIV/HCV genotype 1, treatment-naive subjects, HAI fibrosis stage 0 – 3

**Wk 0**
- ARV Untreated (n=13)
  - CD4 count stable > HIV RNA <500 copies OR
  - CD4 count > 500 cells/mm³

**Wk 12**
- ARV Treated (n=37)
  - CD4 count > 100 cells/mm³
  - HIV RNA < 40 copies
  - Current ARVs ≥ 8 weeks

---

**SOF/LDV (400/90mg)**

- ARV Untreated (n=13)
  - CD4 count stable > HIV RNA <500 copies OR
  - CD4 count > 500 cells/mm³

- ARV Treated (n=37)
  - CD4 count > 100 cells/mm³
  - HIV RNA < 40 copies
  - Current ARVs ≥ 8 weeks

ARVs: tenofovir, emtricitabine, efavirenz, rilpivirine and raltegravir

Osinusi et al. EASL 2014

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**SOF+LDV (Interim Analysis 2014)**

**Graph:**

- % of patients with HCV RNA <LOC (UI) over time

<table>
<thead>
<tr>
<th>Week</th>
<th>ARV Untreated</th>
<th>ARV Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 4</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Wk 8</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>EOT</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>SVR4</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>SVR8</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>SVR12</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>ARV -</th>
<th>ARV +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 4</td>
<td>13/13</td>
<td>37/37</td>
</tr>
<tr>
<td>Wk 8</td>
<td>13/13</td>
<td>37/37</td>
</tr>
<tr>
<td>EOT</td>
<td>12/12</td>
<td>30/30</td>
</tr>
<tr>
<td>SVR4</td>
<td>10/10</td>
<td>22/22</td>
</tr>
<tr>
<td>SVR8</td>
<td>10/10</td>
<td></td>
</tr>
<tr>
<td>SVR12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Osinusi et al. EASL 2014
**TURQUOISE-I: SAFETY AND EFFICACY OF ABT-450/R/OMBITASVIR, DASABUVIR, AND RIBAVIRIN IN PATIENTS CO-INFECTED WITH HEPATITIS C AND HIV-1, Part 1 Study Design**

Open-label Treatment

- **3D + RBV** (N = 31)
- **3D + RBV** (N = 32)

All patients will be followed for 48 weeks after HCV treatment end

Day 1  Week 12  Week 24  Week 36

Sulkowski et al., IAS 2014, Melbourne, Australia

**TURQUOISE-I Results: Virologic Response Rates**

<table>
<thead>
<tr>
<th>3D + RBV Regimen</th>
<th>RVR (Week 4)</th>
<th>EOTR (Week 12 or 24)</th>
<th>SVR4</th>
<th>SVR12</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-Week Arm</td>
<td>31 32</td>
<td>30 31</td>
<td>29 31</td>
<td>29 31</td>
</tr>
<tr>
<td>24-Week Arm</td>
<td>31 32</td>
<td>31 32</td>
<td>31</td>
<td>31</td>
</tr>
</tbody>
</table>

Sulkowski et al., IAS 2014, Melbourne, Australia
MK-5172 + MK-8742 +/- RBV in GT 1 HIV/HCV-infected patients (C-WORTHY): Study Design

Follow-up

MK-5172 + MK-8742 + RBV

N = 29

MK-5172 + MK-8742 (No RBV)

N = 30

Sulkowski M. et al. EASL 2014, Abstract #O63

MK-5172 + MK-8742 +/- RBV in GT 1 HIV/HCV-infected Patients (C-WORTHY): Interim Virological Response

% HCV RNA <25 IU/mL

100
90
80
70
60
50
40
30
20
10
0

TW4
TW8
TW12
SVR4

MK-5172 + MK-8742 + RBV
(n=29)

MK-5172 + MK-8742 (No RBV;
 n=30)

Sulkowski M. et al. EASL 2014, Abstract #O63
Drug:Drug Interactions

Interactions Between HCV & HIV Medications

- Potential challenges in treating HIV/HCV co-infected patients
- Altered concentrations of ARVs and/or DAAs:
  - ↑ risk of toxicity
    - Anemia: ribavirin, zidovudine, DAAs
    - CNS effects: interferon, efavirenz
  - ↓ efficacy, potential development of resistance (HIV and/or HCV)
- Drug interactions may be difficult to predict
  - CYP3A4 inhibition (ritonavir); induction (efavirenz)
### DDI Example: Simeprevir and Antiretroviral Drugs

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Effect on Concentration</th>
<th>Clinical Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRV/r</td>
<td>May increase SMV concentration</td>
<td>All other H/IV PIs – not evaluated in PK studies, but likely similar to DRV/r</td>
</tr>
<tr>
<td>EFV</td>
<td>Significant reduction in SMV exposure</td>
<td>TDF; RPV; RAL – no significant PK interaction have been identified to date.</td>
</tr>
<tr>
<td>ETR, NVP</td>
<td>Reduction in SMV exposure expected</td>
<td>DTG – not evaluated in PK studies, but not expected to alter the PK of SMV; SMV not expected to alter PK of DTG</td>
</tr>
<tr>
<td>EVG/cobi/TDF/FTC</td>
<td>Increase in SMV exposure expected</td>
<td></td>
</tr>
</tbody>
</table>

### DDI Example: Sofosbuvir and Antiretroviral Drugs

- **No interaction between SOF and the following drugs:**
  - Cyclosporine
  - Darunavir/ritonavir
  - Efavirenz
  - Emtricitabine
  - Methadone
  - Raltegravir
  - Rilpivirine
  - Tacrolimus
  - Tenofovir disoproxil fumarate

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Effect on Concentration</th>
<th>Clinical Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>tipranavir/ritonavir</td>
<td>↓ sofosbuvir</td>
<td>Coadministration of SOF with tipranavir/ritonavir is expected to decrease SOF concentration leading to reduced therapeutic effect.</td>
</tr>
</tbody>
</table>
Summary

- Prevalence of HCV in HIV infected individuals can be very high and is dependent on the risk profile
- There is a recent epidemic of HCV infection in HIV + MSM
- HCV in the setting of HIV is associated with adverse outcomes
- Liver disease has become a leading cause of death in HIV infected patients
- Although IFN-based regimens were problematic, the current second generation DAA regimens are safe and efficacious
- Future generation of DAA regimens seem to be even more promising, suggesting that HIV-HCV will have identical cure rates as mono-infected individuals
- Nevertheless, drug-drug interactions must be assessed and closely monitored