Clinical management of HIV-HCV co-infected patients

Pedro Cahn
Acknowledgments

• Jurgen Rockstroh
• David Burger
• Mauro Schechter
<table>
<thead>
<tr>
<th>HCV-HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>• HCV coinfection: some <em>epi</em> data</td>
</tr>
<tr>
<td>• What is the impact on HCV?</td>
</tr>
<tr>
<td>• What is the impact on HIV?</td>
</tr>
<tr>
<td>• HAART and DAAs: New challenges</td>
</tr>
</tbody>
</table>
Background

- HIV accelerates the natural course of hepatitis C
- Successful HAART can slow down fibrosis progression but not back to the rate in HCV mono-infection
- Liver disease associated with HCV infection has become a leading cause of morbidity and mortality among HIV-infected patients

Trends and projections of hepatitis C virus epidemiology in Latin America

David Kershonobich¹, Homie A. Razavi², Juan Francisco Sánchez-Avilá³, Fernando Bessone⁴, Henrique S. Coelho⁵, Lucy Daghe⁶, Fernando L. Gonçalves⁷, Jorge F. Quiroz⁸, Federico Rodríguez-Perez⁹, Barbara Rosado¹⁰, Carolyn Wallace², Francesco Negro¹¹ and Marcelo Silva¹²

Liver International (2011)

Fig. 6. Hepatitis C virus prevalence among adults and genotype distribution in select Latin American countries/territories.
Prevalence of HIV/HCV coinfection

Hepatitis B Virus, Hepatitis C Virus and HIV Coinfection Among People Living With HIV/AIDS in Buenos Aires, Argentina

*Sexually Transmitted Diseases* • Volume 37, Number 5, May 2010

Laufer N1,2,*,#, Quarleri J1,*,# Bouzas MB3,# Juncos G3 Cabrini M2 Moretti F1 Bolcic F1 Fernández-Giuliano S3 Mammana L3 Pérez H2 Salomón H1 and Cahn P2

<table>
<thead>
<tr>
<th>N</th>
<th>POS</th>
<th>%</th>
<th>IC 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HCV</td>
<td>593</td>
<td>129</td>
<td>21,7</td>
</tr>
</tbody>
</table>

67% G1
HIV as a risk factor for HCV transmission

- HCV-RNA is more often detected in semen of HIV+ patients than in HIV-negative\(^1\)
- HIV+ patients have a higher risk for a chronic course of HCV-infection\(^2\)
- HIV+ patients – dependent on CD4 cell-count – have a reduced capability to mount cellular immune responses against HCV\(^3\)
- US study: HIV + women twice as likely to acquire HCV, and a Dutch study showed that HIV + MSM are 43 times at higher risk compared to HIV -
- Cases often have concomittant other STD such as syphilis of lymphogranuloma venereum. STD and high-risk sexual behaviour enhance the risk for blood-to-blood transmission
- Cases more often practice high-risk sexual behaviour with a high risk for mucosal damage, enhancing the risk for blood-to-blood transmission

### Multivariate regression analysis

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>frequent receptive ‘fisting’ without gloves*</td>
<td>6.50 (1.71-24.68; 0.006)</td>
<td>5.94 (1.61-21.98; 0.008)</td>
<td>6.77 (1.67-27.42; 0.007)</td>
</tr>
<tr>
<td>frequent anorectal trauma with bleeding*</td>
<td>5.67 (1.13-28.60; 0.035)</td>
<td>5.20 (1.04-25.87; 0.044)</td>
<td>6.91 (1.25-38.18; 0.007)</td>
</tr>
<tr>
<td>group sex</td>
<td></td>
<td>p=0.073</td>
<td>3.96 (0.97-16.16; 0.055)</td>
</tr>
<tr>
<td>interaction: group sex and NADs§ combined</td>
<td></td>
<td></td>
<td>5.91 (2.04-17.14; 0.001)</td>
</tr>
<tr>
<td>consumption of NADs§</td>
<td></td>
<td>4.02 (1.37-11.82; 0.012)</td>
<td></td>
</tr>
<tr>
<td>... with sharing of equipment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>frequent use of PDE-5§ inhibitors*</td>
<td>p=0.314</td>
<td>p=0.434</td>
<td>p=0.590</td>
</tr>
<tr>
<td>dilative sex toys*</td>
<td>p=0.463</td>
<td>p=0.392</td>
<td>p=0.600</td>
</tr>
<tr>
<td>body piercings</td>
<td>p=0.563</td>
<td>p=0.459</td>
<td>p=0.616</td>
</tr>
<tr>
<td>history of major surgery</td>
<td>p=0.281</td>
<td>p=0.408</td>
<td>p=0.556</td>
</tr>
<tr>
<td>casual sex partners with HIV</td>
<td>p=0.659</td>
<td>p=0.659</td>
<td>p=0.983</td>
</tr>
<tr>
<td>condoms not considered for prevention of STIs</td>
<td>p=0.332</td>
<td>p=0.537</td>
<td>p=0.660</td>
</tr>
<tr>
<td>UA§§ with casual partners**</td>
<td>p=0.226</td>
<td>p=0.160</td>
<td>p=0.419</td>
</tr>
<tr>
<td>frequent insertive AI§§ with casual partners**</td>
<td>p=0.239</td>
<td>p=0.323</td>
<td>p=0.402</td>
</tr>
<tr>
<td>frequent receptive AI§§ with casual partners**</td>
<td>p=0.644</td>
<td>p=0.854</td>
<td>p=0.787</td>
</tr>
<tr>
<td>more than 10 sex partners **</td>
<td>p=0.637</td>
<td>p=0.933</td>
<td>p=0.955</td>
</tr>
<tr>
<td>more than 20 sex partners **</td>
<td>p=0.428</td>
<td>p=0.748</td>
<td>p=0.647</td>
</tr>
<tr>
<td>history of recent bacterial STIs **</td>
<td>p=0.134</td>
<td>2.33 (0.90-16.16; 0.083)</td>
<td>p=0.236</td>
</tr>
<tr>
<td>history of syphilis **</td>
<td>p=0.101</td>
<td>p=0.621</td>
<td>p=0.226</td>
</tr>
</tbody>
</table>

Nagelkerke’s pseudo-R-square 29%  31%  35%

---

* when having sex, since the year 2000; ** in the last 12 months; § NADs = nasally administered drugs; §§ PDE-5 = phosphodiesterase-5; §§§ (U)AI = (unprotected) anal intercourse with casual partners (of unknown/discordant HIV serostatus)
In conclusion, the analyses of HCV subtype 1a strains isolated from patients coinfected with HCV and HIV attended in a single Hospital in Buenos Aires, Argentina, allowed identification of a monophyletic cluster with a potential HCV-1a/HIV co-transmission by phylogenetic analyses.
Development of AIDS is like an impending train wreck

Viral Load = Speed of the train
CD4 count = Distance from cliff

J. Coffin, XI International Conf. on AIDS, Vancouver, 1996
Development of ESLD is like an impending train wreck

- Inflammation = Speed of the train
- Fibrosis = Distance from cliff

HCV infection
HIV Adversely Affects All Stages of Hepatitis C increasing hepatitis C persistence and HCV viral load

Infection

Recovery

Persistence

Viral load

Odds of Persistence

0
0.5
1
1.5
2
2.5
3
3.5

HIV neg
>500
200-500
<200

% Subjects in Viral Load Group

HCV Viral Load

5.3-5.5
5.6-6.0
6.1-6.5
6.6-7.0
7.1-7.5
7.6-8.0
>8.0

HIV -
HIV +

1 Thomas JAMA 2000; 2 Thomas JID 2000
HIV Infection Adversely Affects All Stages of Hepatitis C

Infection → Recovery → Persistence → Viral load → Treatment → Cirrhosis → Liver failure or cancer

Multi-center hemophilia cohort, 1192 HIV pos vs 624 HIV neg, 1985-1998

Rates of Mortality: HIV-1 Infection vs HIV-1/Hep C Coinfection

Mortality According to HIV-1/Hep C Antibody Status

- Hep C-/HIV-1-
- Hep C+/HIV-1-
- Hep C-/HIV-1+
- Hep C+/HIV-1+

Follow Up (Years Since Cohort Entry)

Proportion

0.0
0.2
0.4
0.6
0.8
1.0

Causes of Death in 1246 HIV-Positive Pts Followed in the D:A:D Study (N = 23,441)

66% of liver deaths due to chronic HCV

Figure. Annual age-adjusted mortality rates from hepatitis B and hepatitis C virus and HIV infections listed as causes of death in the United States between 1999 and 2007.
Association of HCV with AIDS-defining events: Increased Risk

Risk of Developing Specific AIDS-Defining Illnesses in Patients Coinfected with HIV and Hepatitis C Virus With or Without Liver Cirrhosis

Antonella d’Arminio Monforte,1 Alessandro Cozzi-Lepri,1,2 Antonella Castagna,2 Andrea Antinori,3 Andrea De Luca,4 Cristina Mussini,5 Sergio Lo Caputo,6 Massimo Ariotti,7 Giacomo Magnani,8 Gianpietro Pellizzer,9 Franco Maggiolo,10 and Massimo Puoti,11 for the Iona Foundation Study Group

1Clinic of Infectious and Tropical Diseases, San Paolo Hospital, University of Milan, and 2Department of Infectious Diseases, Istituto Ricerche Clinica Carattere Scientifico San Raffaele Hospital, Milan, 3Istituto Nazionale Malattie Infettive Lazzaro Spallanzani and 4Clinic of Infectious Diseases, Cattolica University, Rome, 5Clinic of Infectious Diseases, Modena University, Modena, 6Department of Infectious Diseases, Santissima Annunziata Hospital, Bagno a Ripoli, Florence, 7Department of Infectious Diseases, Hospital of Rimini, Rimini, 8Department of Infectious Diseases, Hospital of Reggio Emilia, Reggio Emilia, 9Department of Infectious Diseases, Hospital of Vicenza, Vicenza, 10Department of Infectious Diseases, Riuniti Hospital, Bergamo, and 11Institute of Infectious Diseases, University of Brescia, Italy, and 12Research Department of Infection and Population, Royal Free and University College Medical School, London, United Kingdom

© CID 2009:49 (15 August) • HIV/AIDS
## AIDS - defining events

<table>
<thead>
<tr>
<th>Calculation</th>
<th>HIV-related disease ((n = 59))</th>
<th>Protozoal infection ((n = 27))</th>
<th>Mycotic infection ((n = 154))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV noninfected</td>
<td>HIV-HCV coinfected</td>
<td>HIV noninfected</td>
</tr>
<tr>
<td>No. of events</td>
<td>10</td>
<td>49</td>
<td>7</td>
</tr>
<tr>
<td>PYFU</td>
<td>13,722</td>
<td>13,493</td>
<td>13,793</td>
</tr>
<tr>
<td>Rate per 1000 PYFU (95% CI)</td>
<td>2.7 (0.3–1.3)</td>
<td>3.6 (2.7–4.8)</td>
<td>0.5 (0.2–1.0)</td>
</tr>
<tr>
<td>Competing-risks analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.00</td>
<td>4.98 (2.52–9.84)</td>
<td>1.00</td>
</tr>
<tr>
<td>(P)</td>
<td>&lt;.001</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>Cause-specific analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.00</td>
<td>4.80 (2.34–9.84)</td>
<td>1.00</td>
</tr>
<tr>
<td>(P)</td>
<td>&lt;.001</td>
<td></td>
<td>.009</td>
</tr>
</tbody>
</table>
Meta-Analysis: Increased Mortality Associated with Hepatitis C in HIV-Infected Persons Is Unrelated to HIV Disease Progression

Ting-Yi Chen, Eric L. Ding, George R. Seage III, and Arthur Y. Kim

Wayne State University, Detroit Medical Center, Detroit, Michigan; and Departments of Nutrition and Epidemiology, Harvard School of Public Health, and Division of Infectious Diseases, Massachusetts General Hospital, Boston, Massachusetts

HIV/AIDS • CID 2009:49 (15 November) • 1605
No Association of Hepatitis C with AIDS Defining Events

Hung et al [11]
Klein et al [19]
Rockstroh et al [54]
Stebbing et al [59]
Sulkowski et al [55]
Sullivan et al [56]
Tedaldi et al [57]
Combined
**Results.** Three hundred thirty-seven patients had HCV RNA (chronic infection), 91 had HCV antibodies and no HCV RNA (cleared infection), and 1597 had no HCV markers. Median CD4⁺ T-cell counts/µL were 200 (chronic), 193 (cleared), and 175 (no markers). There were 558 deaths. At a median follow-up of 6.1 years, patients with chronic HCV had a 50% increased risk of mortality compared with patients with no HCV markers (relative risk [RR], 1.5; 95% confidence interval [CI], 1.2–1.9; \( P = .001 \)) in an adjusted model that included known risk factors. Mortality was not increased in patients with cleared infection (RR, 0.9; 95% CI, .6–1.5; \( P = .82 \)). In patients with chronic HCV, 20.4% of deaths were liver related compared with 3.8% in patients without HCV.
When to start ARVs in coinfected patients - DHHS

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

Key Considerations When Managing Patients Coinfected with HIV and Hepatitis C Virus

- All HIV-infected patients should be screened for hepatitis C virus (HCV) infection, preferably before starting antiretroviral therapy (ART).
- ART may slow the progression of liver disease by preserving or restoring immune function and reducing HIV-related immune activation and inflammation. For most HIV/HCV-coinfected patients, including those with cirrhosis, the benefits of ART outweigh concerns regarding drug-induced liver injury (DILI). Therefore, ART should be considered for HIV/HCV-coinfected patients, regardless of CD4 count (BII).
- Initial ART combination regimens for most HIV/HCV-coinfected patients are the same as those for individuals without HCV infection. However, when treatment for both HIV and HCV is indicated, consideration of potential drug-drug interactions and overlapping toxicities should guide ART regimen selection or modification (see discussion in the text).
- Combined treatment of HIV and HCV can be complicated by large pill burden, drug interactions, and overlapping toxicities. Although ART should be initiated for most HIV/HCV-coinfected patients regardless of CD4 cell count, in ART-naive patients with CD4 counts >500 cells/mm³ some clinicians may choose to defer ART until completion of HCV treatment.
- In patients with lower CD4 counts (e.g., <200 cells/mm³), it may be preferable to initiate ART and delay HCV therapy until CD4 counts increase as a result of ART.
When to Start ART: IAS–USA Recommendations 2012

• Patient readiness should be considered when deciding to initiate antiretroviral therapy (ART)

• ART should be offered regardless of CD4 cell count (increasing strength of the recommendation as CD4 decreases)
  - CD4 ≤ 500 cells/µL (AIIa)
  - CD4 > 500 cells/µL (BIII)
  - Pregnancy (AIIa)
  - Chronic HBV (AIIa)
  - HCV (may delay until after HCV treatment if CD4 > 500) (CIII)
  - Age older than 60 (BIIa)
  - HIV-associated nephropathy (AIIa)
  - Acute phase of primary HIV infection, regardless of symptoms (BIII)
Recommendations are graded while taking into account both the degree of progression of HIV disease and the presence of or high risk for developing various types of (co-morbid) conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Current CD4+ lymphocyte count $^{(n,m)}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>350-500</td>
</tr>
<tr>
<td>Asymptomatic HIV infection</td>
<td>C</td>
</tr>
<tr>
<td>Symptomatic HIV disease (CDC B or C conditions) incl. tuberculosis</td>
<td>R</td>
</tr>
<tr>
<td>Primary HIV infection</td>
<td>C</td>
</tr>
<tr>
<td>Pregnancy (before third trimester)</td>
<td>R</td>
</tr>
<tr>
<td>Conditions (likely or possibly) associated with HIV, other than CDC stage B or C disease:</td>
<td></td>
</tr>
<tr>
<td>HIV-associated kidney disease</td>
<td>R</td>
</tr>
<tr>
<td>HIV-associated neurocognitive impairment</td>
<td>R</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>R</td>
</tr>
<tr>
<td>HPV-associated cancers</td>
<td>R</td>
</tr>
<tr>
<td>Other non-AIDS-defining cancers requiring chemo- and/or radiotherapy</td>
<td>C</td>
</tr>
<tr>
<td>Autoimmune disease – otherwise unexplained</td>
<td>C</td>
</tr>
<tr>
<td>High risk for CVD (&gt; 20% estimated 10-yr risk) or history of CVD</td>
<td>C</td>
</tr>
<tr>
<td>Chronic viral hepatitis</td>
<td></td>
</tr>
<tr>
<td>HBV requiring anti-HBV treatment</td>
<td>R</td>
</tr>
<tr>
<td>HBV not requiring anti-HBV treatment</td>
<td>C/R $^{(iv)}$</td>
</tr>
<tr>
<td>HCV for which anti-HCV treatment is being considered or given</td>
<td>R $^{(v)}$</td>
</tr>
<tr>
<td>HCV for which anti-HCV treatment not feasible</td>
<td>R</td>
</tr>
<tr>
<td>Prevención de la transmisión</td>
<td>Indicación</td>
</tr>
<tr>
<td>-------------------------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Gestantes</td>
<td>Recomendar</td>
</tr>
<tr>
<td>Individuos con parejas serodiscordantes</td>
<td>Considerar</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tratamiento antirretroviral</th>
<th>Recuento de CD4/mm³</th>
<th>Indicación</th>
<th>Evidencia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infección síntomas C</td>
<td>Cualquiera</td>
<td>Recomendar</td>
<td>AI</td>
</tr>
<tr>
<td>Infección síntomas B</td>
<td>Cualquiera</td>
<td>Recomendar</td>
<td>AI</td>
</tr>
<tr>
<td>Asintomático</td>
<td>≤ 500</td>
<td>Recomendar</td>
<td>AI</td>
</tr>
<tr>
<td>Asintomático</td>
<td>&gt; 500</td>
<td>Considerar:</td>
<td>BIII</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Más de 50 años</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CV &gt;100,000 copias/ml</td>
<td>CIII</td>
</tr>
<tr>
<td>Hepatitis B activa</td>
<td></td>
<td></td>
<td>BII</td>
</tr>
<tr>
<td>Hepatitis C crónica</td>
<td></td>
<td></td>
<td>CIII</td>
</tr>
<tr>
<td>Descenso rápido de CD4</td>
<td></td>
<td></td>
<td>CIII</td>
</tr>
<tr>
<td>Otras comorbididades (riesgo cardiovascular</td>
<td></td>
<td></td>
<td>CIII</td>
</tr>
<tr>
<td>aumentado, HTA, DBT, cáncer, etc)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nefropatía por HIV</td>
<td></td>
<td></td>
<td>AI</td>
</tr>
<tr>
<td>Todas las personas que estén interesadas en</td>
<td></td>
<td></td>
<td>CIII</td>
</tr>
<tr>
<td>iniciar tratamiento</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Recomenda-se o início de TARV para todos os indivíduos assintomáticos nas seguintes situações:

- LT-CD4+ menor ou igual a 500 células/mm³
- LT-CD4+ acima de 500 células/mm³ na coinfecção pelo vírus da hepatite B (HBV)
- Coinfecção pelo vírus da hepatite C (HCV)

No caso de pacientes com contagens de LT-CD4+ ≤ 500 células/mm³, recomenda-se iniciar TARV e aguardar o aumento dos LT-CD4+ para o início do tratamento do HCV. Nos casos de LT-CD4+ superiores a 500 células/mm³, recomenda-se tratar inicialmente a hepatite C, protegendo o uso de TARV, para evitar interações medicamentosas e sobreposição de toxicidades. Em todas as situações, a abordagem deve ser individualizada e a prioridade de cada um dos tratamentos discutida com profissionais experientes no manejo de ambas as infecções.
Antiretroviral Therapy is not Sufficient to Prevent the Adverse Effects of HIV

• Antiretroviral therapy may slow fibrosis progression somewhat and may improve IFN sensitivity

• Antiretroviral therapy is not sufficient to
  – Reduce the HCV RNA load
  – Restore treatment response
  – Prevent cirrhosis or liver failure

Therapeutic Challenges in HIV infected patients with hepatitis C

- Access to treatment
- Dosages and duration
- Impact of HIV associated immunodeficiency on treatment outcome
- Choice of HAART, DDIs
- Higher HCV viral loads in HIV/HCV co-infection
- Lower probability of EVR?
- Higher risk for resistance development
- Drug-drug interactions between HCV drugs and the new oral HCV agents
- Overlapping drug toxicities
- New drugs are initially tested excluding HIV + patients
Achieving Sustained Virologic Response is important: Impact on Long-Term Outcomes in HIV/HCV-Coinfection

GESIDA 3603 Cohort: 711 pts treated for HCV

Overall Mortality: 0.46* (0.06, 1.65)
Liver-Related Mortality: 0.23† (0.01, 1.27)
Liver Decompensation: 0.23‡ (0.01, 1.27)
Liver Transplantation: 0.83 (0.38, 1.58)
Liver Transplantation: 1.02 (0.50, 1.82)
New AIDS Conditions: 0.93 (0.44, 1.70)

*P=0.003, †P=0.028, ‡P<0.001, and §P=0.034 versus not attaining a sustained virologic response.
n=711 HIV/HCV-coinfected patients receiving interferon (peg or conventional) + ribavirin.

Boceprevir stopping rules: HCV RNA >1000 IU/mL at week 8 or 12; virologic breakthrough at anytime.
ART: ATV/r + 2 NRTIs (50%); RAL + 2 NRTIs (42%).
Baseline characteristics: mean age (52 years); male gender (75%); former IDU (73%); CDC stage C (22%);
mean CD4 (728 cells/mL); HIV RNA <50 copies/mL (95%); HCV genotype 1a (78%).

ANRS HC27 BocepreVIIH Study:
EVR\textsubscript{16} Interim Results

ANRS HC27 BocepreVIH Study:
Safety

- Discontinuations due to toxicity (1.5%)
- Proactive anemia management decreased impact of anemia
  - Anemia: 42%
  - Grade 3/4 (<7 g/dL): 5%
- Neutropenia: 70%
  - Grade 3/4 (<750 g/dL): 17%
- No unexpected adverse events
- No HIV breakthrough
ANRS HC26 TelapreVIH Study: Telaprevir-Based HCV Therapy in HCV/HIV Coinfection

**Phase 2 (n=69)**
- HIV positive
- HCV genotype 1
- Previously failed PR
- On stable ART
- CD4 >200 cells/mm³
- HIV RNA <50 copies/mL
- EPO, G-CSF, TPO-R agonists allowed

**Excluded:**
- Decompensated cirrhosis
- HBV or HIV-2 infection
- Previous null response with cirrhosis

Week 0        4        8                  16                           48                 72                96

Weight-based ribavirin dosing (1000-1200 mg bid).

Telaprevir stopping rules: HCV RNA >1000 IU/mL at week 8 or 12; virologic breakthrough at anytime.

**ART:**
- ATV/r + FTC/TDF (49%)
- EFV/FTC/TDF (19%)
- RAL + FTC/TDF (17%)

Baseline characteristics: mean age (50 years); male gender (80%); former IDU (55%); CDC stage C (19%);
- mean CD4 (630 cells/mL);
- HIV RNA <50 copies/mL (99%);
- HCV genotype 1a (70%).

Telaprevir 750 mg q8h (1125 mg q8h with efavirenz).

**Interim Analysis**

Telaprevir + PR

Complete RVR₈

Follow-Up

SVR₂₄

Partial RVR₃

Follow-Up

SVR₂₄

Telaprevir + PR

RVR₈

EVR₁₆

(HCV RNA <15 IU/mL)

ANRS HC26 TelapreVIH Study: EVR$_{16}$ Interim Results

ANRS HC26 TelaprepVH Study: Safety

- Discontinuations due to toxicity
  - Cutaneous (4.5%), psychiatric (4.5%), anemia (2%)

- Significant hematologic toxicity despite proactive anemia management
  - Anemia: 30%
  - Grade 3-4 anemia, erythropoietin use, transfusion, or RBV dose reduction: 61%

- No unexpected adverse events
- No HIV breakthrough
Study C212: Simeprevir (NS3/4A Inhibitor) + PR in HIV/HCV Coinfection

Phase 3 (n=106)
On ART (88%)
Primary endpoint: SVR12

HCV Treatment-Naïve Relapse
Response Guided Therapy

HCV Partial Response
HCV Null Response
Cirrhotic (F4)

Week 0 12 24 48 72
Interim Analysis

Follow-Up
Follow-Up
Follow-Up

Simeprevir + PR
PR
Simeprevir + PR
PR
Simeprevir + PR
PR

Primary endpoint: SVR12

PR: peginterferon + ribavirin.

ART:
NRTI (3TC, ABC, FTC, TDF): 99%.
Raltegravir: 87%.
Rilpivirine: 15%.
Maraviroc: 3%.
Enfuvirtide: 3%.

Dieterich D, et al. 20th CROI. Atlanta, 2013. Abstract 154LB.
Study C212: SVR4 and SVR12 With Simeprevir + PR in HIV/HCV Coinfection

Patients (%)

Overall (n=35/13)
- SVR4: 86%
- SVR12: 77%

HCV Treatment-Naïve (n=25/8)
- SVR4: 84%
- SVR12: 75%

HCV Previous Relapse (n=10/5)
- SVR4: 90%
- SVR12: 80%

RGT-Eligible (n=34/12)
- SVR4: 85%
- SVR12: 75%

Dieterich D, et al. 20th CROI. Atlanta, 2013. Abstract 154LB.
New Treatment Options for HIV/HCV Genotype 1 Patients: EACS Guidelines

• With first pilot studies in HIV/HCV-coinfected subjects demonstrating significant higher SVR12 rates with triple therapy compared to dual therapy HCV protease inhibitor based therapy with either boceprevir or telaprevir is now the new standard of treatment in HCV genotype 1 infection in HIV-infected individuals where available.

• Although shorter treatment durations of triple therapy have been demonstrated to be very efficacious in HCV monoinfected subjects with rapid virological response this data so far is not available for HIV/HCV coinfected subjects.
Potential for Altered Drug Metabolism in Hep C-Infected Patients

CYP450
- Three quarters of most-used drugs are cleared by metabolism. Of these, two thirds are metabolized by CYP450\(^1\)
  - 50\% of common drugs metabolized by CYP3A4
- Liver primary site of activity\(^3\)
- Activity decreases as liver function declines\(^2\)
- In cirrhosis, reduced clearance of drugs cleared via CYP3A4\(^2\)

UGT
- 10\% of common drugs undergo clearance\(^1\)
- Less likely to be affected in moderate liver impairment, but activity appears reduced in advanced cirrhosis\(^2\)
- Activity at extrahepatic sites\(^4\)

CYP3A4 = cytochrome 3A4; CYP450 = cytochrome P450; UGT = uridine diphosphate glucuronosyltransferase.
A priori expected interactions between ARVs - DAAs

1. DAAs are CYP3A substrates → [DAA]↑ with RTV-boosted HIV PIs

2. DAAs are CYP3A substrates → [DAA]↓ with NNRTIs

3. DAAs are CYP3A inhibitors → [HIV PI/r]↑ (super-boosting)

Courtesy David Burger
# Summary of TVR – ARV interactions

<table>
<thead>
<tr>
<th>HIV drug</th>
<th>Effect on ARV AUC</th>
<th>Effect on TVR AUC</th>
<th>Can be used?</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV*</td>
<td>-7%</td>
<td>-18%</td>
<td>Yes</td>
<td>Van Heeswijk et al. CROI 2011</td>
</tr>
<tr>
<td>ETR</td>
<td>-6%</td>
<td>-16%</td>
<td>Yes</td>
<td>Kakuda et al. HIV PK 2012</td>
</tr>
<tr>
<td>RPV</td>
<td>+79%</td>
<td>-8%</td>
<td>Yes</td>
<td>Kakuda et al. HIV PK 2012</td>
</tr>
<tr>
<td>ATV/r</td>
<td>+17%</td>
<td>-20%</td>
<td>Yes</td>
<td>Van Heeswijk et al. CROI 2011</td>
</tr>
<tr>
<td>DRV/r</td>
<td>-40%</td>
<td>-35%</td>
<td>No</td>
<td>Van Heeswijk et al. CROI 2011</td>
</tr>
<tr>
<td>FPV/r</td>
<td>-47%</td>
<td>-32%</td>
<td>No</td>
<td>Van Heeswijk et al. CROI 2011</td>
</tr>
<tr>
<td>LPV/r</td>
<td>+6%</td>
<td>-54%</td>
<td>No</td>
<td>Van Heeswijk et al. CROI 2011</td>
</tr>
<tr>
<td>MRV**</td>
<td>+849%</td>
<td>No effect</td>
<td>Yes</td>
<td>Vourvahis et al. HIV PK 2013</td>
</tr>
<tr>
<td>RAL</td>
<td>+31%</td>
<td>+7%</td>
<td>Yes</td>
<td>Van Heeswijk et al. ICAAC 2011</td>
</tr>
<tr>
<td>TDF</td>
<td>+30%</td>
<td>0%</td>
<td>Yes</td>
<td>Van Heeswijk et al. ICAAC 2008</td>
</tr>
</tbody>
</table>

*TVR dose 1125mg q8h; **MRV dose 150mg q12h

*Courtesy David Burger
## Summary of BOC – ARV interactions

<table>
<thead>
<tr>
<th>HIV drug</th>
<th>Effect on ARV AUC</th>
<th>Effect on BOC AUC</th>
<th>Can be used?</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF</td>
<td>+5%</td>
<td>+8%</td>
<td>Yes</td>
<td>Kassera et al. CROI 2011</td>
</tr>
<tr>
<td>EFV</td>
<td>+20%</td>
<td>-19%</td>
<td>No</td>
<td>Kassera et al. CROI 2011</td>
</tr>
<tr>
<td>ETR</td>
<td>-23%</td>
<td>+10%</td>
<td>Yes</td>
<td>Hammond et al. JAIDS 2013</td>
</tr>
<tr>
<td>RPV</td>
<td>+39%</td>
<td>-6%</td>
<td>Yes</td>
<td>Rhee et al. CROI 2013</td>
</tr>
<tr>
<td>ATV/r</td>
<td>-35%</td>
<td>-5%</td>
<td>Yes/No</td>
<td>Hulskotte et al. CID 2013</td>
</tr>
<tr>
<td>LPV/r</td>
<td>-34%</td>
<td>-34%</td>
<td>No</td>
<td>Hulskotte et al. CID 2013</td>
</tr>
<tr>
<td>DRV/r</td>
<td>-44%</td>
<td>-32%</td>
<td>No</td>
<td>Hulskotte et al. CID 2013</td>
</tr>
<tr>
<td>MRV*</td>
<td>+128-202%</td>
<td>No effect</td>
<td>Yes</td>
<td>Vourvahis et al. &amp; Martel et al. HIV PK 2013</td>
</tr>
<tr>
<td>RAL</td>
<td>+1%</td>
<td>+7%**</td>
<td>Yes</td>
<td>De Kanter et al. CID 2013</td>
</tr>
</tbody>
</table>

* MRV dose 150mg Q12h; **vs. historical controls
### Summary of key DAA and ARV DDI recommendations

<table>
<thead>
<tr>
<th></th>
<th>TVR</th>
<th>BOC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATV/ r</strong></td>
<td>Monitoring for hyperbilirubinemia</td>
<td>Consider on a case by case basis if deemed necessary</td>
</tr>
<tr>
<td><strong>DRV/ r/, FPV/ r LPV/ r</strong></td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td><strong>EFV</strong></td>
<td>Increase TVR to 1250 mg q8h</td>
<td>Not recommended</td>
</tr>
<tr>
<td><strong>ETR</strong></td>
<td>No dose adjustment needed</td>
<td>No dose adjustment needed</td>
</tr>
<tr>
<td><strong>RPV</strong></td>
<td>No dose adjustment needed</td>
<td>No dose adjustment needed</td>
</tr>
<tr>
<td><strong>RAL</strong></td>
<td>No dose adjustment needed</td>
<td>No dose adjustment needed</td>
</tr>
<tr>
<td><strong>TDF</strong></td>
<td>Increased monitoring is warranted</td>
<td>No dose adjustment needed</td>
</tr>
</tbody>
</table>

Treatment Options for HIV/HCV Genotype 1 Patients: DHHS Guidelines

Preliminary recommendations on use of boceprevir or telaprevir in HIV/HCV genotype 1 coinfected patients¹

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Recommendation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients not on ART</td>
<td>Use either boceprevir or telaprevir</td>
</tr>
<tr>
<td>Patients receiving RAL/ETR/RPV + 2 NRTIs</td>
<td>Use either boceprevir or telaprevir</td>
</tr>
<tr>
<td>Patients receiving ATV/r + 2 NRTIs</td>
<td>Use telaprevir at the standard dose. Do not use boceprevir.</td>
</tr>
<tr>
<td>Patients receiving EFV + 2 NRTIs</td>
<td>Use telaprevir at increased dose of 1125 mg every 7-9 hours. Do not use boceprevir.</td>
</tr>
</tbody>
</table>

*These recommendations may be modified as new drug interaction and clinical trial information become available.
Management of newly diagnosed HIV-HCV co-infected genotype-1 patients

Newly diagnosed chronic HCV GT 1 infection

Perform Fibroscan® and/or serum marker and/or liver biopsy

F0F1<sup>a</sup>

- In general, treatment can be deferred. Consider treatment with Peg/RBV and an HCV protease inhibitor or Peg/RBV alone if low HCV viral load, IL28B CC genotype, absence of insulin resistance and high CD4 count.

F2F3<sup>a</sup>

- Treatment with Peg/RBV and an HCV protease inhibitor.

F4<sup>a</sup>

- Treatment with Peg/RBV and an HCV protease inhibitor if compensated disease. Treatment should be undergone in specialised centres.

<sup>a</sup>Metavir fibrosis score: F0=no fibrosis; F1= portal fibrosis, no septae; F2= portal fibrosis, few septae, F3=bridging fibrosis, F4=cirrhosis; Peg, pegylated interferon; RBV, ribavirin

Ingiliz P, Rockstroh J. Liver International 2012

EACS guidelines, version November 2012
Who should take care of HCV?

- Liver disease
- Staging
- Biopsy
- Rule out other liver diseases
- Bleeding, ascites
- Cirrhosis
- ESLD
- HCC
- Transplantation
- Etc

If you want to go fast, go alone
If you want to go far, go together
(African proverb)

- Infectious disease
- Viral dynamics
- Resistance
- DDIs
- Adherence
- Rule out other infectious diseases
- Work with NGOs
- Earlier treatment initiation
- TASP
- Etc
Summary

- HCV/ HIV-coinfected patients show a faster progression to cirrhosis and increased liver-related mortality compared with HCV monoinfection.
- HCV treatment options need to be evaluated and discussed with the patient.
- HAART should not be withheld in coinfected patients, and needs to be adapted to concomitant HCV therapy.
- HCV treatment decisions need to be based on fibrosis stage, likelihood of treatment response, and previous response to IFN/RBV-based therapies.
- IFN-free regimens are urgently needed to overcome some of the barriers in uptake of HCV therapy.
- Interdisciplinary partnership is required to address this unmet medical need.