Clinical case
HIV HCV coinfection

Dominique Salmon
HUPC, Paris Descartes University

PHC, January 2016
Disclosures

• Board of experts for Gilead and BMS
Objectives

• To discuss:
  – Results of DAA combination in HIV-HCV coinfection
  – Drugs-drugs interactions
  – Failures
  – Reinfections
Clinical case 1

- Didier is a 36 year-old man, business manager in a company of special events.

- In 2011, a rectal abscess leads to the detection of an HCV positive serology (no previous test)
  - G1a
  - HCV RNA: 3 450 601 UI/ml (6,54 log)
  - Elastometry: 4,9 kPa
  - ALT normal
  - HIV negative

No treatment decided
In January, apparition of a skin rash
In January 2013, apparition of a skin rash

- Syphilides ELISA+ VDRL : 32 UI
- HIV acute infection
HIV disease

- Uncomplete HIV Western Blot
- CD4: 388/mm³ - HIV RNA: 980,000 cop/ml
- Genotyping: HIV strain resistant to three classes
  - NVP and EFV
  - IDV and NFV
  - AZT and D4T
  - CCR5 tropism
- HLA B57*01 negative
- HAART was begun on January 24, 2013

??
HIV disease

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  - CCR5 tropism
- HLA B57*01 negative
- HAART begun on January 24, 2013
  - tenofovir/lamivudine/raltegravir
  - switched in 2014 to tenofovir/lamivudine/dolutegravir
• We learned that
  - he his a sex addict and has bank problems (since he lost both parents at young age)
  - No tobacco nor drug usen but alcohol

• In June 2015:
  - CD4: 490/mm³, HIV RNA < 20 cop/ml (few blips)
  - Creatinine: 117 µmol/l, clearance MDRD: 65 ml/mm
  - Weight: 72 kg
  - Treatment with rosuvastatin 10 mg/d
  - HCV RNA still positive, FS: 5.9 KPa

=> Decision to treat HCV + psychological support
What are the options giving more than 90% SVR rate in G1 HIV/HCV coinfection?
Similar efficacy of all DAA regimens in HIV/HCV coinfection and between HIV/HCV and HCV infection

Natural history and treatment of HCV/HIV coinfection: Is it time to change paradigms?

Joop E. Arends¹,², Faydra L. Lieveld¹, Lauke L. Boeijen¹, Clara T.M.M. de Kanter².

Fig. 1. SVR12 rates in IFN-free DAA studies in HIV/HCV co-infected patients with comparator data for HCV mono-infected patients. Studies included solely or mostly HCV genotype 1 patients. HIV/HCV coinfected patients are depicted in light blue bars and the HCV mono-infected patients in dark blue bars. Depicted studies are: SOF/LDV – ION-4 [31] and ION-1 [116]; 3D+RBV – Turquoise-1 [33] and PEARL-III and PEARL-IV [117]; GZR/EBR – C-EDGE COINFECTION [34] and C-EDGE [118]. SOF, sofosbuvir; LDV, ledipasvir; 3D, paritaprevir/ritonavir/ombitasvir/dasabuvir; RBV, ribavirin; GZR, grazoprevir; EBR, elbasvir; DAC, daclatasvir.
Options with a SVR rate > 90% in genotype 1 in HIV/HCV coinfection

6. C Worthy
7. Sulkowski MS, JAMA 2015;313:1223-1231.
Genotype 1 in HIV/HCV coinfection: is 8 weeks a possible option for naïve patients?


Christensen S, al. Sofosbuvir and ledipasvir for 8 weeks in patients with hepatitis C virus (HCV) mono-infection and human immunodeficiency virus (HIV)-HCV co-infection with genotype 1 and 4 in clinical practice – Results from the GErmann hepatitis C COhort (GECCO)- A1081 AASLD 2015
Options with a SVR rate > 90% in genotype 4 in HIV/HCV co-infection

- SOF/LDV/12w, Ion4 n=20
- SOF/DCV/12-24w, French ATU n=41
- GZV/EBR/12w, C-Edge n=22

84% 86% 88% 90% 92% 94% 96% 98%
SVR 12 rate

Options with a SVR rate > 90% in genotype 3 in HIV/HCV coinfection

Rockstroh J et al. A1058, AASLD 2015
Does his background treatment need to be optimized?

Truvada
Dolutegravir
Rosuvastatine
# Drug-drug interactions

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>SIM</th>
<th>DCV</th>
<th>SOF</th>
<th>SOF/LDV</th>
<th>3D</th>
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<td>Abacavir</td>
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<th>Protease inhibitors</th>
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<td>Atazanavir; atazanavir/ritonavir</td>
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<td>Darunavir/ritonavir; darunavir/cobicistat</td>
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<td>Maraviroc</td>
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EASL recommendations 2015
Drug-drug interactions

- We have to think in both directions!

\[ \begin{array}{|c|c|c|c|c|}
\hline
& SIM & DCV & SOF & SOF/LDV \\
\hline
\text{NRTIs} & Abacavir & & & \\
& Didanosine & & & \\
& Emtricitabine & & & \\
& Lamivudine & & & \\
& Stavudine & & & \\
& Tenofovir & & & \\
& Zidovudine & & & \\
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\text{NNRTIs} & Efavirenz & & & \\
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& Nevirapine & & & \\
& Rilpivirine & & & \\
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\text{Protease inhibitors} & Atazanavir; atazanavir/ritonavir & & & \\
& Darunavir/ritonavir; darunavir/cobicistat & & & \\
& Fosamprenavir & & & \\
& Lopinavir & & & \\
& Saquinavir & & & \\
& Dolutegravir & & & \\
\hline
\text{Integrase inhibitors} & Elvitegravir/cobicistat & & & \\
& Maraviroc & & & \\
& Raltegravir & & & \\
\hline
\end{array} \]

\[ \text{simple} = \text{everything sticks perfectly} \]
Drug-drug interactions

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- We have to think in both directions!

⇒ Adapt HIV or HCV treatment ....
Influence of LDV/SOF on TDF PK

⇒ 30-60% increase of TDF exposition in the presence of ledipasvir/sofosbuvir + boosted PI

- Monitor for tenofovir adverse events during coadministration with any TDF-based regimen

1. Data on File, Gilead Sciences.
2. Hoeltenman RMW, et al. 8th ICPHT 2005. Quebec City, Canada. Poster #2.11
3. German P, et al. ICPHT 2014. #06
5. Chilicki GE, et al. AAC. 2006; 50(4):1304-10 (SQV + RTV)
Demographic data et plasma TDF Cmin

**TABLE 3. Multivariate Analysis of Factors Associated With GFR Changes at the Time of TDF Concentration Determination**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men Coefficient</th>
<th>Men P</th>
<th>Women Coefficient</th>
<th>Women P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.865</td>
<td>0.001</td>
<td>-1.043</td>
<td>0.03</td>
</tr>
<tr>
<td>BMI</td>
<td>1.726</td>
<td>0.028</td>
<td>1.552</td>
<td>0.18</td>
</tr>
<tr>
<td>BL-GFR</td>
<td>-0.313</td>
<td>0.007</td>
<td>-0.489</td>
<td>0.01</td>
</tr>
<tr>
<td>CTrough-TDF &gt; 90 ng/mL</td>
<td>-3.201</td>
<td>0.475</td>
<td>-15.307</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-1.946</td>
<td>0.734</td>
<td>20.657</td>
<td>0.18</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-1.346</td>
<td>0.833</td>
<td>14.946</td>
<td>0.22</td>
</tr>
<tr>
<td>HCV-PCR+</td>
<td>2.481</td>
<td>0.623</td>
<td>13.274</td>
<td>0.08</td>
</tr>
<tr>
<td>PI/3</td>
<td>0.399</td>
<td>0.932</td>
<td>-13.109</td>
<td>0.11</td>
</tr>
<tr>
<td>ATV</td>
<td>-4.105</td>
<td>0.364</td>
<td>-6.830</td>
<td>0.37</td>
</tr>
</tbody>
</table>

(Poizot-Martin I et al., JAIDS 2013)

(Gervasoni C et al., Plos one 2013)

- Increase risk of risk of renal clearance changes with tenofovir if
- Plasma TDV Cmin (C24h) > 90 ng/ml

⇒ • Do not give LDV/SOF if TRUVADA + boosted PI
.....at least in female with low weight
EASL recommendations 2015

The fixed-dose combination of sofosbuvir and ledipasvir can be used with all antiretrovirals. However, this regimen should not be used with the combination of tenofovir/emtricitabine with atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir or elvitegravir/cobicistat when possible, or used with caution with frequent renal monitoring (B1).

AASLD recommendations AASLD

Because ledipasvir increases tenofovir levels, concomitant use mandates consideration of creatinine clearance (CrCl) rate and should be avoided in those with CrCl below 60 mL/min. Because potentiation of this effect is expected when tenofovir is used with ritonavir-boosted HIV protease inhibitors, ledipasvir should be avoided with this combination (pending further data) unless antiretroviral regimen cannot be changed and the urgency of treatment is high.

Rating: Class IIa, Level C

Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) (hereafter ledipasvir/sofosbuvir) should NOT be used with cobicistat and elvitegravir, pending further data.

Rating: Class III, Level C

⇒ Recommandations

- EASL: LDV/SOF + TDF/IP/r or ELV/co: use with caution, creat measure
- US: do not use LDV/SOF with TDF/IP/r or ELV/cob
Drug-drug interactions

- Be aware of the numerous co-prescriptions
  - Ex: 18% of HIV HCV patients receive a statin 30% VIH+

Bedimo HIV Med 2010

EASL recommandations 2015
Table 2. Effects of HCV Agents on Transporter Substrates (HCV Agents as Perpetrators of Interactions)

<table>
<thead>
<tr>
<th></th>
<th>Digoxin (P-gp)</th>
<th></th>
<th>Pravastatin (OATP1B1/B3)</th>
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<th>Rosuvastatin (OATP1B1/BCRP)</th>
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<tbody>
<tr>
<td></td>
<td>AUC</td>
<td>Cmax</td>
<td>AUC</td>
<td>Cmax</td>
<td>AUC</td>
<td>Cmax</td>
</tr>
<tr>
<td>ABT450/r/ombitasvir/dasabuvir</td>
<td>↑16%</td>
<td>↑15%</td>
<td>↑82%</td>
<td>↑37%</td>
<td>↑159%</td>
<td>↑613%</td>
</tr>
<tr>
<td>Asunaprevir</td>
<td>↑30%</td>
<td>←</td>
<td>NP</td>
<td>NP</td>
<td>↑41%</td>
<td>↑95%</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>↑27%</td>
<td>↑65%</td>
<td>NP</td>
<td>NP</td>
<td>↑58%</td>
<td>↑104%</td>
</tr>
<tr>
<td>GS-5816</td>
<td>↑34%</td>
<td>↑88%</td>
<td>↑35%</td>
<td>↑28%</td>
<td>↑169%</td>
<td>↑161%</td>
</tr>
<tr>
<td>GS-9451/ledipasvir/tegobuvir</td>
<td>↑34%</td>
<td>NP</td>
<td>↑168%</td>
<td>↑166%</td>
<td>↑699%</td>
<td>↑1670%</td>
</tr>
</tbody>
</table>

AUC=area under the curve, Cmax=maximum concentration, NP=not presented

GS- 5816 : velpatasvir;
GS9451 : NS3 HCV NS3 P
Tegobuvir : NS5a polymerase inhibitor
www.HCV-drug interactions
Sofosbuvir/ledipasvir begun on July 1st, 2015

- HAART maintained: TDF/FTC/dolutegravir
- Rosuvastatin switched for pravastatin

- At month 1
  - HVC RNA < 12 detectable
  - Creatinin raised to 140 mmol/l, MRDR clearance 51 ml/mn
Course of the disease

• TDF decreased to 1 pill every 2 days

• Month 3: < 12 UI/mL detectable
• Month 4: 14.374 UI/mL
• Month 4: 17.851.00 UI/mL
Why this relapse?
What to do now?
Predictors of failure in phase 3 trials of HIV-HCV coinfection

- Cirrhosis (OR=4.9, p=0.012, Photon 2)
- HCV RNA > 6 log (OR=34.4, p=0.02, Photon 2)
- Black race (OR =17.7, p=0.0012, Ion4)
- IL28B TT(OR=4.3, p=0.075, Ion4)

Response to DAA regimen in real life ANRS CO 13 Hepavih Cohort - SVR12 (1)

215 patients ended an all-oral DAA regimen until 01/2015, SVR rate was 92% and 18 patients (8%) failed therapy.

Relapse n = 15
Breakthrough n = 2
Death before SVR12 n = 1

Rencontre Sainte Marguerite, October 2015; CROI 2016
Failure of DAA regimen in HIV/VHC coinfection: ANRS CO13 HEPAVIH Cohort (2)

<table>
<thead>
<tr>
<th>Cirrhosis</th>
<th>71%</th>
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<tbody>
<tr>
<td>Child Pugh B</td>
<td>22%</td>
</tr>
<tr>
<td>Genotype 1/3/4 (%)</td>
<td>66%/17%/17%</td>
</tr>
<tr>
<td>CD4 cells/mm3, median</td>
<td>525</td>
</tr>
<tr>
<td>HIV RNA undetectable, (%)</td>
<td>64%</td>
</tr>
<tr>
<td>RBV (%)</td>
<td>43%</td>
</tr>
<tr>
<td>12 weeks duration planned (%)</td>
<td>43%</td>
</tr>
<tr>
<td><strong>SOF+ DVC (n,%)</strong></td>
<td>10 (57%)</td>
</tr>
<tr>
<td>30 mg/60 mg/90 mg</td>
<td>6/2/1</td>
</tr>
<tr>
<td>SOF+RBV (n,%)</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>SOF+LDV (n,%)</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>SOF+SIM (n, %)</td>
<td>1 (5%)</td>
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</tbody>
</table>
Is it useful to detect RAVs?

What is the best technique?
When to do the test: baseline and/or at failure?
What is the impact on SVR?
Is the impact similar whatever the genotype?
## Resistance associated mutations in HIV HCV coinfection trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Nb failures</th>
<th>RAVs to NS5A</th>
<th>RAVs to NS5B (S282T)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>Baseline</td>
<td>At failure</td>
</tr>
<tr>
<td>Eradicate, SOF/LDV</td>
<td>1</td>
<td>Y93H (38%) →</td>
<td>Y93H (99%)</td>
</tr>
<tr>
<td>Ion 4, SOF/LDV</td>
<td>12</td>
<td>18% RAVs</td>
<td>12/12 (100%) had RAVs emergence</td>
</tr>
<tr>
<td>Ally 2, SOF/DCV</td>
<td>39</td>
<td>17% RAVs (codon 28, 30, 31, or 93)</td>
<td>2/12 relapses had new RAVs.</td>
</tr>
<tr>
<td>Turquoise 1, 3D + RBV</td>
<td>2</td>
<td>2/2 had RAVs resistant to 3 classes</td>
<td></td>
</tr>
<tr>
<td>Photon-2, SOF/RBV</td>
<td>31</td>
<td></td>
<td>4/31 RAVS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-2 low level (L159F, L159N + S282N + V321A)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-2 high level RAVs (L159T)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No variant S282T</td>
</tr>
</tbody>
</table>
Is there a reinfection?

• In C-EDGE coinfection, among 8 failures, at least 2 patients had a new infection
  – Genotype 1a et 1b at baseline ➔ génotype 3.

Rate of HCV reinfection after acute HCV hepatitis in MSM

- 191 HIV+ MSM with acute HCV
- 32 reinfections of 145 cases
  - 25% reinfection within 2 years
- 17 again treated or spontaneous clearance

Martin et al. AIDS Oct. 2013
Conclusion

• Similar SVR rates than in HCV monoinfection
• Be aware of:
  – Drugs-drugs interactions
  – Compliance to therapy
  – HICV reinfection
• Usefulness to detect RAVs: to be further investigated

BACK-UP
DDA 12 weeks trials in HCV/HIV Co-infection: all genotypes

ION4: LDV/S OF G1-4

ALLY2: DCV/S OF G1-4

EDGE: GRZ/E BV G1-4

ULOISE: 1 3D+R BV
DDA 12 weeks trials in HCV/HIV Co-infection: G4

ION4 LDV/S OF C14
ALLEZ DCV/S OF C14
EDGE GRZ/E BV
UOISE 1 3D+R BV

SVR12 (%)
DDA 12 weeks trials in HCV/HIV Co-infection : G1

ION4
LDV/S
OF
G1-4

96

ALLIZ
DCV/S
OF
G1-4

97

EDGE
GRZ/E
BV

96

GUISE
1
3D+R
BV

98