Management of Drug-drug Interactions in Hepatitis C Therapy

David M. Burger
Professor of Clinical Pharmacy
Radboud University Nijmegen Medical Center
The Netherlands
IDPharmacology@akf.umcn.nl
A case to illustrate the clinical relevance of DDIs

- ♂, 46y, from Azerbaijan, HCV genotype 1b, DM II, liver cirrhosis, EtOH abuse in past
- Start of DAA therapy incl. telaprevir, on Feb 13, 2012
- Admitted in hospital on March 14, 2012 feeling very sick.
- Lab results: CK 34,010 (normal: < 170); LD 1,438 (normal: <250); ASAT 882 (normal: <35); creatinine 67
A case to illustrate the clinical relevance of DDIs

- ♂, 46y, from Azerbaijan, HCV genotype 1b, DM II, liver cirrhosis, EtOH abuse in past
- Start of DAA therapy incl. telaprevir, on Feb 13, 2012
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- Lab results: CK 34,010 (normal: < 170); LD 1,438 (normal: <250); ASAT 882 (normal: <35); creatinine 67

- Patient was also treated by cardiologist with simvastatin 80mg QD
- TVR inhibits **CYP3A**-mediated metabolism of simvastatin = contra-indication
Similar cases are now appearing in the medical journals…

Research letters

J Antimicrob Chemother 2013
doi:10.1093/jac/dks518
Advance Access publication 20 January 2013

Serious neuropsychiatric adverse effects in a hepatitis C virus/hepatitis B virus/HIV-coinfected patient receiving bosentan and telaprevir

Minh P. Lê¹*, Anne Gervais², Christine Le Beller³, Kivan Long⁴, Lucile Larrouy⁵, Emmanuelle Papy⁶, Hervé Mal⁶, Diane Descamps⁵ and Gilles Peytavin¹

JAC; 2013; 68(5): 1208-9
Frequently prescribed medications in HCV patients

<table>
<thead>
<tr>
<th>Medication</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zolpidem</td>
<td>17.4%</td>
</tr>
<tr>
<td>Diazepam</td>
<td>7.9%</td>
</tr>
<tr>
<td>Codeine</td>
<td>16.0%</td>
</tr>
<tr>
<td>Bupropion</td>
<td>7.2%</td>
</tr>
<tr>
<td>Prednisone</td>
<td>15.4%</td>
</tr>
<tr>
<td>Trazodone</td>
<td>7.1%</td>
</tr>
<tr>
<td>Tramadol</td>
<td>14.3%</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>6.8%</td>
</tr>
<tr>
<td>Citalopram</td>
<td>13.5%</td>
</tr>
<tr>
<td>Sertraline</td>
<td>6.4%</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>13.1%</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>6.1%</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>13.0%</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>5.4%</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>11.8%</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>5.3%</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>10.2%</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>4.2%</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>8.1%</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>5.0%</td>
</tr>
</tbody>
</table>

“45-65% not mentioned in drug labels”

Mayer et al. AASLD 2012 #136
Outline

• Summary of Ribavirin & IFN-α

• Description of PK profiles of HCV PI therapies

• Interpretation of interpatient PK variability & PK/PD relationships of HCV PIs

• Review of drug-drug interactions with HCV PIs, based on:
  • Clinical data
  • Theoretical assumptions
Ribavirin (RBV) & IFN-α

- RBV: contra-indicated with other myelotoxic agents (ZDV, ganciclovir, etc.)
- RBV: contra-indicated with DDI, d4T because of mitochondrial toxicity
- RBV – abacavir: conflicting results
  - Hypothesis: competition for intracellular phosphorylation → reduced HCV response?
  - Data originate from era when lower doses of RBV were used
  - Alternative (TDF) has also toxicities; ABC no longer contra-indicated
- IFN-α: small increase in methadone levels (??)
## BOC & TVR PK profile

<table>
<thead>
<tr>
<th></th>
<th>BOC</th>
<th>TVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of Metabolism</td>
<td>AKR1C2 + 1C3, CYP3A</td>
<td>CYP3A</td>
</tr>
<tr>
<td>Transporter effects</td>
<td>P-gp substrate</td>
<td>P-gp substrate</td>
</tr>
<tr>
<td>In vitro CYP inhibition</td>
<td>CYP3A</td>
<td>CYP3A</td>
</tr>
<tr>
<td>effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In vitro transporter</td>
<td>P-gp, OATP1B1, BCRP</td>
<td>P-gp</td>
</tr>
<tr>
<td>inhibition effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In vitro CYP induction</td>
<td>None</td>
<td>Low potential to induce CYP2C, 3A, or 1A</td>
</tr>
<tr>
<td>effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein Binding</td>
<td>68-75%</td>
<td>59-76%</td>
</tr>
</tbody>
</table>

*Slide courtesy of Dr Jennifer Kiser (modified)*
Interpatient variability & PK/PD relationships: important for interpretation of drug-drug interactions (1)
Interpatient variability & PK/PD relationships: important for interpretation of drug-drug interactions (2)

Figure 3 Relationship Between Boceprevir $C_{\text{trough}}$ at Week 5 and Early Responsiveness to Combination Treatment With Boceprevir and Peginterferon alfa-2b (log HCV RNA change from baseline at Week 5).

Source: Sponsor's study-report-phase-1-2-pk-pd.pdf, page 18
Overview of drug-drug interaction studies
(published or presented)

1. Effect of telaprevir on PK of other drugs

2. Effect of other drugs on telaprevir PK

3. Effect of boceprevir on PK of other drugs

4. Effect of other drugs on boceprevir PK
Telaprevir
Telaprevir and immunosuppressants

Fig. 1. Dose-normalized mean (SD) blood concentration-time profiles of cyclosporine following administration of cyclosporine alone and with telaprevir (log-linear scale).

Fig. 2. Dose-normalized mean (SD) blood concentration-time profiles of tacrolimus following administration of tacrolimus alone and with telaprevir (log-linear scale).

AUC: 4.1 fold ↑
AUC: 70.3 fold ↑

Garg et al. Hepatology 2011
Telaprevir and midazolam (CYP3A probe) or digoxin (PgP probe)

Recommendation: contra-indication

Telaprevir and other CYP3A substrates:
amlodipine

AUC: 2.79 fold ↑
Recommendation: caution, start with low-dose

atorvastatin

AUC: 7.88 fold ↑
contra-indication

Lee et al. AAC 2011
Telaprevir and oral contraceptives

Recommendation: use 2 alternative non-hormonal methods (because of RBV)

Telaprevir and methadone (1)

AUC: -29%

Recommendation: clinical monitoring as the dose of methadone may need to be adjusted

Van Heeswijk et al. AAC 2013
Telaprevir and methadone (2)

Recommendation: clinical monitoring as the dose of methadone may need to be adjusted

Van Heeswijk et al. AAC 2013
Telaprevir and buprenorphine

AUC: -4%

Recommendation: can be combined

Luo et al AAC 2012
Increased Plasma and Intracellular Ribavirin Concentrations Associated With Telaprevir Use

Kyle P. Hammond¹, Leah Jimmerson¹, Christine E. MacBrayne¹, Michelle Ray¹, Lane Bushman¹, James R. Burton¹, Fafa Baouchi-Mokrane², Gregory T. Everson¹, Peter L. Anderson¹, Jennifer J. Kiser¹

¹University of Colorado Denver, Aurora, CO, ²Denver Health Medical Center, Denver, CO

20th Conference on Retroviruses and Opportunistic Infections
Atlanta, Georgia
March 3-6, 2013
Abstract 34
Background

• When added to peginterferon and ribavirin (PR), the HCV protease inhibitors (telaprevir or boceprevir) significantly increase the rates of sustained virologic response in HCV infected patients.1-5

• However, this triple therapy (TT) is associated with a doubling in the rate of anemia compared to PR alone (dual therapy, DT).6

5. Bacon BR et al. NEJM. 2011; 364(13): 1207-17
Ribavirin Plasma AUC

Plasma ribavirin $AUC_{0-12hr}$ 1.54 fold higher in triple therapy vs. dual therapy group ($p=0.002$)
Ribavirin RBC Concentrations Over Course of Treatment

Dual Therapy
Triple Therapy

Dose Normalized Intracellular Ribavirin Concentration

Telaprevir Discontinued

Day 1 Week 1 Week 2 Week 4 Week 9-14 Week 16 Week 24

DT: n=16 n=16 n=16 n=16 n=16 n=10 n=8
TT: n=5 n=5 n=5 n=5 n=5 n=5 n=4
Possible Mechanism

• **Telaprevir effects transporters?**
  – Induction of influx transporters?
    • Ribavirin is a substrate for concentrative nucleoside transporters (CNT) and equilibrative nucleoside transporters (ENT).
  – Inhibition of efflux transporters?
    • Telaprevir inhibits P-glycoprotein (P-gp), OATP1B1 (liver) and renal drug transporters OCT2 and MATE1.

• **Food effect?**
  – Ribavirin AUC$_{0-192h}$ and C$_{max}$ increased by 42% and 66%, respectively, when ribavirin taken with a high fat meal compared with fasting conditions.

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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)
Telaprevir & boceprevir are CYP3A substrates: boosting by ritonavir?

Figure 1. Pharmacokinetic enhancement of VX-950 and SCH 503034 in rats

Mean plasma concentrations, µg/ml

Time after dosing, h

Closed symbols: oral dosing (5 mg/kg) alone; open symbols: oral co-dosing with ritonavir (5 mg/kg each); triangles: VX-950; circles: SCH 503034. Values represent mean ± SEM.

Mean TVR PK Profiles

AUC = area under the curve

<table>
<thead>
<tr>
<th></th>
<th>TVR alone</th>
<th>TVR + ARV</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>18</td>
</tr>
</tbody>
</table>

TVR concentration (ng/mL)

Time (hours)

TVR alone

TVR + ARV

AUC = area under the curve
Mean HIV PI PK Profiles

LPV/r

AUC ↔

ATV/r

AUC↑ 17%

DRV/r

AUC↓ 40%

fAPV/r

AUC↓ 47%

APV = amprenavir

n=19
n=7
n=16
n=20
n=11
n=18

n=12
n=11
n=11
n=18

Time (hours)

Time (hours)

Time (hours)

Time (hours)

LPV concentration (ng/mL)

ATV concentration (ng/mL)

DRV concentration (ng/mL)

APV concentration (ng/mL)
EFV + TVR: the effect of a TVR dose increase

**Effect of EFV/TDF on TVR**

<table>
<thead>
<tr>
<th>TVR dose</th>
<th>$C_{\text{min}}$</th>
<th>$C_{\text{max}}$</th>
<th>$AUC_{8h}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1125 mg q8h</td>
<td>0.75 (0.66–0.86)</td>
<td>0.86 (0.76–0.97)</td>
<td>0.82 (0.73–0.92)</td>
</tr>
<tr>
<td>1500 mg q12h + E/T</td>
<td>0.52 (0.42–0.64)</td>
<td>0.97 (0.88–1.06)</td>
<td>0.80 (0.73–0.88)*</td>
</tr>
</tbody>
</table>

*Average steady state plasma concentration ($C_{\text{ss,average}}$)
Effect of TVR on RAL exposure

Van Heeswijk et al. 51st ICAAC, poster 1738a
Effect of RAL on TVR exposure

Van Heesijk et al. 51st ICAAC, poster 1738a
Mean (SD) rilpivirine plasma concentration over time, with or without telaprevir

![Graph showing rilpivirine plasma concentration over time with or without telaprevir. The graph illustrates that the mean plasma concentration is significantly increased with the addition of telaprevir (TVR), indicated by an AUC of +79%.](image)
Mean (SD) telaprevir plasma concentration over time, with or without rilpivirine

AUC: -8%
# 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
Boceprevir
Boceprevir and immunosuppressants

Tacrolimus AUC: 17.0 fold ↑

Cyclosporine AUC: 2.6 fold ↑

Hulskotte et al. 16th Hep-DART, 2011
Boceprevir and statins

Atorvastatin AUC: 2.3 fold ↑

Pravastatin AUC: 1.5 fold ↑

Hulskotte et al. 16th Hep-DART, 2011
Boceprevir and escitalopram

Escitalopram AUC: -21%

Recommendation: no dose adjustment needed

Hulskotte et al. 16th Hep-DART, 2011
Boceprevir and oral contraceptives

Figure 1. Arithmetic mean (SD) plasma concentration-time profiles (linear and semi-log scales) of NE following the administration of EE/NE alone and EE/NE plus boceprevir.

Figure 2. Arithmetic mean (SD) plasma concentration-time profiles (linear and semi-log scales) of EE following the administration of EE/NE alone and EE/NE plus boceprevir.

AUC: -4%

Recommendation: use 2 non-hormonal methods (because of RBV)

AUC: -26%

Lin et al. AASLD 2012 abstract #1901
BOC effect on HIV PIs

**ATV/BOC PK**

- Mean ATV concentrations were lower at all time points with BOC + ATV/RTV compared with ATV/RTV alone (Figure 2).

**Figure 2.** Mean (SD) plasma concentration-time profiles for ATV/RTV alone and in combination with BOC.

<table>
<thead>
<tr>
<th>HIV drug</th>
<th>Effect on ARV AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV/r</td>
<td>-35%</td>
</tr>
<tr>
<td>LPV/r</td>
<td>-34%</td>
</tr>
<tr>
<td>DRV/r</td>
<td>-44%</td>
</tr>
</tbody>
</table>

ATV, atazanavir; BOC, boceprevir; MD, multiple dose; RTV, ritonavir; SD, standard deviation.

Hulskotte et al. CID 2013
## Summary of BOC – ARV interactions

<table>
<thead>
<tr>
<th>HIV drug</th>
<th>Effect on BOC AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV/r</td>
<td>-5%</td>
</tr>
<tr>
<td>LPV/r</td>
<td>-34%</td>
</tr>
<tr>
<td>DRV/r</td>
<td>-32%</td>
</tr>
</tbody>
</table>
Boceprevir & Raltegravir

**Figure 1: RAL plasma concentration vs. time curves**

<table>
<thead>
<tr>
<th>HIV drug</th>
<th>Effect on ARV AUC</th>
<th>Effect on BOC AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAL</td>
<td>+1%</td>
<td>+7%*</td>
</tr>
</tbody>
</table>

* vs. historical controls

De Kanter et al. CID 2013
Efavirenz

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LS Mean</th>
<th>Ratio Estimate, % (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effect of EFV (600 mg QD) on BOC (800 mg TID)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>BOC</td>
<td>2038</td>
</tr>
<tr>
<td></td>
<td>BOC + EFV</td>
<td>1871</td>
</tr>
<tr>
<td>$AUC_{(0-8h)}$ (ng·h/mL)</td>
<td>BOC</td>
<td>6913</td>
</tr>
<tr>
<td></td>
<td>BOC + EFV</td>
<td>5630</td>
</tr>
<tr>
<td>$C_{\text{min}}$ (ng/mL)</td>
<td>BOC</td>
<td>94.4</td>
</tr>
<tr>
<td></td>
<td>BOC + EFV</td>
<td>52.5</td>
</tr>
<tr>
<td><strong>Effect of BOC (800 mg TID) on EFV (600 mg QD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>EFV</td>
<td>4573</td>
</tr>
<tr>
<td></td>
<td>EFV + BOC</td>
<td>5077</td>
</tr>
<tr>
<td>$AUC_{(0-24h)}$ (ng·h/mL)</td>
<td>EFV</td>
<td>78667</td>
</tr>
<tr>
<td></td>
<td>EFV + BOC</td>
<td>94655</td>
</tr>
</tbody>
</table>

*Model-based (least squares) geometric mean; ANOVA extracting the effects due to treatment and subject.

AUC, area under the plasma concentration-time curve; BOC, boceprevir; CI, confidence interval; $C_{\text{max}}$, maximum observed plasma concentration; $C_{\text{min}}$, minimum observed plasma concentration; EFV, efavirenz; LS, least squares; QD, once daily; TID, three times a day."
# 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
Preferred ARVs for combined HIV/HCV treatment based on phase I studies in healthy volunteers

- **Telaprevir**
  - Raltegravir
  - Rilpivirine
  - Etravirine
  - Atazanavir/rtv
  - Maraviroc

- **Boceprevir**
  - Raltegravir
  - Etravirine
  - Maraviroc
  - (Atazanavir/rtv)
Examples contra-indicated drugs and cautions

- Rifampin, rifabutin and other enzyme inducers (anti-epileptics, St John’s wort)
- Alfuzosin
- Ergot derivatives
- Atorvastatin, simvastatin
- Pimozide
- Sildenafil, tadalafil
- Midazolam, triazolam
- Calcium channel blockers (other than amlodipine)
- Corticosteroids (systemic and inhaled/nasal)
- Azole antifungal agents
- Antiarrhythmics, digoxin
- Colchicine
- Methadone
Other HCV agents in phase III: drug interactions?

- **Simeprevir (TMC-435)**: CYP3A substrate & CYP3A/CYP1A2 inhibitor

- **Faldaprevir (BI-201335)**: CYP3A inhibitor & substrate (?)

- **Daclatasvir (BMS-790052)**: CYP3A substrate, no CYP3A inhibitor; PgP substrate & inhibitor

- **Asunaprevir (BMS-650032)**: CYP3A substrate & inducer; CYP2D6 inhibitor; OATP1B substrate; PgP inhibitor

- **Sofosbuvir (GS-7977)**: no interactions expected (nucleoside)

*All agents being tested with (some) ARVs prior to phase II/III*
AAA in Management of DDI in HCV therapy

• **A**wareness: check co-medication; discuss with patient

• **A**void if possible / Alternatives
  • Stop statin
  • Low dose amlodipine if CCB needed
  • Beclomethasone inhalation
  • Paroxetine instead of escitalopram (?)
  • Azithromycin instead of clarithromycin
  • Etc.

• **A**sk your clinical pharmacologist ([IDPharmacology@akf.umcn.nl](mailto:IDPharmacology@akf.umcn.nl))
Clinical management of drug–drug interactions in HCV therapy: Challenges and solutions

David Burger¹,* David Back² Peter Buggisch³ Maria Buti⁴ Antonio Craxi⁵ Graham Foster⁶ Hartwig Klinker⁷ Dominique Larrey⁸ Igor Nikitin⁹ Stanislas Pol¹⁰ Massimo Puoti¹¹ Manuel Romero-Gómez¹² Heiner Wedemeyer¹³ Stefan Zeuzem¹⁴
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