Section 6: Treatment of Hepatitis C virus (HCV)

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Training “Hepatitis C and HR for PWUD”,
9th-13th May 2016, Hanoi, Vietnam
Learning objective of the session: understanding and explaining key elements of HCV treatment
Objective of HCV treatment

» 1st goal of HCV treatment: cure/to get rid of the virus. People have cured their HCV when there is no virus in their bloodstream 3 months (12 weeks) after they have finished treatment (this is called sustained virological response, or SVR).

» 2nd goal of treatment: reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma.
HCV life cycle and treatment

» Hepatitis C virus is replicated in liver cells and can as well be detected in the blood

» Hepatitis C drugs work by blocking different steps in the virus life cycle; this prevents HCV from replicating

» People need to stay on HCV treatment for a certain amount of time to make sure cure is achieved

» Hepatitis C treatment duration depends of the treatment regimen, eventually on the genotypes of the virus, and if the patient has cirrhosis.

» To assess if the treatment has worked, patients need to do a viral load test 12 or 24 weeks after completing the treatment course to measure whether there is still virus in their blood.
Therapeutic development: DAAs

![Graph showing the percentage of patients with sustained virological response (SVR) over time for different treatment regimens: IFN, IFN + RBV, PEG-IFN + RBV, PEG-IFN + RBV + new PI, and INF-free regimens.](image)

- **1999**: IFN and IFN + RBV with 24 W and 48 W treatments.
- **2002**: IFN + RBV with 48 W treatment.
- **2011**: PEG-IFN + RBV with 48 W treatment and INF-free regimens with 12 weeks.
- **2016**: 95-100% SVR for INF-free regimens.

*Slide courtesy of Karine Lacombe*
Image of a diagram showing the relationship between efficacy and tolerability of different treatments, with treatment options such as PEG-IFN/RBV, PEG-IFN/RBV/SMV, PEG-IFN/RBV/TVR, PEG-IFN/RBV/BOC, IFN/RBV, IFN, SOF/LDV, SOF/SMV, and SOF/SMV/450/OBT/DSB/RBV. The diagram is color-coded by treatment duration: 12 weeks, 24 weeks, 24-48 weeks, and 48 weeks.
Peg-INF + Ribavirin (RBV)
Peg-INF + Ribavirin (RBV)

» General antiviral activity
» Cures rates: 40-80% depending on the genotype
  – Less effective for people with cirrhosis
  – Less effective for people who are HIV+ (especially if they have genotype 1)
» Duration: 24 to 48 weeks depending on the genotype
» Heavy side effects:
  – fatigue (interferon and ribavirin)
  – flulike symptoms: fever, headache, muscle ache (interferon and ribavirin)
  – mild anxiety (interferon)
  – depression (interferon)
  – skin rash (ribavirin)
  – gastrointestinal symptoms: nausea, diarrhea (interferon and ribavirin)
» Monitoring for severe side effects (eg, marked anemia) is an important part of treatment follow-up
SVR by HCV Genotype with pegylated interferon and RBV

- **GENOTYPE 1** ~50%
- **GENOTYPE 2** ~75%
- **GENOTYPE 3** ~60%
- **GENOTYPE 4** 40% - 70%
- **GENOTYPE 5** 49% - 60%
- **GENOTYPE 6** 60% - 90%
## Monitoring in pegINF/RBV treatments

<table>
<thead>
<tr>
<th>Time</th>
<th>TOXICITY</th>
<th>EFFICACY</th>
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<tbody>
<tr>
<td></td>
<td>FBC, creatinine, ALT</td>
<td>IFN/ RBV</td>
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<tr>
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<tr>
<td>Week 1*</td>
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<td>Week 2*</td>
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<td>Week 4</td>
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<td>X</td>
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<tr>
<td>Week 8</td>
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</tr>
<tr>
<td>Week 12 EOT^b</td>
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<td>X</td>
</tr>
<tr>
<td>Week 24 EOT^c</td>
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<td>X</td>
</tr>
<tr>
<td>Week 36</td>
<td>X</td>
<td></td>
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<tr>
<td>Week 48 EOT^d</td>
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<tr>
<td>Week 12 after EOT</td>
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<td></td>
</tr>
<tr>
<td>Week 24 after EOT</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

*Note: X indicates monitoring for both toxicity and efficacy.*

- **Week 0:** Monitoring begins before treatment starts.
- **Week 1 & Week 2:** Early monitoring for potential side effects.
- **Week 4:** Monitoring for adherence and side effects.
- **Week 8:** Intermediate monitoring for efficacy.
- **Week 12 EOT** & **Week 24 EOT:** Monitoring for complete treatment and effectiveness.
- **Week 36:** Long-term monitoring for sustained response.
- **Week 48 EOT:** Additional long-term monitoring.
- **Week 12 & 24 after EOT:** Monitoring for residual effectiveness and side effects.
Direct-Acting Antivirals (DAAs) for HCV

- Oral DAAs are replacing interferon-based treatment as standard of care
- DAAs target different steps of the virus lifecycle, preventing replication

- 4 classes of drugs
  - (NS3/4A) protease inhibitors (PIs)
  - NS5B nucleoside polymerase inhibitors (NPIs)
  - NS5B non-nucleoside polymerase inhibitors (NNPIs)
  - and NS5A inhibitors
NS5B - HCV Nucleoside/Tide Polymerase Inhibitors: Sofosbuvir

» Drugs ending on –BUVIR
» pan-genotypic
» high resistance barrier
» used with PEG-IFN and RBV, RBV alone, and other DAAs
» few DDIs
» few side effects (but hard to tell, since used with other drugs)
» once-daily
HCV Protease Inhibitors: Simeprevir + PARITAPREVIR/RITONAVIR

» Drugs ending on –REVIR
» First generation: BOCEPREVIR+TELAPREVIR not relevant any more
» active against some genotypes (usually 1 & 4)
» low barrier to resistance
» tend to have DDIs with ARVs and other commonly-used drugs (OST is usually OK)
» used with PEG-IFN/RBV or + other DAAs
HCV NS5A Inhibitors: LEDIPASVIR + DACLATASVIR (OMBITASVIR)

- Drugs ending on: –ASVIR
- Some are pan-genotypic, others not so much
- Low resistance barrier
- Used with other DAAs, with or without RBV
- Some DDIs
- Few side effects
- Once-daily
Approved in USA+Europe and evaluated by WHO

» Two fixed-dose combinations
  - sofosbuvir/ledipasvir (GS)
  - and Ombitasvir/paritaprevir/ritonavir plus dasabuvir (Abbvie)

» Three DAAs
  - Sofosbuvir (GS)
  - Daclatasvir (BMS)
  - Simeprevir (J+J)
Figure 4. Overview of DAAs on the market and in the pipeline (phase II and III).

Source: UNITAID.
QUEST-1: PEG-IFN/RBV/Simeprevir

Genotype 1 treatment naïve, 24-48 weeks

SVR12 %

PEG/RBV (n=113)  PEG/RBV/SMV (n=229)  PEG/RBV (n=17)  PEG/RBV/SMV (n=31)

F0-3  F4

NEUTRINO: PEG-IFN/RBV/Sofosbuvir

Genotype 1 (+4/5/6) treatment naïve, 12 weeks

SVR12%

GT1 (n=292)    GT4 (n=28)    GT5/6 (n=7)    Cirrhosis (n=54)

Lawitz E et al. NEJM 2013;368:1878-1887
Sofosbuvir/Ribavirin

Genotype 3, treatment naïve and experienced, 24 weeks

Zeuzem S et al, AASLD 2013
Gilead: Sofosbuvir/Ledipasvir

Genotype 1, treatment naive and experienced

ALLY-2: DAC/SOF in HIV/HCV

**SVR12 by HCV Genotype: 12-Week Groups**

- **Naive**
  - Genotype 1a: 96%, 68/71
  - Genotype 1b: 97%, 32/33
  - Genotype 2: 100%, 12/12
  - Genotype 3: 100%, 11/11
  - Genotype 4: 100%, 6/6

- ** Experienced**
  - Genotype 1a: 100%, 100/100
  - Genotype 1b: 100%, 100/100
  - Genotype 2: 100%, 100/100
  - Genotype 3: 100%, 100/100
  - Genotype 4: 100%, 100/100
DAAs

» Radically simplify and improve HCV treatment
» Cure rates have topped 95%—even for people with HIV and people with cirrhosis
» Safe; tolerable: AE-associated discontinuation rates were < 3% across DAA clinical trials, even with RBV
» Because DAAs are so safe and effective, monitoring requirements are minimized – increases feasibility in RLS
» HIV does not impair response to IFN-free DAA therapy
» HCV resistance will not be a major clinical issue

» Challenges: GT3 + F4 and DDI
DAAs: perfectovir

Desirable characteristics:

» **Short** - treatment duration: 12 weeks

» **Easy to take** – all oral, no injection, does not require refrigeration

» **Pan-genotypic action**: no genotyping required

» **High activity in cirrhosis**: less liver disease assessment
W0 PCR  W4 PCR  W8 PCR  W12 PCR  W24 PCR  W48

Ribavirin

Boceprevir

8H + snack

8H + snack

8H + snack

Telaprevir

8H + snack

8H + snack

PegIFN

Slide courtesy of Karine Lacombe
Approved in USA+Europe and evaluated by WHO

» Two fixed-dose combinations
  - sofosbuvir/ledipasvir (GS)
  - and Ombitasvir/paritaprevir/ritonavir plus dasabuvir (Abbvie)

» Three DAAs
  - Sofosbuvir (GS)
  - Daclatasvir (BMS)
  - Simeprevir (J+J)
### TABLE 7.5 Summary of recommended preferred regimens with treatment durations*

<table>
<thead>
<tr>
<th>Persons without cirrhosis</th>
<th>Daclatasvir/sofosbuvir</th>
<th>Ledipasvir/sofosbuvir</th>
<th>Sofosbuvir/ribavirin</th>
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</thead>
<tbody>
<tr>
<td>Genotype 1</td>
<td>12 weeks</td>
<td>12 weeks(^a)</td>
<td></td>
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<tr>
<td>Genotype 2</td>
<td></td>
<td></td>
<td>12 weeks</td>
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<tr>
<td>Genotype 3</td>
<td>12 weeks</td>
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<td>24 weeks</td>
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<tr>
<td>Genotype 4</td>
<td>12 weeks</td>
<td>12 weeks</td>
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<tr>
<td>Genotype 5</td>
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<td>12 weeks</td>
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<tr>
<td>Genotype 6</td>
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<td>12 weeks</td>
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</table>
### WHO 2016 HCV treatment guidelines

#### Persons with cirrhosis

<table>
<thead>
<tr>
<th></th>
<th>Daclatasvir/sofosbuvir</th>
<th>Daclatasvir/sofosbuvir/ribavirin</th>
<th>Ledipasvir/sofosbuvir</th>
<th>Ledipasvir/sofosbuvir/ribavirin</th>
<th>Sofosbuvir/ribavirin</th>
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<tbody>
<tr>
<td>Genotype 1</td>
<td>24 weeks</td>
<td>12 weeks</td>
<td>24 weeks</td>
<td>12 weeks(^b)</td>
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<td>Genotype 2</td>
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<td>16 weeks</td>
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<td>Genotype 4</td>
<td>24 weeks</td>
<td>12 weeks</td>
<td>24 weeks</td>
<td>12 weeks(^b)</td>
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<td>Genotype 5</td>
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<td>24 weeks</td>
<td>12 weeks(^b)</td>
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<td>Genotype 6</td>
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<td>24 weeks</td>
<td>12 weeks(^b)</td>
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* Treatment durations are adapted from the 2015 guidelines of the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL).

\(^a\) Treatment may be shortened to 8 weeks in treatment-naïve persons without cirrhosis if their baseline HCV RNA level is below 6 million (6.8 log) IU/mL. The duration of treatment should be shortened with caution.

\(^b\) If platelet count < 75 x 10^3/µL, then 24 weeks' treatment with ribavirin should be given.
Table 4A. Drug-drug interactions between HCV DAAs and HIV antiretrovirals.

<table>
<thead>
<tr>
<th></th>
<th>SIM</th>
<th>DCV</th>
<th>SOF</th>
<th>SOF/LDV</th>
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<td>Didanosine</td>
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<td>Emtricitabine</td>
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<td>Lamivudine</td>
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<td>Stavudine</td>
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<td>Tenofovir</td>
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<td>Zidovudine</td>
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<td><strong>NNRTIs</strong></td>
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<td>Etravirine</td>
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<td>Nevirapine</td>
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<td>Rilpivirine</td>
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<td><strong>Protease inhibitors</strong></td>
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<td>Atazanavir; atazanavir/ritonavir</td>
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<td>Darunavir/ritonavir; darunavir/cobicistat</td>
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<td>Fosamprenavir</td>
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Table 4B. Drug-drug interactions between HCV DAAs and illicit recreational drugs.

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<tr>
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<th>SOF/LDV</th>
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<tr>
<td>Amphetamine</td>
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<td>Cannabis</td>
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<tr>
<td>Cocaine</td>
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<tr>
<td>Time</td>
<td>DAA alone</td>
<td>DAA + ribavirin</td>
<td>DAA + pegylated interferon + ribavirin</td>
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<tr>
<td></td>
<td>FBC, renal, liver function</td>
<td>Adherence, side-effects</td>
<td>HCV RNA</td>
<td>FBC, renal, liver functions</td>
<td>Adherence, side-effects</td>
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<td>Baseline</td>
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<td>Week 24 after end of treatment</td>
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ALT: alanine aminotransferase; DAA: direct-acting antiviral; FBC: full blood count
DAAs and the question of price

5g of diamonds
25 1-carat ($1900 each)
Cost = $48,000

5g of daclatasvir
12 weeks of treatment, 60mg/day
Cost = $63,000 (US price)

Slide Courtesy of Andrew Hill
DAAs can be affordable

Sofosbuvir Retail Price for 12-weeks treatment in March 2016

Source: significant reductions in costs of generic production of sofosbuvir and daclatasvir for treatment of hepatitis C, Hill et al, EASL 2016
Cost of API = $4,770/kg

API per 12 weeks = $163

Formulated drug = $228

Packaged drug = $229

Final generic Price = $344

API needed per person = 34g (400mg x 84 days)

Formulation = 40%

Packaging = $0.35/month

Profit margin = 50%

For end 2015, Prices falling rapidly

Slide Courtesy of Andrew Hill
DAAs are cheap to produce

<table>
<thead>
<tr>
<th>DAAs</th>
<th>Calculated price for 12-week treatment (1)</th>
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</thead>
<tbody>
<tr>
<td>Sofosbuvir (SOF)</td>
<td>$95</td>
</tr>
<tr>
<td>Daclatasvir (DCV)</td>
<td>$17</td>
</tr>
<tr>
<td>Ledipasvir (LED)</td>
<td>$136</td>
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<tr>
<td>Sofosbuvir/ daclatasvir</td>
<td>$112</td>
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<tr>
<td>sofosbuvir/ ledipasvir</td>
<td>$231</td>
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Source: Dr Andrew Hill, Presentation in Bangkok mid-March 2016
## Price of DAAs generic versions

<table>
<thead>
<tr>
<th>DAAs</th>
<th>Lowest Indian generic price for 12-week treatment (2)</th>
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<tbody>
<tr>
<td>Sofosbuvir (SOF)</td>
<td>$900</td>
</tr>
<tr>
<td>Daclatasvir (DCV)</td>
<td>$276</td>
</tr>
<tr>
<td>Sofosbuvir/ledipasvir</td>
<td>~ $1,152</td>
</tr>
</tbody>
</table>

SOF/LED ~ 306$/bottle

SOF/LED ~ 380$/bottle

Source: TreatAsia
DAAs allow for increased treatment access including for hard-to-reach populations through

– More **decentralized** models of care
– **Integration** of treatment in harm reduction, drug dependency programs and HIV program
– Shorter treatment with less side effects
– Better adherence
...but challenges remain

- DAAs are not yet registered in Vietnam and not covered by Health Insurance (HI)
- By now DAAs remains expensive in Vietnam (~ 2,700 USD for 12 weeks)

Need for registration of DAAs + price reduction through generic competition + inclusion of DAAs in HI
but challenges remain

HCV treatment will only be effective to reduce HCV prevalence if strong prevention services are implemented targeting most at risk population

Need for better coverage of comprehensive harm reduction services
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