Web Annex 1. Decision-making table, PICO question on when to treat

In: Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection

July 2018
Acknowledgement

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A. BACKGROUND

- WHO estimates that in 2015, 71 million persons (1% of the population) were living with HCV infection in the world. As the estimated number of new infections in 2015 (N=1.75 million) exceeded the estimated number of deaths from end-stage HCV infection (N=399 000) and cures (N=843 000), the global epidemic still expanded in magnitude in 2015. To achieve elimination by 2030 (65% reduction in mortality and 90% reduction in incidence), 90% of HCV-infected persons need to be identified and, of those identified, 80% need to be treated.
- In April 2016, WHO updated its Guidelines for the screening, care and treatment of persons with chronic hepatitis C virus infection. These guidelines recommended that direct-acting antiviral (DAA) regimens be used for the treatment of persons with HCV infection. While WHO considered that all HCV-infected persons could be considered for treatment in principle, it recommended prioritizing those with increased risk of death, risk of accelerated fibrosis, metabolic syndrome, extrahepatic manifestations and those for whom treatment could lead to reduction of incidence (e.g. persons who inject drugs, HIV-infected men who have sex with men, prisoners, sex workers, women with childbearing potential and health-care workers).
- In 2017, WHO gave consideration to recommending treating all persons identified with HCV infection, independently of the stage of the liver disease. This recommendation would lead to more individual health benefits, since more persons would become eligible for treatment. It could be an important step toward ensuring equitable and universal access to treatment. It could also lead to a secondary benefit in terms of prevention of HCV infections. However, it could also potentially lead to more side-effects among those receiving treatment and would require more resources to meet the needs of all patients living with HCV.
- The principle of “Treat all” is that among those already diagnosed with HCV (over the age of 12 years and/or above 35 kg in weight, with the exception of pregnant women), public health programmes and clinicians would no longer apply any of the prioritization criteria proposed in the 2016 Guidelines and consider treating everyone.
- To address this issue and lead to the formulation of a recommendation, the steering group formulated the following PICO question:

**PICO question 1. Should all persons with a diagnosis of chronic HCV infection be treated with direct-acting antiviral therapy?**

**POPULATION:** adults and adolescents over the age of 12 years and/or above 35 kg in weight with chronic hepatitis C infection (with the exception of pregnant women)

**INTERVENTION:** initiation of DAA therapy

**COMPARISON:** initiation of DAA therapy in patients with chronic hepatitis C infection with advanced disease

**OUTCOMES:** Individual health benefits: (HCV mortality and morbidity, extrahepatic manifestations), transmission (incidence, prevalence), serious adverse events, retention, adherence, cost–effectiveness
**SETTING:** primarily for LMICs  

**PERSPECTIVE:** public health approach
B. SUMMARY AND QUALITY OF EVIDENCE

B. 1. Morbidity and mortality from chronic liver diseases

A 2017 systematic review and meta-analysis indicated that both treatment of HCV infection and sustained virologic response (SVR) secondary to treatment of HCV infection led to a reduction in the incidence of hepatocellular carcinoma (HCC), a reduction in liver-related mortality and a reduction in all-cause mortality. Additional work is in progress to identify data stratified according to the level of fibrosis before treatment.

<table>
<thead>
<tr>
<th></th>
<th>HCV treatment OR</th>
<th>SVR OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC</td>
<td>0.392</td>
<td>0.203</td>
</tr>
<tr>
<td>Liver-related mortality</td>
<td>0.363</td>
<td>0.126</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.38</td>
<td>0.255</td>
</tr>
</tbody>
</table>

Other population-based studies (e.g. UK) point to the impact of DAAs on the incidence of HCC at the population level.

B. 2. Morbidity and mortality from extrahepatic manifestations

A systematic review and meta-analysis concluded that treatment and SVR secondary to antiviral treatment reduces mortality due to extrahepatic causes (OR: 0.44, 0.28–0.67*). For morbidity, the extrahepatic manifestations examined that were improved following SVR included the following:

<table>
<thead>
<tr>
<th>Manifestation (selected outcomes)</th>
<th>SVR OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryoglobulinaemia complete clinical response</td>
<td>20.76 (6.73–64.05)</td>
</tr>
<tr>
<td>Lymphoproliferative disease response</td>
<td>6.49 (2.02–20.85)</td>
</tr>
<tr>
<td>Cardiovascular major adverse disease events</td>
<td>0.37 (0.22–0.62)</td>
</tr>
<tr>
<td>Incidence of de novo diabetes</td>
<td>0.27 (0.18–0.40)</td>
</tr>
<tr>
<td>Depression</td>
<td>0.59 (0.11–3.07)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>0.86 (0.49–1.52)</td>
</tr>
<tr>
<td>Fatigue at follow up</td>
<td>0.52 (0.29–0.93)</td>
</tr>
</tbody>
</table>

B. 3. Impact on horizontal HCV transmission in the population

Existing national and subnational models were used to estimate the impact in terms of prevention of treating a fixed number of HCV infections in various regions. Estimates were produced either through treating infected persons at random or through treating specific populations (e.g. injection drug users, younger versus older cohorts, persons with cirrhosis).

- Random allocation of treatment leads to the prevention of about one infection over 20 years for each case treated if the outbreak is generalized. However, the effect of treatment as prevention is smaller if (1) injection drug use accounts for a substantial proportion of new cases, or if (2) outbreaks are on the decline.
- Targeting PWID when the prevalence of HCV infection exceeds about 50% among PWID leads to a negative number of cases prevented among PWID because the treated PWID return to the pool of susceptible persons and quickly become reinfected (in the absence of stringent and effective harm reduction). However, if substantial transmission also occurs in the general population then this negative impact will be compensated by infections prevented in the general population. To achieve prevention benefits among people who inject drugs (PWID) in these high-prevalence
scenarios, HCV treatment needs to be given continuously at a higher rate (e.g. at about 5% of infections treated per year in Australia).

- Conversely, if the HCV prevalence in PWID is less than 50%, then positive prevention benefits are achieved among PWID and the general population, irrespective of the amount of treatment.

- The analysis across 77 countries (84% of the global population) indicated that:
  - 0.34 infections were prevented per 1000 people treated through random allocation over 20 years, with the following key drivers of effect:
    - A 1% increase in the at-risk population growth rate (−1 to 3.5%) leads to an increase of 0.2 in the infections prevented per treatment.
    - A 10% increase in the fraction of infections attributable to injection drug use (0–100%) leads to a decrease of 0.06 in the infections prevented per treatment.
    - A 10% increase in the prevalence of HCV infection in PWID (0–100%) leads to a decrease of 0.05 in the infections prevented per treatment.
  - In HCV epidemics where prevalence and incidence are high among PWID, a continuous high level of treatment coverage is needed, and a higher intensity of harm reduction interventions reduces the level of treatment coverage necessary.

### C. HARMS/BENEFITS

#### Benefits of a “treat all” recommendation

- A systematic review with meta-analysis that used meta-regression (Thein et al. 2008) included 111 studies with chronic HCV infections (n=33,121) were included. The estimated prevalence of cirrhosis at 20 years after the initial infection was 16% (14–19%) for all studies, 18% (15–21%) for cross-sectional/retrospective studies, 7% (4–14%) for retrospective–prospective studies, 18% (16–21%) for studies conducted in clinical settings, and 7% (4–12%) for studies conducted in nonclinical settings.
- The prevalence of the three most common extrahepatic manifestations is depression (24.5%), diabetes mellitus (15%) and chronic renal disease (10.1%) among persons with HCV infection. The occurrence of extrahepatic manifestations is usually independent of liver fibrosis.

Extrahepatic manifestations in HCV infection: prevalence, attributable fraction (adapted from: systematic review, Younossi et al. Gastroenterology, 2016)

- More persons infected with HCV infection benefit from treatment through an impact on hepatic and extrahepatic manifestations.
- At the community level, a “treat all” policy would simplify patient management, which could improve access to treatment to the largest number.
- Higher treatment coverage could lead to more rapid progress towards the WHO 2030 elimination targets.
- A “treat all” recommendation would prevent the loss to follow up for patients who are diagnosed and their treatment deferred because they have only mild fibrosis.
- A “treat all” recommendation would reduce stigma and discrimination, including among migrant workers.

### Table: Are the desirable anticipated effects large?

| X Benefits clearly outweigh harms |
| Benefits and harms are balanced |
| Potential harms clearly outweigh potential benefits |

- No
- X Probably
- Uncertain
- Yes
- Varies
Harms of a “treat all” recommendation

- At the individual level, treatment of persons who do not have clinical manifestations or are at a low risk of liver sequelae could unnecessarily expose them to the side-effects of DAAs.
- Anti-HCV treatment may lead to reactivation of hepatitis B virus (HBV) infection among some persons with HBV infection (hepatitis B surface antigen [HBsAg] positive). These patients may need treatment for HBV.
- The risk of reactivation among persons who are anti-HBc positive but HBsAg negative is very low.
- At the community level, large-scale use of DAAs could lead to rare side-effects that were not detected during clinical trials or during treatment programmes that targeted a smaller number of patients.
- A 2017 systematic review suggests treatment of HCV with DAAs in people with cirrhosis reduces the risk of HCC by 70%.
- A “treat all” recommendation could lead to the false perception that making treatment available is sufficient for PWID and that harm reduction services are not necessary.

### D. ACCEPTABILITY, VALUES AND PREFERENCES

Four studies were identified that assessed patient preferences related to HCV treatment. From these studies, the most important patient-relevant outcome was overall efficacy (likelihood of cure) followed by the risk of adverse events.

**Survey of people living with HCV infection:**

- As per an online feasibility survey to which 100 people responded, nearly all people living with HCV infection favoured a “treat all” policy and advocated for universal access to treatment for all those with HCV infection. Even though there is widespread support for a “treat all” policy among people who live with HCV infection, there was a concern reported about acceptability with respect, for instance, to the treatment of patients without fibrosis or with only mild fibrosis, reported by 18% of respondents.

**Survey of health-care workers:**

- As per an online feasibility survey among 111 health-care providers, 45% of respondents already had a “treat all” policy at their place of work. Nearly all perceived it as feasible and desirable.
- Health-care workers highly value cure for patients.
- Health-care workers express a preference for simplified patient management algorithms.

**Perspective of programme managers:**

- Cure of patients lead to progress towards elimination.
- Removing the staging process can facilitate implementation and task-shifting.
- Decision-makers express a preference for strategies that will represent cost-effective use of the resources available.
- Decision-makers need to accept that by treating all patients, they are buying health outcomes that will occur further away in the future.

<table>
<thead>
<tr>
<th>Is the option acceptable to key stakeholders?</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ No</td>
</tr>
<tr>
<td>□ Probably</td>
</tr>
<tr>
<td>□ Uncertain</td>
</tr>
<tr>
<td>X Yes</td>
</tr>
<tr>
<td>□ Varies</td>
</tr>
</tbody>
</table>
### E. EQUITY, ETHICS AND HUMAN RIGHT IMPLICATIONS

**Will the recommendation raise questions around equity?**

- Progress towards a “treat all” concept would reduce practical obstacles towards treatment by simplifying patient management (e.g. staging) that can be resource- and/or time-intensive. This would lead to a broader offer of treatment that would reduce inequities if treatment is made accessible to all. This implies the organization of treatment access in the context of universal health coverage.
- Exclusion of specific groups from the “treat all” policy (e.g. PWID) would raise equity issues.

**Are there ethical implications to this recommendation?**

- Taking into account the benefit of treatment as prevention to justify treating all those infected in the community would lead to ethical issues if the harm-to-benefit ratio was not favourable for those persons with fewer clinical manifestation or those with a lower risk of progression.
- “It may not be reasonable and ethical to develop therapeutic guidelines that restrict an individual’s access to HCV treatment when cure rates are over 95%.” (Hellard et al. Editorial. J Hepatol. 2017;66:270–2).

### F. RESOURCE USE AND FINANCIAL IMPLICATIONS

A systematic review examined the cost–effectiveness of HCV treatment with DAAs in a variety of different settings.

#### F. 1. Cost–effectiveness of DAAs

- In general, DAAs, despite their high costs, are cost effective for the large majority of patient subgroups (defined in terms of those who have received prior treatment, fibrosis stage and HCV genotype with which they are infected) in many countries.
- The vast majority of published cost–effectiveness analyses do not include HCV transmission or the risk of reinfection. This is a limitation when considering a “treat all” approach. The net effect of these forces on the cost–effectiveness of treatment or delayed treatment is unclear, and likely depends on both individual and community factors, particularly on the force of infection in the population.
  - Omitting the impact on transmission likely underestimates the benefits and cost reductions associated with the effect of treatment as prevention.
  - Omitting the risk of reinfection (e.g. PWID, HIV-infected MSM) likely overestimates the benefits and cost savings associated with treatment.

#### F. 2. Cost–effectiveness of universal versus prioritized treatment

- *General population.* When applying stated country-specific willingness-to-pay thresholds, several studies from high-income countries (HICs) and Egypt reported that expanding treatment in the general population is cost effective, though it may add substantial short-term costs to pay for treatment. The cost–effectiveness of treatment expansion for individuals above 65 years of age with mild fibrosis is highly sensitive to treatment price and, in some settings, where relatively high prices remain, may not be cost effective.
- *PWID.* The cost–effectiveness of HCV treatment in PWID is influenced by...
the potential for preventing new infections and by the risk of reinfection. Studies from the Australia, Canada, the Netherlands and the UK reported that it is generally cost effective to treat HCV-infected PWID. Furthermore, some studies find that: (1) intensified case-finding in this group is cost effective along with treatment scale up; (2) treatment for PWID regardless of fibrosis stage is cost effective compared to delaying treatment until after progression to later-stage fibrosis; and (3) treatment can be cost effective even in a declining epidemic.

- An important caveat to these observations is high-incidence/high-prevalence settings. When the HCV prevalence exceeds 50%, the cost–effectiveness of preventing onward transmission via treatment is diminished by the high probability of reinfection. The effect of treatment as prevention is difficult to realize without extremely high rates of diagnosis and treatment or significant concurrent HCV-transmission prevention efforts through highly effective and cost-effective harm reduction programmes.

- *Incarcerated individuals.* Studies from the US and the UK report that it is generally cost effective to treat HCV-infected incarcerated individuals. Testing upon entry to prison can be cost effective if there is linkage to a treatment that can be completed in prison or after through continuity of care. Similar to the findings in PWID communities, concurrent investments in HCV prevention programmes complement investments in HCV treatment and make HCV treatment more cost effective by reducing the probability of reinfection.

F.3. Cost–effectiveness of treat all in highly stratified populations

- Cost–effectiveness analyses of highly stratified subpopulations suggest that there may be some subpopulations for whom treatment is not cost effective (typically older individuals with less advanced fibrosis).
- Less stratified analyses will calculate a cost–effectiveness ratio averaged over subpopulations for whom treatment is cost effective and those for whom it is not, and hence will mask these differences.

F.4. Limited evidence from low- and middle-income countries

- The price of medicines is the key driver of the cost–effectiveness of a “treat all” recommendation
- The review identified cost–effectiveness analyses related to access to hepatitis C treatment for Chile, China, Egypt, India, Iran, South Africa and Thailand.

F.5. Budget impact

- While the fall in prices will make DAAs more and more cost effective independent of the stage of the liver disease, the budget impact of a “treat all” recommendation may be high in a number of countries, given the size of the population to treat.
- Budget impact depends on testing activities that also increase the size of the population to treat.

G. FEASIBILITY AND CONSTRAINTS TO IMPLEMENTATION

| Is the option feasible to |  |
**Survey of persons living with HCV infection:**
- According to an online feasibility survey to which 100 people responded, nearly all people living with HCV infection favoured a “treat all” policy. However, the following concerns were reported:
  - 22% reported concerns about drug interactions
  - 22% reported concerns about side-effects
  - 12% reported concerns about coercion into starting HCV treatment
  - A few reported concerns about costs.

**Survey of health-care workers:**
- As per an online feasibility survey that reached 111 respondents, the main challenges reported to implementing a “treat all” policy included capacity limitations to cope with demand (31%), difficulties in identifying patients (19%), lack of skills of health-care workers (15%), lack of appropriate medicine formulations (12%), out-of-pocket costs of medicines where applicable (10%) and lack of appropriate tests to diagnose infection (7%).

**Survey of programme managers:**
- An online feasibility survey reached seven programme managers from Cameroon, Egypt, Georgia, Iceland, Morocco, Pakistan and Zimbabwe. Four out of the seven countries already had a “treat all” policy in place. All seven countries perceived a “treat all” policy as feasible and desirable to implement, and all seven countries had national strategies and action plans in place. The main challenges reported to implementing a “treat all” policy included a lack of a testing strategy/appropriate tests (four countries), lack of skills and experience of health-care workers (four countries), issues surrounding the identification of eligible patients for treatment (two countries) and lack of funding and resources (three countries).

**Relevance to different settings/populations**
*Are any major barriers expected for the implementation of this recommendation?*  
*Will this recommendation be most relevant for particular settings (e.g. endemcity)?*

- In many countries, especially LMICs, the low proportion of diagnosis is a barrier to connecting HCV-infected persons with treatment. Therefore, sufficient expansion of testing is key to achieving the potential of treatment, in terms of delivery to as many people as possible within as short a time as possible between infection, diagnosis and treatment.
- In a “treat all” scenario, when subgroups at high risk for transmitting HCV are included in treatment expansion, the required magnitude and rapidity of expansion depends on the prevalence of HCV in these high-risk subgroups. The higher the prevalence, the larger and more rapid the expansion of testing, diagnosis and treatment must be, especially in settings where current service levels are particularly low.
- The high costs of DAAs and affordability of treating everyone eligible for treatment in a particular setting is a barrier.

**H. DRAFT RECOMMENDATION:**
WHO recommends offering treatment to all individuals diagnosed with HCV infection who are 12 years of age or older.†

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† With the exception of pregnant women
### I. RATIONALE FOR RECOMMENDATION:
- Moderate evidence of large beneficial effects of antiviral treatment on hepatic clinical outcomes (all-cause mortality, liver-related mortality, hepatocellular carcinoma) with small/minimal harms; epidemiological evidence of decreased incidence of hepatocellular carcinoma following introduction of DAAs.
- Low/very low evidence on effects of antiviral treatment on extrahepatic outcomes.
- Potential beneficial effects of antiviral treatment on horizontal transmission and population-level incidence.
- Treat-all approach is favoured by persons living with HCV infection and other stakeholders, and would increase equity if implemented appropriately.
- Treat-all approach is cost–efficient under most assumptions, though budget impact would be large.

### J. STRRENGTH OF RECOMMENDATION
- **Strong**

### K. IMPLEMENTATION CONSIDERATIONS
- If the budget impact of a “treat all” recommendation remains too high, national programmes may consider allocating resources preferentially to patients at higher risk of hepatic and extrahepatic morbidity and mortality.
- Treatment of PWID needs to be integrated with harm reduction services to prevent reinfections, particularly in settings where the prevalence of HCV infection exceeds 50% in PWID.
- Persons with HBV infection (HBsAg positive) may need to be treated for HBV before they are treated for HCV.
- The implementation and budget impact of a recommendation to treat all patients diagnosed with HCV infection needs to be considered in the context of testing activities that identify more patients to be treated.

### L. RESEARCH GAPS
- Long-term clinical studies of patients with early-stage HCV treated with antiviral therapies, particularly DAAs.
- Post-marketing surveillance for adverse events and drug resistance with expansion of antiviral treatment.
- Cost–effectiveness and budget-impact studies in low-income countries.
- Studies on effects of treatment vs no treatment on extrahepatic outcomes and quality of life.
- Studies on effects of antiviral treatment with DAAs on incidence of HCV infection.
## Summary of judgements

<table>
<thead>
<tr>
<th></th>
<th>Judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Problem</strong></td>
<td>No</td>
</tr>
<tr>
<td><strong>Certainty of evidence</strong></td>
<td>Very low</td>
</tr>
<tr>
<td><strong>Balance of benefits and harms</strong></td>
<td>Potential harms clearly outweigh potential benefits</td>
</tr>
<tr>
<td><strong>Large desirable effects</strong></td>
<td>No</td>
</tr>
<tr>
<td><strong>Efficient use of resources</strong></td>
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</tr>
<tr>
<td><strong>Are required resources small?</strong></td>
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</tr>
<tr>
<td><strong>Equity</strong></td>
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</tr>
<tr>
<td><strong>Acceptability</strong></td>
<td>No</td>
</tr>
<tr>
<td><strong>Feasibility</strong></td>
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</tbody>
</table>