

# Have a Heart, Save My Liver!

## Which Countries Restrict Treatment?

2021

### Global State of HCV Treatment Restrictions<sup>1</sup>

Since 2013, all oral, direct-acting antivirals (DAAs) have been approved for the treatment of the hepatitis C virus (HCV). The initial launch of sofosbuvir (Sofaldi) carried a list price of US\$84,000 for a 12-week course in high-income countries, amounting to US\$1,000 per pill. Eight years later, due to upfront bulk purchases, regional buying schemes, government price negotiations, rebate programs, and intellectual property flexibilities—including voluntary and compulsory licenses and patent oppositions that spurred generic competition among pharmaceutical manufacturers—DAA prices have been significantly reduced to less than US\$100 per 12-week treatment course. Yet, two-thirds of people with HCV in low- and middle-income countries (LMICs) are still not able to access DAAs due to price.<sup>2</sup> Efforts to lower prices through a combination of these strategies have yielded some gains in achieving affordable access to DAAs in 12 high burden low- and middle-income countries.<sup>3</sup>

To date, 62 countries<sup>4</sup> have at least one version of sofosbuvir/daclatasvir, sofosbuvir/ledipasvir, or sofosbuvir/velpatasvir registered.<sup>5</sup> However, our recent analysis<sup>6</sup> shows inequitable access to all-genotype (or pangenotypic) treating DAAs among our scope of 119 countries. Our scope includes 82 high-burden and PEPFAR<sup>7</sup>-funded LMICs, plus 27 European Union countries, and 10 Eastern European and Central Asian countries:<sup>8</sup>

Unfortunately, the launch price cast a shadow on accelerating registration and expanding access, with many governments rationing treatment based on what national health budgets could cover. In the case of HCV, the extortionate pricing and subsequent treatment rationing is a social construct that has resulted in limiting treatment primarily to people with advanced liver disease, people who were already known to have HCV and awaiting treatment, those with insurance which covers the costs, or those who could afford to pay for the cure out-of-pocket.

HCV treatment rationing aims to stagger the number of treatments prescribed and is generally based on national budgets and supply, not medical decisions.

Registration of a medicine in a country does not always translate into access. Key populations and marginalized communities disproportionately affected by HCV face stigma, discrimination, and exclusion, which prevent them from accessing a range of health and non-health related services, including the supports needed to initiate treatment on DAAs. Treatment rationing occurs through different forms of restrictions: based on liver disease stage, abstinence from alcohol and/or substances, and on who is authorized to prescribe DAAs. High-income and LMICs alike have maintained HCV treatment restrictions in different ways due to the misassumption that the launch price remains the same everywhere; lack of access to generic DAAs and generic prices; health budget constraints; and

| Pangenotypic Regimen     | Number of Countries Registered |
|--------------------------|--------------------------------|
| sofosbuvir/daclatasvir   | 23                             |
| sofosbuvir/velpatasvir   | 24                             |
| glecaprevir/pibrentasvir | 1                              |
| Epclusa                  | 35                             |
| Mavyret                  | 8                              |

stigma and discrimination towards highly affected populations, including people who use and inject drugs and incarcerated people.

### What Do the WHO Treatment Guidelines Say?

In 2015, DAAs were included in the World Health Organization (WHO) essential medicines list because they offer safe, effective, tolerable, all-oral treatments for chronic HCV. DAAs have a cure rate of over 95% with a treatment course of 12 weeks<sup>9</sup> for people without advanced liver disease or liver failure. Longer treatment of 24 weeks may be required for people depending on liver scarring, stage of liver disease, if they were not cured on previous treatments, have difficult-to-treat genotypes<sup>10</sup> or subtypes, or other health conditions. DAAs are a radical change from previous HCV care and treatment, which involved torturous, lengthy, and highly ineffective injectables of pegylated interferon and ribavirin.

There are newer treatments, such as ravidasvir, which are under review by the WHO.

According to the 2018 WHO Guidelines (to be updated in 2022):<sup>11</sup>

- Every person diagnosed with an HCV infection who is 12 years of age or older (except during pregnancy) should start DAA treatment, irrespective of disease stage.
- Pangenotypic DAAs should be used for people with chronic HCV infection aged 18 years and above.
- For non-pregnant adolescents aged 12–17 years or who weigh at least 35 kilograms with chronic HCV infection, DAA options can be selected based on genotypes:
  - sofosbuvir/ledipasvir for 12 weeks = genotypes 1, 4, 5 and 6
  - sofosbuvir/ribavirin for 12 weeks = genotype 2
  - sofosbuvir/ribavirin for 24 weeks = genotype 3
- Pegylated interferon should no longer be used as HCV treatment.
- People with advanced liver disease, including those who have been cured (achieved sustained virologic response [SVR]), should be regularly screened for liver cancer.
- Screening for alcohol use and counselling to reduce moderate or high levels of alcohol consumption is recommended before starting treatment.

**Table 1. Summary of DAA Regimens**

| DAA Regimen                                       | WHO Essential Medicines List                                    | Pangenotypic |
|---|---|--------------|
| daclatasvir                                       | Y   |              |
| dasabuvir   | Y   |              |
| elbasvir + grazoprevir                            | Y   |              |
| glecaprevir + pibrentasvir                        | Y   | Y            |
| ombitasvir + paritaprevir + ritonavir             | Y   |              |
| simeprevir  | Y   |              |
| sofosbuvir  | Y   |              |
| sofosbuvir + ledipasvir                           | Y   |              |
| sofosbuvir+velpatasvir                            | Y   | Y            |
| sofosbuvir + daclatasvir (fixed dose combination) | *The 2 separate drugs are on the list and can be taken together | Y            |
| sofosbuvir + velpatasvir + voxilaprevir           |   | Y            |
| ravidasvir + sofosbuvir                           |   |              |

Several pediatric DAA regimens have been approved by the U.S. Food and Drug Administration and European Medicine Agency, but are under review by the WHO:

- sofosbuvir/velpatasvir (Epclusa) = all genotypes for 12 or 24 weeks; 6 years and older, or weighing 17 kilograms
- glecaprevir/pibrentasvir (Mavyret) = all genotypes for 8 weeks; 12 years and older, or weighing 30-45 kilograms
- sofosbuvir/ledipasvir (Harvoni) = genotypes 1, 4, 5, 6 for 12 weeks, or weighing 35 kilograms

Pediatric doses of sofosbuvir/daclatasvir and sofosbuvir + ribavirin are under investigation.

## Forms of Treatment Restrictions

Despite the global guidelines, there are prevalent treatment restrictions implemented at national levels. We focus on three of the most common ones.

### 1. Fibrosis Restrictions = Exclude patients who are seen as not sick enough for treatment

Fibrosis restrictions refer to requirements that people with HCV present advanced liver diseases before being eligible to start treatment. In practice, this results in people living with HCV to go untreated for months or years, which can further damage the liver and contribute to transmitting the virus to other people. Fibrosis restrictions may only allow patients with moderate/severe liver disease or liver failure (fibrosis scores F2 or higher) to start treatment. Treating all diagnosed patients with chronic HCV prevents health complications that further lead to costly medical interventions and averts unnecessary suffering. In addition, despite the clear cost-benefit for both health systems and patients.

1 in 5 countries, (or 23 countries of the 119 countries in our scope) implement fibrosis restrictions.

### 2. Abstinence-based Restrictions = Exclude disproportionately affected key populations

Abstinence-based restrictions require people to abstain from drugs or alcohol for a certain period of time (often six months to a year) before being eligible for HCV treatment. Abstinence-based restrictions further stigmatize already marginalized key populations and communities who are systematically neglected and face structural violence, including people who inject and use drugs, people who are incarcerated, sex workers, immigrants, migrants, and refugees, and people in the LGBTQI+ community. The exclusion of people who inject and use drugs and incarcerated people is based on a stigmatizing attitude among some health providers that these groups will become reinfected through drug use and “waste” a treatment course.

Research has shown high HCV treatment adherence among people who inject drugs. We also achieve the same cure rates as people who do not use drugs.<sup>12</sup>

Housing, support systems, and other social determinants of health are key factors in cure rates and other health outcomes among people who inject and use drugs.

Yet roughly 1 in 10 countries, (or 13 of the 119 countries in our scope) implement abstinence-based restrictions.

### 3. Specialist or Prescriber Restrictions = Limit who prescribes treatment

Prescriber restrictions require that only liver disease and infectious diseases specialists can prescribe HCV treatment. These restrictions are based on previous and more complicated standards of care that involved regular injections of pegylated interferon and additional laboratory tests.

With oral, pangenotypic DAAs, HCV care can be simplified and decentralized, and tasks can be shifted to general practitioners, nurses, pharmacists, etc.

This task-sharing approach can integrate HCV treatment to existing health programs such as HIV, tuberculosis, sexual health, and harm reduction programs, and circumvent the lack of specialized medical care which is often encountered in LMICs. An access barrier related to prescriber/specialist status is the complex process of reimbursing treatment costs instituted by some countries' health systems. DAA reimbursement may be limited based on prescriptions only by specialists or dependent on the type of insurance coverage. A retired patient may have different hurdles to reimburse DAAs than a working patient.<sup>13</sup> For patients in carceral or congregate settings, such as nursing homes, countries may have different reimbursement rules and budgets, which may exclude patients.<sup>14</sup>

Based on our research, roughly one-third of countries, (or 40 of the 119 countries in our scope), implement specialist or prescriber restrictions.

## Other Restrictions

We encountered other forms of treatment restrictions but did not reflect them in the maps.

- **Age restrictions before starting treatment:** Restrictions that prevent treating diagnosed patients under 18 years of age. There are approved treatments for children 6 years and older, but these treatments may not be available in many countries. WHO recommendations are currently for patients 12 years and older (at least 35 kilograms); guidelines are under review for children 12 years and younger. In countries that require patients to reach 18 years before starting treatment, this can lead to unnecessary liver damage and suffering.
- **Exclusion of patients who became reinfected:** There should be no treatment restrictions towards patients who become reinfected because this is not done in practice for other types of patients, such as cancer patients when their cancer returns. Harm reduction materials, such as sterile injecting equipment, and other prevention supports should be offered to patients to help mitigate reinfections.
- **Exclusion of patients who do not achieve cure rates on the first treatment course:** DAAs have a high cure rate, but they may

not cure all patients who receive treatment. Not achieving SVR on the first treatment course can happen due to a difficult-to-treat genotype or subtype, later stage fibrosis, or decompensated cirrhosis. The re-treatment of patients who already received a course of DAAs should address the root cause of not achieving SVR and provide the patient with the best DAA alternative, counselling, or other patient support for their specific situation.

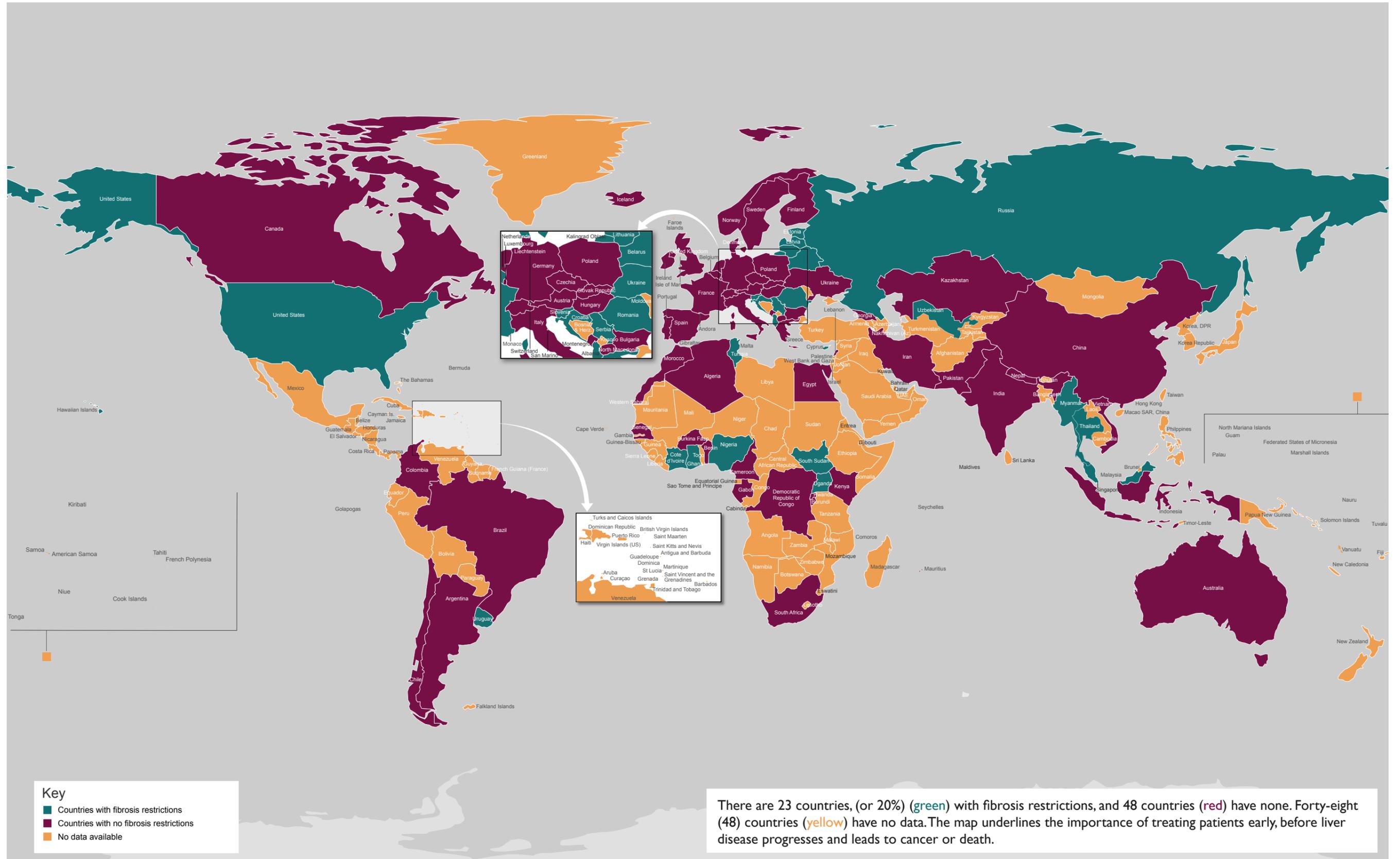
- **Exclusion of incarcerated populations or people based on immigration status:** DAAs and comprehensive HCV care may not be covered by prison or immigrant health policies and budgets. These groups are often excluded from treatment guidelines. This exclusion contributes to their stigmatization, misses an opportunity to cure disproportionately affected communities, and could fuel onward transmission. Treating and testing HCV within carceral and detention facilities is cost-efficient for the overall general population and can avoid long-term costs.<sup>15</sup>
- **Exclusion of other stigmatized populations:** Sex workers, people in the LGBTQI+ community, and other stigmatized populations may encounter deliberate exclusion from treatment guidelines, or indirect exclusion due to misinterpretation of policies. Public health policies should clearly state the inclusion of these key populations when developing and implementing HCV treatment guidelines.

## Methodology

Crowd-sourced data was collected from 119 countries, provided by 60 in-country contributors and partner organizations and captured in the free, public mapCrowd platform. Data was collected from 19 November, 2020 to 30 September, 2021.

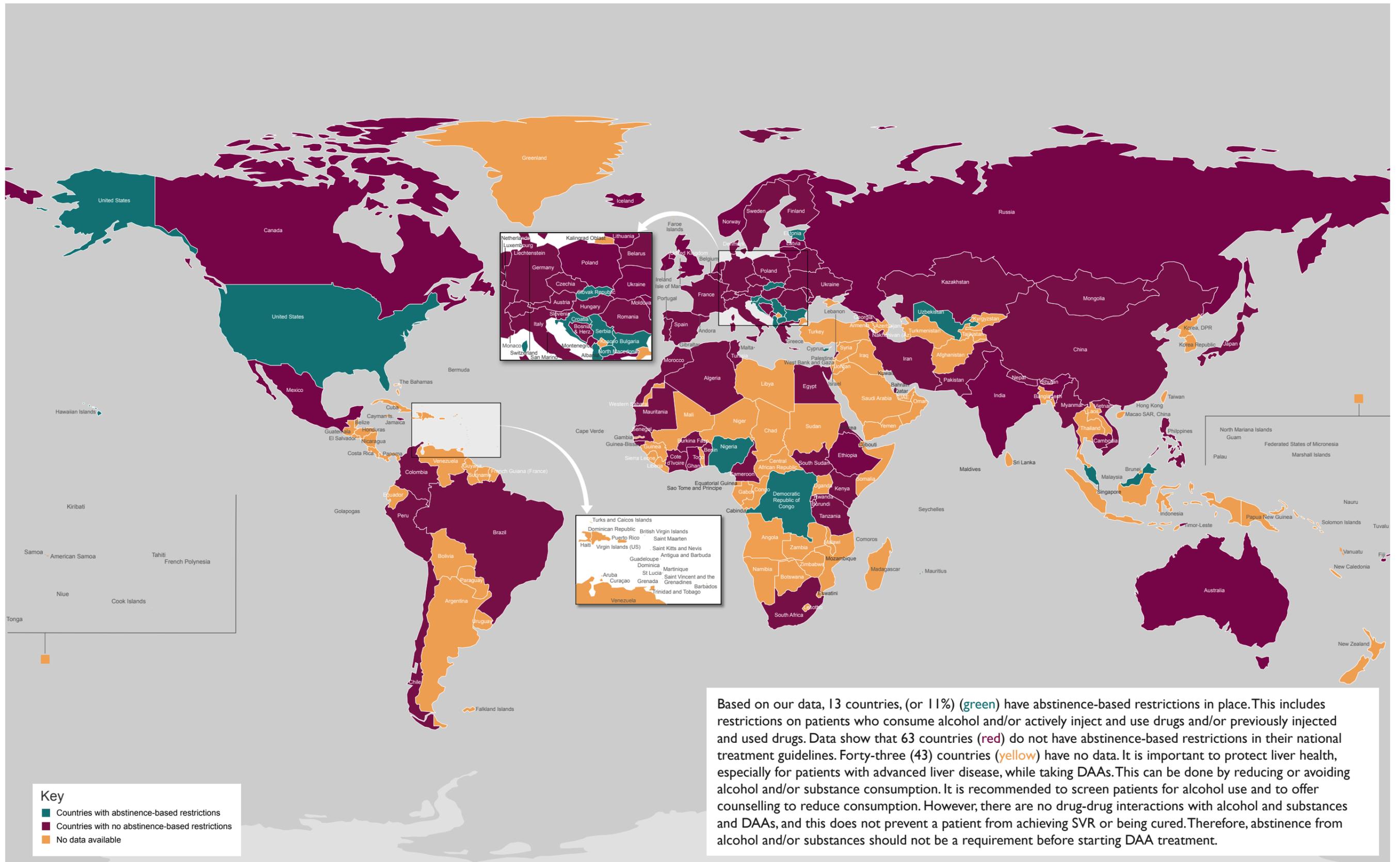
We recognize the limitations of the crowd-sourced data which rely on where we have in-country contributors and networks. We focused on three (3) treatment restrictions: restrictions based on liver stage (fibrosis); those requiring abstinence from drugs or alcohol; and specialist or prescriber status. We mention other restrictions that may exist and prevent patients from being treated in those countries.

Map 1 Global Fibrosis Restrictions

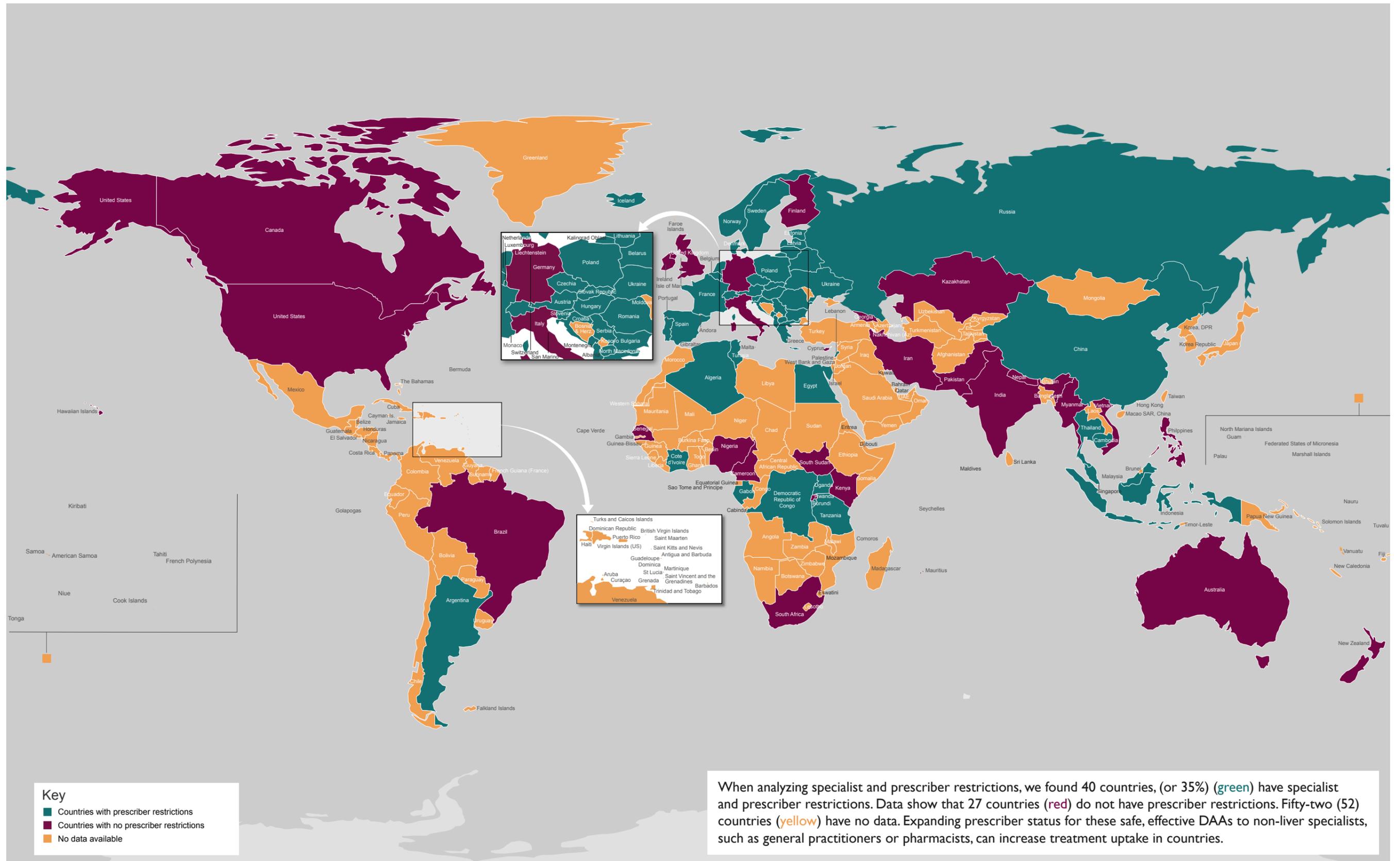


There are 23 countries, (or 20%) (green) with fibrosis restrictions, and 48 countries (red) have none. Forty-eight (48) countries (yellow) have no data. The map underlines the importance of treating patients early, before liver disease progresses and leads to cancer or death.

Map 2 Global Abstinence-based Restrictions



### Map 3 Global Specialist or Prescriber Restrictions



## Strengthening Health Systems to Facilitate the Lifting of Treatment Restrictions

We understand that treatment restrictions are not the only barriers to equitable access to the hepatitis C cure but lifting treatment restrictions may be a relatively low administrative hurdle that involves updating national treatment guidelines and holding medical professional and peer worker trainings regarding their interpretation and implementation. This includes anti-stigma, anti-discrimination, and cultural competency trainings to ensure community-friendly healthcare. Widely disseminating, interpreting, and effectively communicating information and the latest science to the public can increase demand and expand treatment to anyone diagnosed with HCV.

Integrating HCV test and treat programs into harm reduction, sexual health, prison, and immigrant health systems is part of health systems strengthening and can further generate demand for DAAs.

We demand governments:

- Expand HCV treatment eligibility to include, people who use and inject drugs, people who are incarcerated, immigrants, migrants, and refugee populations, people who have been reinfected, and all other key populations;
- Allow all people diagnosed with HCV to access treatment independent of liver fibrosis stage;
- Remove drug and alcohol abstinence requirements for people who use and inject drugs, including requirements to enroll in medication for opioid use disorder/medication-assisted treatment (MOUD/MAT), rehab, and similar programs to qualify for HCV treatment;
- Implement proactive testing, especially among key populations, to diagnose and treat HCV;
- Remove limits to the reimbursement of DAA costs so that people who were prescribed by non-specialists can have their treatment covered;
- Integrate HCV services in harm reduction programs;
- Integrate HCV services in healthcare for incarcerated populations, and for refugee, migrant, and other detained populations;
- Explore different paths for the procurement and expanded uptake of DAAs, including but not limited to regional bulk purchases, use of intellectual property flexibilities, generic registration, and supplier competition.

## References

- <sup>1</sup> Fact sheet developed with immense gratitude to the invaluable contributions and information-sharing from our partners at, Africa Hepatitis Initiative, Alliance for Public Health Ukraine, Coalition PLUS, CORRELATION Network, Drugs for Neglected Diseases initiative, European AIDS Treatment Group, FIPRA, GAT Portugal, Médecins du Monde, Médecins Sans Frontières Access Campaign, and World Hepatitis Alliance.
- <sup>2</sup> World Health Organization. Accelerating Access to Hepatitis C Diagnostics and Treatment: Overcoming Barriers in Low-and Middle-Income Countries. Geneva:WHO; 2021 January 21. <https://www.who.int/publications/i/item/9789240019003%20>.
- <sup>3</sup> Ibid.
- <sup>4</sup> Ibid; mapCrowd database.
- <sup>5</sup> Sofosbuvir-based DAAs are “available” in 105 countries under the Gilead voluntary licenses, and glecaprevir/pibrentasvir is “available” in 96 countries under the AbbVie voluntary license. mapCrowd/ hepCoalition. Have a Heart, Save My Liver! Where is the Cure Registered? Fact sheet. 2021 October [https://www.hepcoalition.org/IMG/pdf/have\\_a\\_heart\\_save\\_my\\_liver\\_where\\_is\\_the\\_cure\\_registered\\_.pdf](https://www.hepcoalition.org/IMG/pdf/have_a_heart_save_my_liver_where_is_the_cure_registered_.pdf).
- <sup>6</sup> Ibid.
- <sup>7</sup> President’s Emergency Plan for AIDS Relief.
- <sup>8</sup> The 119 countries in our scope are: Albania, Algeria, Angola, Argentina, Armenia, Australia, Austria, Azerbaijan, Barbados, Belarus, Belgium, Bolivia, Bosnia and Herzegovina, Botswana, Brazil, Bulgaria, Burkina Faso, Burundi, Cambodia, Cameroon, Canada, Chile, China, Colombia, Congo Democratic Republic of the, Costa Rica, Cote d’Ivoire, Croatia, Cyprus, Czechia, Denmark, Dominican Republic, Ecuador, Egypt, El Salvador, Estonia, Eswatini, Ethiopia, Finland, France, Georgia, Germany, Ghana, Greece, Guatemala, Guyana, Haiti, Honduras, Hungary, India(50), Indonesia, Ireland, Italy, Jamaica, Kazakhstan, Kenya, Kosovo, Kyrgyz Republic, Lao PDR, Latvia, Lesotho, Liberia, Lithuania, Luxemburg, Malawi, Mali, Malta, Mauritius, Mexico, Mongolia, Montenegro,, Morocco, Mozambique, Myanmar, Namibia, Nepal, Netherlands, Nicaragua, Nigeria, North Macedonia, Pakistan, Panama, Papua New Guinea, Paraguay, Peru, Philippines, Poland, Portugal, Republic of Moldova, Romania, Russia, Rwanda, Senegal, Serbia, Sierra Leone, The Slovak Republic, Slovenia, South Africa, South Sudan, Spain, Suriname, Sweden, Tajikistan, Tanzania, Thailand, Togo, Trinidad and Tobago, Tunisia, Turkey, Turkmenistan, Uganda, Ukraine, Uruguay, United States of America, Uzbekistan, Venezuela, Vietnam, Zambia, and Zimbabwe.
- <sup>9</sup> One exception, Glecaprevir/pibrentasvir (Mavyret) has a cure rate at 8 weeks for people without advanced liver disease or liver failure.
- <sup>10</sup> Genetic variations in the hepatitis C virus.
- <sup>11</sup> Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. Geneva:World Health Organization; 2018. <https://apps.who.int/iris/bitstream/handle/10665/273174/9789241550345-eng.pdf>.
- <sup>12</sup> Kattakuzhy S, Mathur P, Gross C, et al. High SVR in PWID with HCV despite imperfect medication adherence: data from the anchor study. *Hepatology*. 2018;68(S1). doi: 10.1002/hep.30256; Grebely J et al. Sofosbuvir and velpatasvir for hepatitis C virus infection in people with recent injection drug use (SIMPLIFY): an open-label, single-arm, phase 4, multicentre trial. *Lancet Gastroenterol Hepatol*. 3.3; 2018:153-61. doi: [10.1016/S2468-1253\(17\)30404-1](https://doi.org/10.1016/S2468-1253(17)30404-1); Graf C et al. Efficacy of direct-acting antivirals for chronic hepatitis C virus infection in people who inject drugs or receive opioid substitution therapy: a systematic review and meta-analysis. *Clin Inf Dis*. 70.11; 2020: 2355-65. <https://doi.org/10.1093/cid/ciz696>.
- <sup>13</sup> Example from mapCrowd database in Denmark.
- <sup>14</sup> Example from mapCrowd database in the Netherlands.
- <sup>15</sup> Kwon JA, Chambers GM, Luciani F, Zhang L, Kinathil S, Kim D, Thein HH, Botha W, Thompson S, Lloyd A, Yap L, Gray RT, Butler T. Hepatitis C treatment strategies in prisons: A cost-effectiveness analysis. *PLoS One*. 2021 Feb 11;16(2):e0245896. doi: 10.1371/journal.pone.0245896.