

HCV

TOOLKIT



make
medicines
affordable
END UNFAIR MONOPOLIES

 **ITPC**
INTERNATIONAL TREATMENT
PREPAREDNESS COALITION

ABOUT ITPC

The International Treatment Preparedness Coalition (ITPC) is a worldwide network of community activists unified by our vision of a longer, healthier, more productive life for all people living with HIV (PLHIV). ITPC's mission is to enable communities in need to access optimal HIV treatment. As a grassroots movement based primarily in the Global South, ITPC is the community's voice on HIV treatment and is driven by and committed to the human rights of those most impacted by the HIV epidemic.

ITPC is a global coalition that includes eight regional networks in Africa, Asia, Latin America and the Caribbean, Eastern Europe, and the Middle East. Through its different campaigns, ITPC is committed to providing accurate and timely HIV treatment information that can improve the lives of PLHIV. Many of the tools developed under this program are also intended to be used for advocacy initiatives.

Additional information about ITPC is available at: www.itpcglobal.org

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ABBREVIATIONS

AIDS	acquired immunodeficiency virus
API	active pharmaceutical ingredient
ART	antiretroviral therapy
ARV	antiretroviral
CL	compulsory license
DAA (s)	direct-acting antiviral (s)
DCV	daclatasvir
EBR	elbasvir
ERP	Expert Review Panel
EML	essential medicines list
FDA	Food and Drug Authority
FDC	fixed-dose combination
G/P	glecaprevir/ pibrentasvir
GPO	Government Pharmaceutical Organization
GZR	grazoprevir
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	Human Immunodeficiency Virus
IP	Intellectual property
LDV	ledipasvir
LMIC	low- and middle-income countries
MIC	middle-income countries
MSM	men who have sex with men
MSF	Médecins Sans Frontières
NDRA	National Drug Regulatory Authority
NSP	needle syringe program
OAT	opioid agonist therapy
OMB	ombitasvir
PEG-IFN	pegylated interferon
PTV/r	paritaprevir/ ritonavir
PWID	people who inject drugs
PWUD	people who use drugs
r/	ritonavir
RBV	ribavirin
RDT	rapid diagnostic test
SMV	simeprevir
SOF	sofosbuvir
SRA	stringent regulatory authority
SVR	sustained virologic response
TPP	target product profile
TRIPS	Trade-Related Aspects of Intellectual Property Rights
US	United States
US FDA	United States Food and Drug Administration
VEL	velpatasvir
VOX	voxilaprevir
VL	voluntary license
WHO	World Health Organization
WHO-PQ	World Health Organization Pre-Qualification

INTRODUCTION TO AND PURPOSE OF THE RESOURCE

Although the world has the tools – and a plan¹ – to eliminate hepatitis C virus (HCV), it remains a threat to global public health. Untreated HCV can lead to cirrhosis and liver cancer. Each year, nearly 400,000 people die from these complications of HCV, although it has become easy to cure with 12 weeks of once-daily oral medicines, called direct-acting antivirals (DAAs). High prices have prevented access to life-saving HCV treatment across low-, middle-, and high-income countries; as of 2017, globally, only five million people of the 71 million estimated had been treated with DAAs.

Actions can be taken to dramatically increase access to affordable generic DAAs. Such actions have saved governments millions of dollars and facilitated improved HCV treatment access. In Egypt, where 7% of adults were living with HCV in 2015, the patents on key DAAs were rejected, which made it possible for the government to treat over two million people with generic DAAs and facilitated Egypt's plan to eliminate HCV by 2020. Malaysia's government issued a compulsory license (CL) for sofosbuvir (SOF), a DAA that is the backbone of HCV treatment. Malaysia was subsequently included in the SOF voluntary license (VL). Subsequently, the price for a 12-week course of SOF dropped from RM 45,000 (US \$11,000) for the originator version to RM 1,225 (US \$300) for generic SOF. In 2016, local activists from several middle-income countries, including Argentina, Brazil, China, India, Russia and Ukraine, filed oppositions on sofosbuvir-related patent applications. Their actions have triggered significant price reductions in most of these countries: in Ukraine, the price for SOF dropped from US 750 to approximately US 60 per 12-week treatment course, and a similar price reduction was achieved in Kazakhstan; in Argentina, the price for 12 weeks of SOF dropped from US 5,541.28 to US 358.62.

This community resource was developed for activists who plan to use or are using Trade-Related Aspects of Intellectual Property Rights (TRIPS) flexibilities to increase access to DAA treatment for HCV in their countries. While knowing the strength of patents on DAAs is essential, it is also important to have additional criteria for prioritizing target DAAs, such as knowing national epidemiology and DAA clinical characteristics. This toolkit provides additional information for identifying priority DAAs, including an overview of HCV epidemiology, transmission, prevention, natural history and treatment; insight into the development of DAAs from 'bench to bedside'; a target product profile for DAAs, HCV treatment recommendations from the World Health Organization (WHO), and information about drug registration.

¹ WHO. Global Health Sector Strategy on Viral Hepatitis 2016- 2021. Available from: <https://apps.who.int/iris/bitstream/handle/10665/246177/WHO-HIV-2016.06-eng.pdf;jsessionid=57EB0EE3A0EFAA062440621EDADAA617?sequence=1>

HCV and COVID-19

COVID-19 has had a severe impact on global health systems, including those that deliver HCV prevention, testing, care and treatment. An estimate of the impact of a 1-year delay in HCV services predicted the most severe effects in low- and middle-income countries (LMICs), where there would be an 85% increase in HCV incidence, a 72% increase in missed treatment, and a 59% increase in liver-related death by 2030.

The combination of sofosbuvir (SOF) and daclatasvir (DCV), which is WHO-recommended for HCV treatment, is also being studied in COVID-19, based on promising but preliminary results in the laboratory and in people. Results from randomized, controlled trials of SOF/DCV in people with COVID-19 from several countries are expected in Q3 of 2020. If SOF/DCV proves to be an effective treatment for COVID-19, access to HCV testing and treatment could improve. HCV testing would be necessary to identify people who require a full 12-week treatment course of SOF/DCV for HCV - in addition to treating their COVID-19.

Continued, and increased pressure from activists – including work to ensure that affordable generic DAAs are available everywhere and especially in high-burden countries and to people that are members of high-prevalence groups – is necessary, to ensure that people with HCV receive prevention, testing, care and treatment.

Sources:

Blach S, Kondili L, Aghemo A, et al. Impact of COVID-19 on Global Hepatitis C Elimination Efforts. *J Hepatology* [Online] August 6, 2020 [Cited 2020 August 26]
Available from: <https://doi.org/10.1016/j.jhep.2020.07.042>

Carolina Q. Sacramento C Q, Fintelman-Rodrigues N, Temerozo JR, et al. The *in vitro* antiviral activity of the anti-hepatitis C virus (HCV) drugs daclatasvir and sofosbuvir against SARS-CoV-2. Pre-print [Online] June 16 2020 [Cited 2020 August 26]
Available from: <https://www.biorxiv.org/content/10.1101/2020.06.15.153411v1.full.pdf>

Sadeghi A, Asgari AA, Norouzi A, et al. Sofosbuvir and daclatasvir as a potential candidate for moderate or severe COVID-19 treatment, results from a randomised controlled trial (Abstract: 11125) *AIDS 2020* [Online] July 10 2020 [Cited 2020 August 27]
Available from:
<https://aids2020.org/wp-content/uploads/2020/07/COVID-19-press-conference-abstracts.pdf>

HEPATITIS C VIRUS (HCV)

EPIDEMIOLOGY

Hepatitis C is a blood borne virus that enters the bloodstream and infects liver cells. Worldwide, as of 2015, an estimated 71 million people were living with chronic HCV. Middle-income countries (MIC) bear the largest burden; they are home to an estimated 49 million people living with HCV.

Each year, over 1.7 million people are newly infected with HCV. HCV is common among members of certain key populations, especially people who inject drugs (PWID); over 50% of them are living with HCV. Up to 85% of people who acquired HIV from injecting drugs with shared needles, syringes and other equipment are living with HCV co-infection. Prisoners and men who have sex with men (MSM), especially those who are living with HIV, have higher HCV prevalence than the general population.

TRANSMISSION AND PREVENTION

Although HCV is easy to prevent, it continues to spread, especially among PWID, who make up 23% of all new infections. HCV is a tiny and tough virus; it is more concentrated in a small amount of blood than HIV and can live in syringes for days to weeks. Using sterile needles, syringes and other equipment each time a person injects drugs lowers their risk for HCV by over 50%; adding opioid agonist therapy (OAT) reduces it by 74%. Yet coverage of, and access to harm reduction are inadequate in nearly every country, making it impossible for people who use drugs (PUD) to protect themselves and each other. Although WHO currently recommends provision of 200 needle/syringes per person injecting drugs per year (increasing to 300 by 2030) and OAT access for 40 of every 100 PWID, globally only 1% of all people who inject drugs have access to these interventions.

HCV can be transmitted in other ways, such as:

- Smoking or snorting drugs with shared, unsterilized equipment;
- Sexually, especially at parties and in the context of drug use (called Chemsex), among men who have sex with men, especially if they are living with HIV.
- During invasive medical or dental procedures with unsterilized equipment, including dialysis;
- Through blood transfusions, although many countries have improved the safety of their blood supply;
- Needlestick accidents during healthcare provision;
- Tattooing (or piercing) with shared, unsterilized needles, ink and inkwells;
- From being born to a mother living with HCV, which can happen during pregnancy, labor, or at birth²;
- Sharing razors, manicuring tools, toothbrushes, hair clippers and other personal items that may have blood on them.

² The risk of HCV vertical transmission is approximately 5%. Currently, there are no interventions to prevent it, aside from treating women of childbearing potential before pregnancy (although research is ongoing). Untreated, HIV coinfection doubles the risk for vertically transmitted HCV. Antiretroviral therapy (ART) protects the mother's health, while reducing the risk for vertically transmitted HCV and HIV.

NATURAL HISTORY

HCV becomes chronic in 55-85% of people who acquire it; some people have a robust immune response that clears the virus without treatment. Untreated HCV can cause serious liver scarring, called cirrhosis. Men are at higher risk for cirrhosis than women. HIV co-infection, heavy alcohol intake, hepatitis B virus (HBV) co-infection and both aging and longer duration of infection increase the risk for cirrhosis among people living with HCV. People with HCV-related cirrhosis are at risk for liver failure and liver cancer. In 2015, 399,000 people died from these HCV complications. HCV also causes a range of systemic health problems that lower quality of life, including type 2 diabetes, kidney and heart disease, and depression.

There are 6 common strains of HCV, called genotypes; these were numbered in the order that they were discovered. Each genotype has subtypes, which are given a letter (such as genotype 1a or genotype 1b). Some sub-genotypes of HCV may be more difficult to cure, such as 4r, which is common in sub-Saharan Africa.³ Globally, genotype 1 is the most common, followed by genotypes 3, 2, 4, 6 and 5. Genotypes 1, 2 and 3 are found all over the world; genotype 4 is found mainly in Central Africa and the Middle East; genotype 5 is primarily found in Southern Africa and genotype 6 is most common in South East Asia.

Although the genetic diversity of HCV has made it difficult to develop a preventive vaccine, some DAAs are effective against all HCV genotypes (called pan-genotypic). Nonetheless, genotype 3 is considered more likely to lead to cirrhosis and liver cancer than other HCV genotypes; it is also more difficult to cure in people who also have cirrhosis.

People can become infected with more than one HCV genotype; this is known as a mixed infection. This is most likely to happen among people who acquired HCV from injection drug use with shared, unsterilized needles, syringes and other equipment, and recipients of blood products or multiple blood transfusions. Also, people can become re-infected with a different HCV genotype after they have been cured or cleared HCV on their own, without treatment.

³ For more information, see: https://www.treatmentactiongroup.org/wp-content/uploads/2020/02/TAG_hcv_subtypes_sub_saharan_africa_brief.pdf

DIAGNOSTICS

WHO recommends HCV testing for adults and adolescents from the most affected populations⁴ and for adults, adolescents and children who have signs and/or symptoms of HCV. In addition, in settings where overall HCV prevalence is $\geq 2\%$ or $\geq 5\%$, testing is recommended for the general population. In settings with low prevalence among the general population, birth cohort-based HCV testing is sometimes recommended for older persons who were at high risk for HCV in the past.⁵

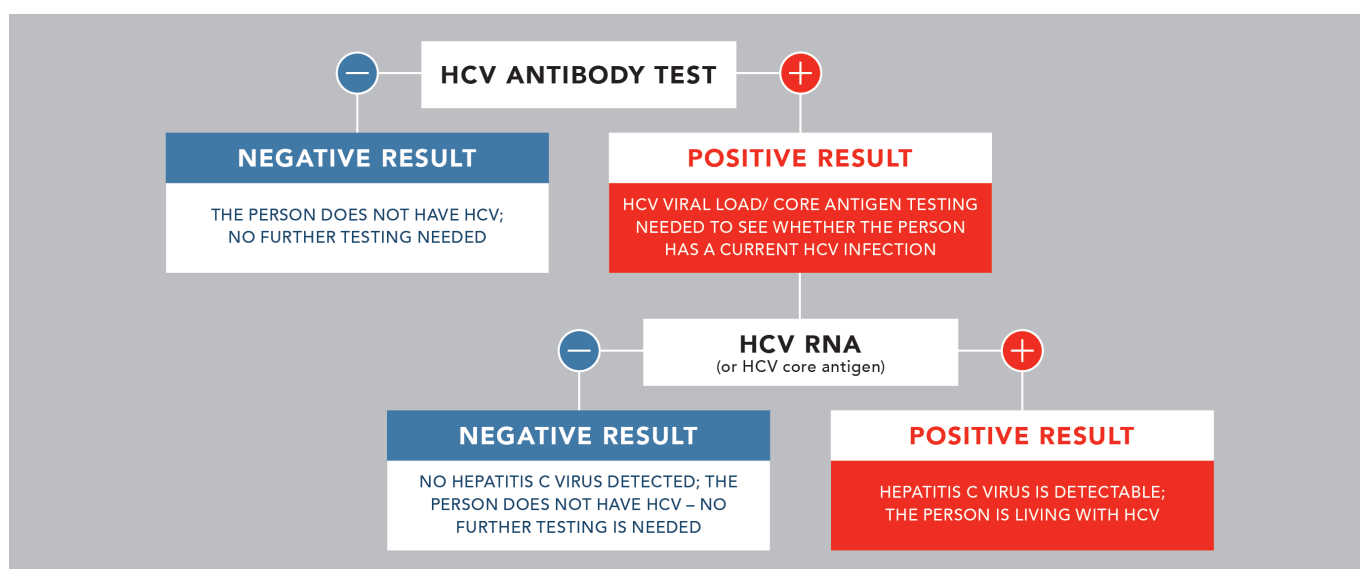
Currently, HCV testing is a two-step process. The first step is testing for HCV antibodies,⁶ either with a rapid diagnostic test (RDT) or laboratory-based testing. Most people will make antibodies within 3 months of becoming infected with HCV, although people who have weakened immune systems may not be able to produce them; they should receive a viral load test if they have been at risk for HCV. Between 15% - 45% of people who have been infected with HCV clear it without treatment, but they remain antibody-positive. People with a positive antibody test result need an additional test (called HCV RNA or viral load) to see if they have a current HCV infection.

Viral load testing is more expensive than HCV antibody testing. Many of the same viral load machines can be used for HCV and HIV. High prices and other barriers⁷ limit access to viral load testing, despite WHO recommendations for its use in HCV and HIV.⁸

HCV genotyping is used to determine the type and duration of DAA treatment, although it can be eliminated by using pan-genotypic regimens.

A range of barriers, including high prices due to IP-related monopolies, limit access to HCV diagnostics. Each testing platform requires a significant investment for the machine as well as staff training and it is not possible to switch to better and/or cheaper tests and reagents from another producer, unless a new machine is purchased. The lack of generic reagents and general compatibility standards across testing platforms helps to keep a monopoly on most HCV diagnostic products.

Figure 1. HCV Diagnostics



⁴ WHO considers most affected populations as: PWID, people in prisons and other closed settings, MSM, sex workers, people living with HIV, healthcare workers and partners or family members of people living with HCV.

⁵ For example, past exposure to unscreened or inadequately screened blood products or poor injection safety.

⁶ Antibodies are Y-shaped proteins made when the immune system responds to an infection.

⁷ As an example, diagnostic companies may offer exclusive licensing, when their machine can only be used for a single infection, and different cartridges, reagents, or other testing components must be used to run tests for other infections

⁸ For HIV, WHO recommends routine viral load monitoring during HIV antiretroviral therapy (ART); for HCV, viral load testing is used to diagnose HCV and to determine treatment outcome.

TREATMENT

The goal of HCV treatment is a cure. HCV is considered cured when there is no virus in a person's blood 12 weeks after they have finished treatment (this is also known as sustained virologic response, or SVR). Being cured has many benefits. A cure reduces the risk of liver-related illness and death - and the risk of death from other causes - at any stage of liver disease. Being cured stops liver disease progression and may lower the risk for, or improve other HCV-related health problems, including pre-diabetes, type 2 diabetes, cardiovascular disease and depression, and prevents onward transmission.

Before 2013, when oral, interferon-free DAA regimens became available, HCV treatment was toxic, expensive and relatively ineffective – the standard of care was 24 to 48 weeks of pegylated interferon (PEG-IFN) injections and twice-daily oral ribavirin (RBV). The first DAAs, boceprevir and telaprevir, had to be used with PEG-IFN and RBV in complex, poorly tolerated response-guided regimens for HCV genotype 1. The evolution of HCV treatment continued: within a few years, once-daily, pan-genotypic DAAs that cured 95% of people without RBV in 8 to 12 weeks became available.

Figure 2. DAA approval timeline

2011	First reported proof-of-concept for interferon-free oral HCV treatment.
	United States Food and Drug Administration (US FDA) approval of the first DAAs, boceprevir and telaprevir (used with PEG-IFN and RBV).
2012	Numerous DAA trials, with and without PEG-IFN and/or RBV.
2013	US FDA approval of sofosbuvir (the first interferon-free regimen for genotypes 2 and 3).
	US FDA approval of simeprevir (with PEG-IFN and RBV).
2014	US FDA approval of 3 oral, interferon-free regimens.
2015	Boceprevir and telaprevir are discontinued in the US. ⁹
	US FDA approval of daclatasvir for use with sofosbuvir for genotype 3.
2016	US FDA approval of the pan-genotypic, fixed-dose combination (FDC) sofosbuvir/ velpatasvir.
	US FDA approval of the grazoprevir/elbasvir FDC.
2017	US FDA approval of the pan-genotypic FDC glecaprevir/ pibrentasvir.
	US FDA approval of the pan-genotypic FDC sofosbuvir/ velpatasvir/ voxilaprevir.
2018	Daclatasvir 90 mg tablets are discontinued in the US.
2019	Paritaprevir/ ritonavir/ ombitasvir and dasabuvir are discontinued in the United States (US). ¹⁰
	Daclatasvir 30 and 60 mg tablets are discontinued in the US. ¹¹
	USFDA approval of glecaprevir/pibrentasvir for adolescents ages 12-17.
2020	USFDA approval of sofosbuvir/velpatasvir in children ages 6 years and above, who weigh at least 17 kg.

⁹ In high-income countries, all-oral DAA regimens rapidly replaced interferon-based treatment

¹⁰ These DAAs were discontinued for clinical reasons; the market for genotype-specific regimens, especially those requiring subtyping and use of RBV, dwindled once better options became available

¹¹ DCV was not discontinued for clinical reasons; it was a victim of the patent monopoly on sofosbuvir. Pan-genotypic FDCs from AbbVie and Gilead were significantly less expensive than DCV/SOF (launched at US\$ 84,000 and US\$ 63,000 per 12-week treatment course, respectively).

There are 4 classes, or types of DAAs: protease inhibitors, nucleotide polymerase inhibitors, non-nucleoside polymerase inhibitors¹² and NS5A inhibitors. Each DAA class targets a specific step of the HCV lifecycle. HCV is usually treated with two DAAs from different classes.

Table 1.
DAAs by Class, Characteristic and Mechanism of Action (WHO-recommended DAAs in red)

DAA class	Mechanism of Action	Characteristics
NS5A inhibitors daclatasvir (DCV) velpatasvir (VEL) pibrentasvir (P) elbasvir (EBR) ledipasvir (LDV)* ombitasvir (OMB)	NS5A inhibitors work in multiple ways that are not fully understood, including by blocking HCV production inside of infected cells, and preventing the assembly and release of new hepatitis C viruses, called virions	Pan-genotypic (daclatasvir, velpatasvir, pibrentasvir only) Once-daily Potent Low barrier to resistance Long-lasting resistance Some drug interactions
NS5B nucleotide polymerase inhibitor sofosbuvir (SOF)	NS5B inhibitors interfere with HCV's genetic material so it cannot reproduce	Pan-genotypic Once-daily High barrier to resistance Limited drug interactions
NS5B non-nucleoside polymerase inhibitor dasabuvir	NS5B inhibitors interfere with HCV's genetic material so it cannot reproduce	Genotype 1 only Once-daily No information on resistance barrier or drug interactions
NS3/4A protease inhibitor glecaprevir (G) grazoprevir (GZR) paritaprevir/ritonavir (PTV/r) simeprevir (SMV) voxilaprevir (VOX)	NS3/4A protease inhibitors work by blocking viral processing that is necessary for HCV replication.	Pan –genotypic (glecaprevir and voxilaprevir only) Once-daily High resistance barrier Likely to interact with other medicines

DAAs have dramatically improved both the effectiveness and safety of HCV treatment. Some are safe for all stages of liver disease, including compensated or decompensated cirrhosis,¹³ and for people with kidney disease. HCV treatment is safe and highly effective for people living with HIV/HCV coinfection, although drug interactions between WHO-recommended DAAs and antiretrovirals (ARVs) may need consideration.

The antiretroviral dolutegravir (DTG) is now WHO-recommended as part of first-line HIV treatment. DTG can be used with DAAs, but it is not available everywhere. Patents on dolutegravir do not expire in many MICs until 2029 or later, while many upper-middle income countries are excluded from the voluntary license between ViiV healthcare and the Medicines Patent Pool (e.g. Brazil, China, Russia, Kazakhstan). It is important to address patent monopolies to improve access to DTG.

¹² Dasabuvir is the only approved non-nucleoside polymerase inhibitor; it is not WHO-recommended.

¹³ Compensated cirrhosis usually has no symptoms: at this stage, the liver can still function, despite scarring. Decompensated cirrhosis is a more advanced stage of cirrhosis when life-threatening complications develop. Although people with decompensated cirrhosis can be treated and cured, some may need a liver transplant.

Table 2.
Drug Interactions Between WHO-Recommended DAAs and ARVs

SOF/DCV	SOF/VEL	G/P
Adjust DCV dose if used with efavirenz or atazanavir/ritonavir(r). Co-administration with NVP is not recommended, due to lack of data.	Cannot be used with efavirenz; monitor for renal toxicity if used with tenofovir and an HIV protease inhibitor Co-administration with NVP is not recommended, due to lack of data.	Cannot be used with atazanavir/r, darunavir/r, lopinavir/r and efavirenz Co-administration with NVP is not recommended, due to lack of data.

The revolutionary improvements in HCV treatment led WHO to issue the *Global Health Sector Strategy for Viral Hepatitis* in 2016, with time-bound targets for eliminating HCV as a threat to global public health by 2030. WHO also updated its HCV guidelines in 2018, including an HCV ‘treat-all’ recommendation¹⁴ and a call for countries to simplify procurement and treatment delivery with pan-genotypic DAA regimens especially in settings where genotyping, fibroscan and other commonly used tests are not available.

DAAs have radically simplified HCV treatment delivery, including pre-treatment assessment and monitoring during treatment. Pan-genotypic regimens have eliminated the need for costly pre-treatment genotyping. DAAs have streamlined on-treatment monitoring, since they are safe, and so effective that it is no longer necessary to perform viral load testing during treatment.

Figure 3.
WHO-Recommended Monitoring Before, During and After DAA Treatment

Before starting treatment	Full blood count, renal and liver function, pregnancy testing ¹⁵ , assess for cirrhosis with non-invasive, simple blood tests; check for comorbidities and potential drug interactions <i>If DAA regimens are not pan-genotypic, or for treating adolescents ages 12-17, perform HCV genotyping to determine treatment type and duration</i> ¹⁶
During treatment (week 4)	<i>If regimen includes RBV</i> ¹⁷ , perform full blood count, renal and liver function testing
After treatment (12 weeks later)	Assess treatment outcome with HCV RNA

¹⁴ Except for pregnant women and children under age 12, pending data on DAAs.

¹⁵ HCV treatment is not recommended during pregnancy, due to lack of data on DAA safety and efficacy.

¹⁶ In 2020, SOF/VEL was approved for use in children ages 6 and over.

¹⁷ Sofosbuvir/RBV was WHO-recommended for adolescents with HCV genotypes 2 and 3 in 2018; since then, other options have become available: as of 2019, G/P was approved for use in adolescents and SOF/VEL was approved in 2020 for children ages 6 and over weighing at least 17 kg.

ACCESS ISSUES

RATIONAL SELECTION

Sometimes national guidelines, national essential medicines lists, reimbursement lists, nomenclatures or terms of reference for procurement and other regulatory lists may include either outdated medicines no longer recommended by WHO or medicines with significant budget impact that have no advantage over the current standard of care. It is important for activists to be in close dialogue with relevant state authorities to ensure that only medicines with scientifically proven clinical effectiveness, safety and cost-effectiveness are on these regulatory lists.

Activists may prioritize and pursue access to HCV drugs that are not WHO-recommended, or drugs that have not yet been approved by a regulatory agency. A target product profile (TPP) can be helpful in making these decisions, as well as consultations with a range of different stakeholders.

TARGET PRODUCT PROFILE (TPP) FOR DAAs

A TPP can be used as criteria for evaluating medicines.
Typical elements of a TPP for HCV treatment include:

- **Safe**, including for people with the most advanced liver damage and people who have other conditions, such as HIV and/or kidney disease;
- **Effective**, with cure rates of 85% for people with cirrhosis and 95% for people who do not have cirrhosis
- **Tolerable**; few side effects, which are mild
- **Potent**, with a high barrier to resistance; forgiving when doses are occasionally missed
- **Simple**: minimal assessment/monitoring requirements, once-daily, FDC, no food requirements, temperature stable, two-year shelf life, fixed duration
- **Universal**: pan-genotypic, can be used in all populations, with hormonal contraceptives, antiretrovirals, OAT and other commonly-used medicines, safe during pregnancy and breast-feeding.
- **Affordable**, for governments and those who must pay out-of-pocket.

Table 2.
WHO-Recommended DAA Regimens

REGIMEN	POPULATION	DURATION	COMMENTS
SOF/DCV	Adults without cirrhosis	12 weeks	<ul style="list-style-type: none"> • Cannot be used by people with severe renal impairment • Dose adjustment needed with some ARVs • May be less effective for people with genotype 3 and cirrhosis • SOF: used in persons age 12 and over • DCV: used in persons age 18 and over (although it has been studied in children over age 7) • Can be taken with or without food • Once daily FDC • Generic versions available
	Adults with compensated cirrhosis	12 or 24 weeks	
SOF/VEL	Adults with or without compensated cirrhosis	12 weeks	<ul style="list-style-type: none"> • Cannot be used by people with severe renal impairment • Cannot be used with efavirenz; no data on use with NVP • Used in persons age 6 and over • Can be taken with or without food • Once-daily FDC • Generic versions available
G/P	Adults without compensated cirrhosis	8 weeks	<ul style="list-style-type: none"> • Cannot be used by people with Child-Pugh Class B or Class C cirrhosis • Cannot be used with atazanavir, darunavir, efavirenz, lopinavir, ritonavir and medicines containing ethinyl estradiol ; no data on use with NVP • Approved for use in adolescents ages 12-17 • Taken with food • 3 tablets once a day • VL announced in 2018; agreement with Mylan announced in February 2020; no generics available as of August 2020
	Adults with compensated cirrhosis	12 weeks	

WHICH DAAs REALLY MATTER?

WHO recommendations are the international standard, and a useful framework for identifying priority DAAs. However, there are other considerations, including access, price, registration status and perspectives from people living with hepatitis C, doctors and other healthcare providers and policymakers.

Considerations for Selecting Target DAAs

- Your national epidemic – what are the most common HCV genotypes?
 - For example, genotype 3 is harder to cure in people who have cirrhosis; they may need 24 weeks of SOF/DCV vs. 12 weeks of SOF/VEL or G/P
- Which coinfections and comorbidities are common in your country?
 - Is HBV treatment available, affordable and accessible?
 - Is dolutegravir available, affordable and accessible?
- Infrastructure in your country
 - Laboratory capacity
 - Access to viral load testing
 - Access to HCV genotyping
- Access to fibrosis assessment with fibroscan or other non-invasive methods
- DAA selection
 - IP interventions (if needed)
 - Ensure that generic versions enter the market
 - Foster competition between generics producers to lower prices and increase access.

AFFORDABLE PRICES

TRANSPARENCY ABOUT PRICING

Transparency about drug pricing is fundamental to obtaining better prices. In many countries, there are existing laws on access to public information, which activists could use to get the current price for procuring state-funded HCV medicines. Reference prices can be found in several databases, which include Global Fund PQR database¹⁸ and published reports including the WHO *Progress Report on Access to Hepatitis C Treatment*¹⁹ and the Clinton Health Access Initiative's *Hepatitis C Market Report*.

TARGET PRICES

It is important to identify the optimal target price for the given medicine to prepare for future pricing negotiations with manufacturers. Production costs, including milligram count, are an important consideration, and pricing also depends on sales volume. Some DAAs may be more complicated and expensive to produce than others.

Experts have been tracking the cost of the active pharmaceutical ingredient (API) for key DAAs, using it to estimate profitable mass-production costs for generic DAAs. Since 2014, demand has risen and API prices have lowered – API for SOF by 90%, and API for DCV by 88%.

¹⁸ https://public.tableau.com/profile/the.global.fund#!/vizhome/PQRTransactionSummary_V1/TransactionSummary

¹⁹ <https://www.who.int/hepatitis/publications/hep-c-access-report-2018/en/>

Table 3.
Estimated Production Costs, Including Profit, per 12-Week Course of Generic WHO-Recommended DAAs vs. Prices in Low and Middle- Income Countries (as of 2020)²⁰

	SOF/ DCV	SOF/ VEL	G/P
Estimated price, based on cost/profit	\$31	\$85	No data
Prices in Low-, Middle, and High-Income Countries			
Argentina	\$30,012	\$37,499	\$24,085
Azerbaijan	\$348		
Brazil	\$25,732	\$13,632	\$12,724
India	\$41	\$410	US (8-week treatment course) \$26,400
Kazakhstan	\$84		
Moldova	\$772		
Russia	\$8,976		
Thailand	\$7,021		
Ukraine	\$78		

People living with HCV may prefer shorter regimens or those that do not require them to switch any of the other medications they rely on, such as HIV antiretrovirals. Doctors may prefer to use familiar products, or the newest medicines (especially if they work closely with representatives from pharmaceutical corporations). Also, some regimens may be used less frequently, since they might only be necessary for certain groups, such as people with severe kidney disease, people on certain medications, or for re-treatment. These may remain costly, since it will not be possible to achieve economies of scale. Policy makers may only be concerned with DAA prices, without knowing that it may be more cost-effective to use simpler, pan-genotypic regimens.

²⁰ Barber M, Gotham D, Hill A. Cost-based Estimated Prices for Key HCV, HIV and MDR-TB Medicines. AIDS 2020. (Abstract 5788) July 2020.

BRANDED OR GENERIC MEDICINES – WHAT IS THE DIFFERENCE?

Because of patent monopolies, originator pharmaceutical corporations are the only source for certain medicines for at least 20 years. When no patent barriers exist, generics companies can produce their own versions of these medicines.

To enter the market, generic versions of medicines must have the same quality, strength, efficacy and safety as branded medicines (see Quality, below) A generic medicine must have the same active ingredient as a branded medicine, and it must reach the same amount in the bloodstream as a branded medicine, from the time a person takes it until it passes out of their body (called bioequivalence). Generic versions of branded medicines must be given at the same dose, and by the same route (tablet, syrup, injection).

- In Egypt, more than a million people have been treated with locally produced generic DAAs through a government- funded program. A 12-week course of SOF and DCV costs \$79 (\$23/month for SOF and \$3.30/month for DCV, versus the originator launch prices of \$28,000/month for SOF and \$21,000/month for DCV).²¹ In Egypt, cure rates among 18,378 people were over 95% after 12 weeks of locally-produced generic SOF/DCV or SOF/DCV/RBV.
- A study of treatment outcomes among people who purchased generic DAAs through three Buyer's Clubs reported that over 95% of them were cured.
- Generic versions of SOF and DCV from demonstrated bioequivalence with originator versus generic SOF and DCV.²²

PATENTS

Most DAA medicines were developed recently and are broadly patented around the world. Due to efforts by local manufacturers in several countries (e.g. Egypt) and voluntary licensing by originator companies, many generic DAAs are available. But access to generic DAAs is very limited in UMICs (e.g. Brazil, Russia) that are seen as emerging markets, and HICs (US, EU countries) that were not included in the list of countries where the generic versions can be sold. Various strategies could be used to overcome granted patents or pending patent applications. In the case of pending patent application(s) where patent laws permit it, activists should contemplate pre-grant opposition(s), third party observation(s) or having dialogues with the patent office about the scientific arguments against granting patent(s). In cases where patents have been granted, activists may choose to undertake post-grant patent opposition or patent invalidation through the court or requesting that the government consider issuing a compulsory license for public non-commercial use.

²¹ WHO. Egypt: 35 million people receive hepatitis C test [Online] March 30 2019 [Cited 2019 July 10] Available from: <https://www.who.int/hepatitis/news-events/egypt-hepatitis-c-testing/en/>

²² Hill A Tahat L , Mohammed MK, et al. Bioequivalent pharmacokinetics for generic and originator hepatitis C direct-acting antivirals. Bioequivalent pharmacokinetics for generic and originator hepatitis C direct-acting antivirals. J Virus Erad [Online] 2018 [Cited 2019 July 9]; 4: 128–131. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5892672/>

THE CASE OF SOFOSBUVIR

During the spring of 2015, in collaboration with I-MAK and Fundación Grupo Efecto Positivo (Fundación GEP) of Argentina, Grupo de Trabalho sobre Propriedade Intelectual (GTPI) of Brazil, the International Treatment Preparedness Coalition of Russia (ITPC-ru) and the All-Ukrainian Network of People Living with HIV/AIDS of Ukraine filed patent oppositions against sofosbuvir-related patent applications. I-MAK filed in India with the Delhi Network of Positive People, helped Médecins du Monde file an opposition with the European Patent Office and filed a patent challenge in China.²³ Civil society organizations conducted campaigns against Gilead's patent monopoly on sofosbuvir (e.g. Morocco).²⁴ In September 2017, Malaysia issued a government use (compulsory) license on sofosbuvir, which led to significant price reductions, up to 97%.²⁵ These collective actions and Malaysia's compulsory license have contributed to significant price reductions on sofosbuvir in many countries (e.g. Argentina, Belarus, Malaysia, Morocco, Ukraine, Thailand).

Information About Overcoming IP Barriers to Increase Access to HCV Diagnostics and Treatment

1. International Centre for Trade and Sustainable Development, United Nations Conference on Trade and Development, World Health Organization. Guidelines for the examination of pharmaceutical patents: developing a public health perspective – A Working Paper [Online] 2006 [Accessed 2020 January 17]. Available from: <https://apps.who.int/medicinedocs/documents/s21419en/s21419en.pdf>
2. Medicines Patent Pool. MedsPal: the medicines patents and licenses database. [Accessed 2020 January 17]. Available from: <https://www.medspal.org/?page=1>
3. MSF Access Campaign. Patent Opposition Database [Cited 2020 August 23] Available from: <https://www.patentoppositions.org>
4. Unitaid. Technology and Market Landscape: Hepatitis C Medicines. [Online] August 2017 [Accessed 2020 June 19]. Available from: https://unitaid.org/assets/HCV-Medicines-Landscape_Aug-2017.pdf
5. Unitaid. Review of Glecaprevir Patent Landscape: A Scoping Report. March 2017 [Online] [Accessed 2020 June 19]. Available from: http://unitaid.org/assets/Glecaprevir_patent-landscape_March2017.pdf
6. Unitaid. Review of Velpatasvir Patent Landscape: A Scoping Report. March 2017 [Online] [Accessed 2020 June 19]. Available from: http://unitaid.org/assets/Velpatasvir_patent-landscape_update_March2017.pdf
7. Unitaid. Review of Voxilaprevir Patent Landscape: A Scoping Report. March 2017 [Online] [Accessed 2020 June 19]. Available from: https://unitaid.org/assets/UTD17004_04_Voxilaprevir_v04.pdf
8. Unitaid. Review of Pibrentasvir Patent Landscape: A Scoping Report. March 2017 [Online] [Accessed 2020 June 19]. Available from: https://unitaid.org/assets/Pibrentasvir_patent-landscape_March2017.pdf
9. United Nations Development Program. Good Practice Guide: Improving Access to Treatment by Utilizing Public Health Flexibilities in the WTO TRIPS Agreement [Online] 2010, [Accessed 2020 January 17]. Available from: <https://www.undp.org/content/dam/aplaws/publication/en/publications/poverty-reduction/poverty-website/good-practice-guide-improving-access-to-treatment-by-utilizing-public-health-flexibilities-in-the-wto-trips-agreement/Good%20Practice%20Guide-Improving%20access%20to%20treatment%20by%20utilizing%20public%20health%20flexibilities%20in%20the%20WTO%20TRIPS%20agreement.pdf>
10. UN Secretary-General's High-Level Panel on Access to Medicines: Promoting Innovation and Access to Health Technologies. Report. [Online] September 2016 [Accessed 2020 January 17]. Available from: <http://www.unsgaccessmeds.org/final-report>

²³ <http://infojustice.org/archives/34506>

²⁴ <https://www.ip-watch.org/2018/05/10/collective-efforts-civil-society-groups-bar-way-hepatitis-c-patents/>

²⁵ <https://www.ip-watch.org/2017/09/15/malaysia-grants-compulsory-licence-generic-sofosbuvir-despite-gilead-licence/>

COMPETITIVE TENDERING AND POOLED PROCUREMENT

Without competition, patent monopolies allow pharmaceutical corporations to charge whatever the market can bear for their products, which keeps them out of reach for millions of people who need them.

There is compelling evidence that generic competition lowers the price of medicines. For example, generic competition enabled significant price reductions for HIV ARVs, making global treatment scale-up possible. But having a generic product available on the market is not enough to foster competition – as an example, in Morocco, where for two years a pair of generics producers have formed a duopoly, by pricing their versions of SOF/DCV identically, at \$1350 per treatment course.

Competition is essential for HCV treatment scale up, since no global donors are providing support for governments to procure DAAs (with some exceptions for treating HCV in people who are living with HIV). Funding for DAAs usually comes from national budgets. Robust competition is needed, since the more companies that are producing generic drugs, the lower prices can go. Lower prices will enable governments to scale-up treatment without creating budgetary imbalances. Country programs often do regional-, national- and district-level 'competitive tendering' to procure medicines. To ensure that this process is truly competitive, and will lead to lower prices, it is important that it is fully transparent, different regimens are available, and that there are different suppliers for each generic product.

Further price reduction could be achieved by strategies to increase the volume of orders (bulk or pooled procurement). These strategies include: avoiding duplication within same therapeutic categories as much as possible; creating a centralized national procurement service for medicines; combining orders from several treatment facilities; combining different budgets/systems orders (combining orders from penitentiary services and orders from Ministry of Health facilities, as an example), or by pooling procurement from different countries (such as by commissioning a procurement agency (United Nations Development Programme, Crown Agents, etc).

PRICE REGULATION

Activists need to be aware of legislation that can create an unfair market for generics manufacturers. For example, governments may decide to regulate medicine prices by limiting their retail mark-up. Instead of a fixed mark-up rate (such as USD .50 per pack), the mark-up may be a percentage of the medicine's price (such as 25% per pack). This could incentivize pharmacies to promote higher-priced branded products to increase their profit, instead of lower-priced generic medicines. Doctors may prescribe medicines using their trade names instead of specifying use of generic versions. Also, unnecessarily burdensome or prolonged registration procedures can delay the market entry of generic products.

REDUCTION OR ELIMINATION OF TAXES AND DUTIES

Various taxes, such as VAT, customs duties may stimulate suppliers to increase their prices. Considering the importance of DAAs for public health, tax exemptions for DAA procurement could be introduced. There could be introduced tax exemptions of procurements of DAAs. The Global Fund already has set this policy in place by introducing tax exemptions on health-related products in 2015.

QUALITY

National Drug Regulatory Authorities (NDRAs), which are often called Food and Drug Authorities (FDAs), regulate and oversee the development, approval, manufacturing, importing and marketing of medicines to ensure the safety, efficacy and quality of drugs, vaccines, diagnostics and other medical products. Before drugs reach the market, they must secure regulatory approval.

Although WHO recommendations consider access and affordability, generic DAAs are not always accessible - or affordable. As examples:

- G/P was WHO-recommended in the absence of a VL; although one was granted in 2018, no generic versions were available as of August 2020, and there is no information about current registration status in the licensed territories.
- Although the VL for SOF and VEL includes over 100 countries, as of Gilead's most recent update in June of 2019, SOF has only been registered in 29, and filed in 1; SOF/VEL has only been registered in 21 countries and filed in 7.^{26, 27}
- DCV is registered in 21 countries, and filed in 29 more.²⁸ DCV/SOF is registered in 3 countries and filed in 16 more. In March of 2020, BMS announced that it would either withdraw marketing applications or allow them to lapse in certain countries;²⁹ BMS will also allow patents in those countries to lapse and will not enforce them after the lapse or withdrawal of marketing applications.³⁰

Each NDRA has its own pathways, requirements, procedures and timelines. Many things can cause the 'regulatory lag' of generic medicines, sometimes for years, including:

- Lack of, or limited NDRA capacity and resources
- Delayed and bureaucratic regulatory processes and/ or heavy workload
- Data exclusivity, which prevents generics manufacturers from accessing data from originator clinical trials
- Failure among originator companies to prioritize registration in low- and middle-income countries
- In some countries, originator products must be registered before generic versions
- Poor quality dossiers
- Requirement for local clinical trials as a prerequisite for approval

However, other measures can be taken to provide access to DAAs (and other medicines). The WHO pre-qualification (WHO-PQ) programme reviews quality, safety, and efficacy of generic DAAs that are not SRA-approved. WHO invites manufacturers of eligible medicines (these are recommended by WHO treatment guidelines; and/or are included in, or submitted an application for inclusion in the Essential Medicines List [EML]) to submit an expression of interest for WHO-PQ. Manufacturers must submit a dossier including data on the product's quality, safety, efficacy, which is assessed by an expert panel; their production sites – and any organizations that conducted clinical trials of the product- must be inspected and demonstrate compliance with WHO good manufacturing processes, good clinical practices and good laboratory practices (for more information, see: <https://www.who.int/news-room/fact-sheets/detail/prequalification-of-medicines-by-who>).

²⁶ Gilead Sciences. Sovaldi Registration in the Developing World [Online] May 2019 [Cited 2019 June 23] Available from: https://www.gilead.com/-/media/files/pdfs/aoem-%20registrations/sovaldi_registration.pdf?la=en&hash=A1C56DDC36C8388E5D08EC9355A0C320

²⁷ Gilead Sciences. Epclusa Registration in the Developing World [Online] May 2019 [Cited 2019 June 23] Available from: https://www.gilead.com/-/media/files/pdfs/aoem-registrations/epclusa_registration.pdf?la=en&hash=83CDB4E0C2D7FBF3DE87E9E5F5C60BE6

²⁸ Medicines Patent Pool. Daclatasvir. [Online] January 2019 [Cited 2019 June 23] Available from: https://medicinespatentpool.org/uploads/2018/11/DAC_MPP-update-on-activities-for-access-Jan-2019-7.pdf

²⁹ Albania, Armenia, Belarus, Bosnia, Bulgaria, Chile, Colombia, Egypt, Jordan, Kazakhstan, Kosovo, Kyrgyz Republic, Lebanon, Macedonia, Malaysia, Mexico, Moldova, Montenegro, Peru, Romania, Serbia, Thailand, Tajikistan, Ukraine, Uruguay, and Venezuela.

³⁰ <https://medicinespatentpool.org/news-publications-post/affordable-versions-of-hepatitis-c-medicine-daclatasvir-soon-available-in-additional-countries/>

The following generic DAAs have been WHO-PQ: ³¹

- SOF from Mylan (July 2017)
- SOF from Cipla (September 2017)
- SOF from Hetero (February 2018)
- SOF from Pharco (December 2018)
- SOF from Strides (March 2020)
- DCV from Mylan (May 2019)
- DCV from Hetero and Cipla (December 2019)
- SOF/DCV from Cipla (December 2019)

The following DAAs have been submitted to the ERP: ³²

- DCV from Larus Labs
- SOF/DCV from Mylan
- SOF/LDV from Strides and Mylan
- SOF/VEL from Mylan

Approval by a stringent regulatory authority (SRA), such as the European Medicines Agency (EMA) or the USFDA can facilitate accelerated NDRA registration of medicines that fulfill public needs – or their export. The USFDA issues tentative approval ³³ for generic fixed-dose combinations and co-packaged antiretroviral products used in the President’s Emergency Plan for AIDS Relief (PEPFAR), working closely to build capacity among generics manufacturers and prioritizing their applications.

Some countries – including Brazil ³⁴ and Thailand - produce their own generic medicines, which must meet national quality standards. Thailand’s Government Pharmaceutical Organization (GPO) has been producing generic antiretrovirals for national use since 2003; in 2018, GPO’s efavirenz was WHO-prequalified.

WHO has developed a procedure for sharing dossiers with NDRA’s, who will work to issue a decision on their registration within 90 days. For more information, see: <https://extranet.who.int/prequal/content/faster-registration-fpps-approved-sras>

Expert Review Panel (ERP) approval is used to identify products to meet an urgent supply need; these products are not WHO-PQ or approved by a stringent regulatory authority (SRA). To be eligible, dossiers for such products must be accepted by WHO-PQ or an SRA, and there must be evidence of compliance with good manufacturing processes. For more information, see: https://extranet.who.int/prequal/sites/default/files/documents/73_ERP_Feb2019.pdf

Some countries (Armenia, Georgia, Kyrgyzstan, Moldova, Ukraine) have simplified procedures for marketing authorization. In these countries, products that are WHO-prequalified, or approved by FDA, EMA or another SRA can be available quickly (in less than 30 days in some cases). These procedures help to ensure higher competition on state tenders and quick introduction and uptake of newly available products on the international market.

³¹ Data from: <https://extranet.who.int/prequal/content/prequalified-lists/medicines>

³² Data from : https://3cdmh310dov3470e6x160esb-wpengine.netdna-ssl.com/wp-content/uploads/2020/05/Hepatitis-C-Market-Report_Issue-1_Web.pdfx

³³ These products must meet the same safety, efficacy and marketing quality standards used for marketing in the US; approval is “tentative” rather than “full” only because they are under patent protection.

³⁴ Brazil’s 1999 Generic Drug Act requires that generic products demonstrate bioequivalence – meaning that there is no significant difference in bioavailability (the rate and extent of how a generic versus a branded drug is absorbed into the body) and also, that generic and branded drugs become available to act on their intended target over a period of time in the same way, when they are given at the same dose and under the same conditions.

HCV DRUG DEVELOPMENT

In drug development, science, regulation, commerce (and sometimes, people's health needs) overlap. DAAs – and other medicines – go through a series of steps before they are approved.

Unmet Needs

Unlike HIV, where a significant amount of publicly funded research has explored how to optimize antiretroviral therapy, HCV drug development has been driven by the pharmaceutical industry. While market concerns may overlap with priorities of people living with HCV – such as once-daily, fixed-dose combinations – the emphasis has been on getting DAAs approved as quickly as possible. This situation has led to the neglect of certain populations as well as important clinical questions. These unmet needs include:

- Lowering the risk for vertical HCV transmission - safety and efficacy of DAAs during pregnancy (and breastfeeding);
- Safety and efficacy of DAAs in children (age <6 years);
- Constructing regimens with best-in-class DAAs instead of using products that are owned by a single pharmaceutical corporation;
- Fixed-dose combinations of DAAs from different pharmaceutical corporations
- Head-to-head trials to compare safety, efficacy and tolerability of DAA regimens from different pharmaceutical corporations;
- Identifying the optimal re-treatment regimen for people who were not cured by an NS5A-containing regimen, especially those with genotype 3 and cirrhosis; and
- Developing long-acting DAA formulations to further simplify treatment and adherence.

Second-line treatment

When HCV treatment fails, it is often because of pre-existing drug resistance – usually to NS5A inhibitors, and most likely in people who have cirrhosis. WHO has not made recommendations for re-treatment, given the overall lack of access to DAAs and limited retreatment data (since cure rates have been so high, it has been challenging to find enough people who were not cured for trials). Currently, retreatment strategies include use of a triple-class DAA regimen, extending treatment duration and/or adding RBV, which is a twice-daily drug with many side effects. More research is needed to optimize HCV retreatment regimens.

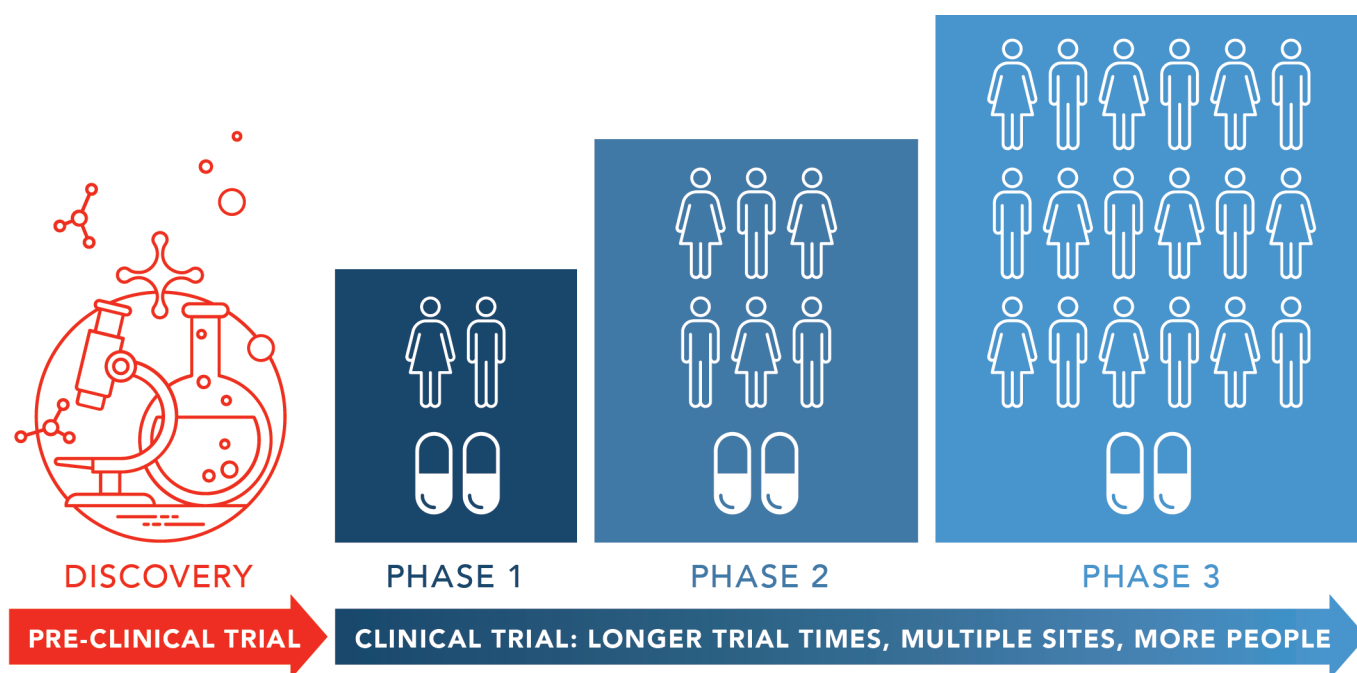
The Cost of Drug Development

The cost of developing drugs is often used to justify their high prices. Pharmaceutical corporations are notorious for their unwillingness to disclose what they actually spend on it. However, it is possible to estimate the cost of bringing SOF to market,³⁵ since Gilead purchased Pharmasset specifically to obtain SOF, which was in phase 2 trials at the time. Gilead paid US \$11.8 billion, and its later-stage SOF clinical trials were unlikely to have cost more than US \$500 million, bringing the total cost to an estimated US \$12.3 billion. According to Gilead, just over \$880 million dollars was spent on developing SOF-based regimens during 2013, 2013 and 2014.³⁶ SOF became the backbone of Gilead's DAA regimens; since 2013, Gilead's hepatitis C revenues have exceeded US \$58 billion, with an estimated profit of US\$ 25.8 billion.

³⁵ Initially, SOF was developed with the help of US\$ 62.4 million dollars from the National Institutes of Health.

³⁶ [https://www.finance.senate.gov/imo/media/doc/2%20Introduction,%20Hepatitis%20C%20Background,%20Development%20of%20Sovaldi%20and%20Gilead's%20Acquisition%20of%20Pharmasset%20\(Introduction,%20Sections%201&2\).pdf](https://www.finance.senate.gov/imo/media/doc/2%20Introduction,%20Hepatitis%20C%20Background,%20Development%20of%20Sovaldi%20and%20Gilead's%20Acquisition%20of%20Pharmasset%20(Introduction,%20Sections%201&2).pdf)

Figure 4. The Drug Development Process



Pre-clinical Trials

Researchers select a target, such as a step in the HCV lifecycle, and identify and improve on a lead compound. During this stage, assessments of what the drug does to the body (called pharmacodynamics), what the body does to the drug (called pharmacokinetics), how the drug is absorbed (called bioavailability), its stability, toxicity, and other characteristics are performed in the laboratory.

Before a drug can be studied in human beings, it must go through trials in at least two species of mammals, which are chosen because of their relevance for assessing risks in humans. Preclinical trials look at the organs a drug passes through, whether it harms any organs or causes cancer, and its impact on reproduction and breast-feeding.³⁷

These early stages of drug development are often government-funded, with additional support from foundations. As an example, from 2010 to 2016, the National Institutes of Health contributed over US \$100 billion to basic science research which led to the development of 210 drugs, 84 of them first-in-class.

³⁷ Despite this precaution, sometimes drugs that are harmful to humans do not cause problems in animals.

Clinical Trials

Clinical trials are experiments in human beings to look at the safety and efficacy of drugs, interventions and treatments for a certain condition. There are four phases of clinical trials.

Phase I

These first-in-human trials are short (weeks to months) and small (20 to 80 people). They begin in healthy volunteers, then may move into people with the given condition, to look at the activity of the drug. Phase I trials look at the safety and tolerability of a drug compared to placebo and at different doses, and a drug's potential for doing short- or long-term harm.

Phase II

These trials are often called 'make it or break it'. They usually include over 100 people, and are conducted at different sites and in different countries, and usually last from months to years, depending on the condition that is being studied. Usually, people with milder forms of the illness, who do not have any comorbidities, are eligible for phase II trials. These trials look at safety, tolerability and efficacy; Phase II DAA trials have looked at treatment dosing, duration and strategy.

Phase III

Phase III trials are the final step before registration. These trials enroll hundreds to thousands of people, and are performed at multiple sites in different countries. They primarily look at efficacy, safety and adverse events, lasting from months to years. Phase III trials are generally more inclusive, and tend to enroll people with more advanced forms of an illness – a more 'real-life' scenario – than earlier trials, although people with the most urgent need are often left to seek experimental drugs through compassionate use or named patient programs.

Phase IV

These trials are conducted after a drug has been approved. Regulators can require post-marketing studies, including for drugs that received accelerated approval and for pediatrics. Sometimes regulators ask for post-marketing studies because they want longer follow-up, information in certain groups of people who were under-represented in, or excluded from trials (the elderly, women, people from certain countries, ethnic/racial groups, people with other medical conditions or more advanced illness, such as people with advanced cirrhosis), or to explore different treatment strategies.

Pipeline

After a flurry of drug development, the pipeline for DAAs has run dry. However, there is still a need for some improvements, including more effective treatment for people with genotype 3 and cirrhosis, long-acting DAA formulations, and a vaccine to prevent HCV (trials are ongoing).

Getting information

Information about HCV treatment is often presented at conferences and scientific meetings, in journal articles and conference reports. Reliable sources for HCV information include:

HIV i-Base
Médecins Sans Frontières Access Campaign
Prescribing information (approved drugs only)
Treatment Action Group
WHO treatment guidelines

Advocacy Context

As HCV treatment became more effective, safer, more tolerable and simpler to deliver, momentum increased around the possibility of eliminating it as a threat to global public health. In 2016, the WHO launched its Global Health Sector Strategy (GHSS) for Viral Hepatitis. The GHSS calls for a public health approach to combat HCV and includes targets to monitor progress towards elimination; it has been adopted by 184 Member States.

Figure 2.
GHSS Targets for Eliminating HCV as a Threat to Global Public Health

	2020 TARGETS	2030 TARGETS
Incidence (new infections)	30% reduction*	80% reduction*
Mortality 2	10% reduction*	65% reduction*
Harm reduction coverage 2015 baseline of 20 syringes	200 syringes per person injecting drugs, per year	300 syringes per person injecting drugs, per year
Diagnosis rate 2015 baseline of 5%	30%	90%
Treatment rate 2015 baseline of <1%	3 million people	80% of all eligible persons

* from baseline (2015) levels

STEPS TO INCREASE ACCESS TO OPTIMAL HCV DIAGNOSTICS AND TREATMENT

The HCV diagnostic and treatment landscape is complex, and likely to remain so in the coming years. In addition to assessing the strength and status of patents, clinical, pragmatic and country-specific factors need to be considered. While WHO guidelines are internationally recognized, promising drugs or regimens may be in the pipeline. Consultations with people with HCV, doctors, researchers, and policymakers can shed light on which products are most important.

To ensure that the procurement process is truly competitive, and will lead to lower prices, it is important for generics producers to easily bring their medicines to a robust market once patents have expired or been removed by use of TRIPS flexibilities. Activists and their organizations have an important role to play by creating demand by:

1. Identifying the optimal treatment and diagnostic products and raising awareness about them among the community of people affected by HCV, health professionals and government officials;
2. Empowering effective price negotiations by sharing information about target prices based on production costs;
3. Helping governments to address patent monopolies for HCV medicines and combinations by requesting compulsory licenses or by filing patent oppositions;
4. Facilitating the marketing authorization process and rational inclusion of the most effective HCV drugs in national treatment guidelines, national essential medicines lists, reimbursement lists, procurement nomenclature and/or terms of reference for procurement;
5. Monitoring the transparency, timeliness and efficiency of state procurement and supply chain management for HCV diagnostics and medicines, and helping to coordinate stakeholder efforts to lower the risk of, or address stockouts of these products; and
6. Introducing legislative or normative proposals to remove unnecessary regulatory barriers and create mechanisms to improve access to optimal HCV diagnostics and treatment.

RESOURCES

Clinton Health Access Initiative. Hepatitis C Market Report. Issue 1 [Online] May 2020 [Accessed 2020 August 23]. Available from:

https://3cdmh310dov3470e6x160esb-wpengine.netdna-ssl.com/wp-content/uploads/2020/05/Hepatitis-C-Market-Report_Issue-1_Web.pdf

Harm Reduction International. The Global State of Harm Reduction 2018. Sixth Edition. [Accessed 2019 June 22] Available from:

<https://www.hri.global/files/2019/02/05/global-state-harm-reduction-2018.pdf>

Hawkins L. World Health Organization/HAI. WHO/HAI Project on Medicine Prices and Availability. Review Series on Pharmaceutical Pricing Policies and Interventions Available from:

<https://haiweb.org/wp-content/uploads/2015/08/Competition-final-May-2011a1.pdf>

<https://hepcoalition.org>

Hill A, Barber MJ, Gotham D. [Accessed 2019 June 22] Estimated costs of production and potential prices for the WHO Essential Medicines List. BMJ [Online] 2018.

[Accessed 2019 June 22]. Available from:

<https://gh.bmj.com/content/bmjgh/3/1/e000571.full.pdf>

See also Hill, A. Prices versus costs of medicines in the WHO Essential Medicines List. [Online] 2018 [Cited 2019 September 2] Available from:

<https://www.who.int/phi/1-AndrewHill.pdf>

MSF Access Campaign. MPP Licence Agreement with AbbVie for Glecaprevir/Pibrentasvir (G/P): Analysis and Recommendations. [Online] Technical Brief March 2019 [Accessed 2019 June 22] Available from:

<https://msfaccess.org/msf-access-campaign-analysis-mpp-licence-agreement-abbvie-glecaprevirpibrentasvir-gp>

World Health Organization. Progress report on HIV, viral hepatitis and sexually transmitted infections, 2019. Accountability for the global health sector strategies, 2016–2021. [Online] May 2019 [Cited 2019 June 22] Available from:

<https://apps.who.int/iris/bitstream/handle/10665/324797/WHO-CDS-HIV-19.7-eng.pdf?ua=1>

World Health Organization. Access to Hepatitis C Testing and Treatment for People who Inject Drugs and People in Prisons – a Global Perspective. [Online] Policy Brief. April 2019 [Accessed 2019 June 22] Available from:

<https://apps.who.int/iris/bitstream/handle/10665/312116/WHO-CDS-HIV-19.6-eng.pdf?ua=1>

World Health Organization. Progress Report on Access to Hepatitis C Treatment. Focus on overcoming barriers in low- and middle-income countries. [Online] March 2018 [Accessed 2019 June 21]. Available from:

<https://apps.who.int/iris/bitstream/handle/10665/260445/WHO-CDS-HIV-18.4-eng.pdf?sequence=1>

World Health Organization. Guidelines for the Care and Treatment of Persons Diagnosed with Chronic Hepatitis C Virus Infection. [Online] July 2018 [Cited 2019 June 22] Available from:

<https://apps.who.int/iris/bitstream/handle/10665/273174/9789241550345-eng.pdf>

RESOURCES

World Health Organization. Global Report on Access to Hepatitis C Treatment - Focus on Overcoming Barriers. [Online] October 2016. [Accessed 2019 June 21] Available from:

<https://apps.who.int/iris/bitstream/handle/10665/250625/WHO-HIV-2016.20-eng.pdf?sequence=1>

World Health Organization. Global Health Sector Strategy on Viral Hepatitis 2016-2021. [Online] June 2016 [Accessed 2019 June 22] Available from:

<https://apps.who.int/iris/bitstream/handle/10665/246177/WHO-HIV-2016.06-eng.pdf;jsessionid=679CB3EF5D6A9844C1177FD058C87A62?sequence=1>

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