

DISEASE  
NARRATIVE  
HEPATITIS C

FEBRUARY 2020



# EXECUTIVE SUMMARY

The *Disease Narrative for hepatitis C* provides an overview of Unitaid's strategic approach to maximize effectiveness of its hepatitis C interventions. It complements Unitaid's hepatitis C Technology and Market Landscapes.

Globally, 71 million people have chronic hepatitis C infection, and in 2015, 400,000 people died from HCV-related liver disease (mostly due to liver cirrhosis and liver cancer). Moreover, while mortality of major infectious diseases, such as HIV, TB or malaria, is declining, the number of HCV-related deaths is increasing.

In 2016, WHO called for elimination of viral hepatitis, including hepatitis C, as a major public health threat by 2030. This helped spur action, though acceleration will be required in order to meet the 2030 elimination target.

## **A revolutionary cure exists, but does not reach people**

Until a few years ago, diagnosis and treatment of hepatitis C was complex. Suitable tools for screening and diagnosis in resource-limited settings were lacking, and treatment was hampered by limited efficacy and severe side effects.

New medicines have revolutionized HCV treatment: infection with the hepatitis C virus (HCV) can now be cured in 8-12 weeks. This offers a huge opportunity to address HCV, including in HIV/HCV co-infected people, who progress faster to serious disease than HCV mono-infected people.

Though initially launched at high prices, affordable generic versions of these medicines are increasingly available. In many (though not all) low- and middle-income countries, it ought to be possible to procure HCV treatment at less than US\$ 100 per person cured – that is, comparable to the cost of one year of HIV treatment. Nevertheless, these treatments are not reaching enough people.

## **Unitaid helped to develop the key tools for an effective HCV response in countries**

Recognizing the need and transformative potential of the new HCV medicines early on, Unitaid invested in HCV since 2015. These investments accelerated the development of key tools for low- and middle-income countries that seek to initiate or scale-up their response to hepatitis C.

Through its projects, Unitaid contributed to the simplification of algorithms, the launch of WHO guidelines, the development of better HCV tests and an increased awareness about hepatitis C. Moreover, evidence is being collected on the implications and efficiency of different approaches to HCV testing and diagnosis. Recently, Unitaid decided to invest in the development of a potential long-acting treatment (a 'one-shot cure'). These various tools will facilitate the provision of HCV care in low- and middle-income countries.

## A number of challenges remain

Despite considerable progress since the launch of the new treatments, gaps and challenges remain. Although better solutions are being developed, the diagnostic pathway remains composed of multiple steps which results in people dropping out or not being linked to care.

Insufficient scaling up of screening and testing to find the people with chronic HCV infection poses another major challenge. It is compounded by insufficient prevention, leading to new infections, especially among high risk – and often marginalized – populations (such as people who inject drugs and prisoners).

Furthermore, due to the lack of international scale-up partners, governments will have to fund most of the expansion of HCV services with domestic resources. As evidence is increasing that it is both feasible and affordable to cure HCV infection, momentum is starting to build gradually in an increasing number of countries – though it will take some time for concrete progress to materialize.

## Unitaid can address some challenges in the HCV response

Given its investments and leadership in this space, Unitaid is in a unique position to further support the HCV response, catalyzing action toward elimination.

The Secretariat has, through a review of literature and on the basis of input from partners, identified a comprehensive list of challenges that currently hamper the global response and the interventions available to address them. From this list, Unitaid identified those challenges where it may be best positioned to play a catalytic role:

- **Demonstrate the feasibility of treating and preventing HCV among key populations**, notably people who inject drugs and prisoners. Through HCV testing, treatment and harm reduction services tailored to their needs and circumstances, these populations can be reached.
- **Integrate HCV testing and treatment** in other services, including harm reduction services. This can help reach more people and make HCV testing and treatment more efficient and cost-effective – which, in turn, can facilitate the allocation of resources by countries. It can also help Unitaid to develop and pioneer new models of scaling-up.
- **Expand HCV testing** to find people with chronic infection. Tools for diagnosing HCV exist and better tools that allow for testing closer to the point of care or interaction are being developed. Accelerating their introduction and supporting countries to make optimal use of them and to tackle HCV, will both support HCV elimination and help prevent future deaths from liver cancer.
- **Retain people in care** by ensuring that they can complete the testing algorithm and be linked to treatment. Unitaid is already working on this, notably through its support for the development of a HCV cAg RDT test and a potential long-acting treatment (a ‘one-shot cure’).

# TABLE OF CONTENTS

Executive Summary	1
Table of contents	3
Abbreviations	4
<b>1 INTRODUCTION</b>	<b>5</b>
<b>2 DISEASE CONTEXT</b>	<b>5</b>
2.1 Disease introduction	5
2.1.1 HIV/HCV co-infection	6
2.2 Disease burden	6
2.3 Global goals and targets	7
2.4 Progress and remaining gaps in the HCV response	7
2.5 Innovation has revolutionized HCV treatment, but access remains limited	8
2.6 Diagnostic tools are imperfect but improving	9
2.7 Prevention: a major gap	9
2.8 The question of scaling up	10
2.9 Unitaid's investments to date	10
2.10 Global partners' landscape in HCV	11
<b>3 IDENTIFYING AND PRIORITIZING CHALLENGES</b>	<b>13</b>
3.1 Challenges threatening progress towards global goals	13
3.2 Reviewing challenges for possible Unitaid intervention	14
3.2.1 Treatment	15
3.2.2 Diagnosis	15
3.2.3 Prevention of transmission through the health system	16
3.2.4 Prevention of transmission outside the health system	16
3.2.5 Data, planning and financing	17
3.2.6 Health systems	17
3.2.7 Social and environmental factors	18
3.3 Priority challenges for possible Unitaid intervention	18
<b>4 POTENTIAL OPPORTUNITIES</b>	<b>20</b>
<b>ANNEX I</b>	<b>21</b>
<b>ENDNOTES</b>	<b>22</b>

# ABBREVIATIONS

CHAI	Clinton Health Access Initiative
DAA	Direct acting antiviral
HBV	Hepatitis B virus
HBeAg	Hepatitis B virus e-antigen
HCV	Hepatitis C virus
HCV cAg	Hepatitis C virus core-antigen
HIV	Human Immunodeficiency Virus
LICs	Low income countries
LMICs	Low- and middle-income countries
MSF	Médecins Sans Frontières
MSM	Men who have sex with men
PLHIV	People living with HIV
PWIDs	People who inject drugs
RDT	Rapid diagnostic test
TB	Tuberculosis
WHO	World Health Organization

## 1 INTRODUCTION

This document provides an overview of Unitaid's strategic approach to hepatitis C, its portfolio of grants, and potential opportunities that contribute to achieving the goal of eliminating hepatitis C as a public health problem by 2030. It builds on Unitaid's 2015 Disease Narrative for Hepatitis C in the context of co-infection with HIV by providing an update on global progress against the goals set out in the Global health sector strategy on viral hepatitis 2016-2021, challenges impeding the hepatitis response, and Unitaid's activities since the last Disease Narrative. The report identifies current challenge areas where Unitaid may be well-suited to influence, and opportunities that Unitaid could consider supporting to accelerate progress towards achieving the global goal of eliminating hepatitis C as a major public health threat by 2030.

The disease narrative is not intended to be a full-fledged strategy but, rather, a document that provides visibility on the context and potential focus areas.

## 2 DISEASE CONTEXT

### 2.1 Disease introduction

Hepatitis is an inflammation of the liver. Infection with an hepatitis virus is the most common cause of hepatitis, but some other infections and certain toxic substances (e.g. alcohol) can also cause hepatitis. There are 5 main, and unrelated, hepatitis viruses that are referred to as types A, B, C, D and E. Hepatitis B and C, in particular, lead to chronic disease in millions of people and, together, are the most common cause of liver cirrhosis and liver cancer<sup>1</sup>. Both usually occur as a result of percutaneous contact with infected body fluids<sup>2</sup>.

Hepatitis C is caused by the hepatitis C virus (HCV), a bloodborne virus that infects liver cells. HCV infection results in illness that ranges from mild and transient to chronic and life-threatening. Acute HCV infection may occur within 2 weeks to 6 months following initial exposure to the virus. Approximately 80% of persons with acute HCV infection exhibit no symptoms. An estimated 15-45% of people with acute HCV infection mount an immune response that effectively clears the virus within 6 months of infection.

Infected people who do not naturally clear the infection develop chronic HCV infection. This infection, if left untreated, can result in cirrhosis (i.e. severe scarring of the liver) or liver cancer.

The primary modes of HCV transmission are sharing of injecting equipment during drug use, and re-use or poor sterilization of medical and dental equipment, especially needles and syringes, in some countries. In countries where blood donations are not routinely screened for bloodborne pathogens, blood transfusions or the use of other blood products may lead to HCV transmission. Sexual transmission is uncommon, except among HIV-positive men who have sex with men.

Through bloodborne routes, HCV is about 10 times more infectious than HIV.

There are six primary genotypes of HCV (and multiple subtypes). Genotypes 1 and 3 are the most prevalent, accounting for around 46% and 30% of HCV cases worldwide, respectively. Together, genotypes 2, 4 and 6 represent around 23% of HCV cases, while genotype 5 accounts for less than 1%. Between regions, there is substantial variation in genotype distribution.<sup>3</sup>

### 2.1.1. HIV/HCV co-infection

HIV-positive people are six times more likely to be infected with HCV than people who are not HIV-positive.<sup>4</sup> It is estimated that, worldwide, approximately 2.3 million people are co-infected with HIV and HCV.<sup>5</sup>

People living with HIV (PLHIV) who also contract HCV suffer increased rates of liver disease, increased risk of mortality, and increased treatment complications due to liver damage and toxicity.<sup>6</sup> As the lifespan of PLHIV is extended due to the scale-up of antiretroviral treatment, severe HCV-related liver damage is increasing and in some areas is the leading cause of death among PLHIV.<sup>7</sup>

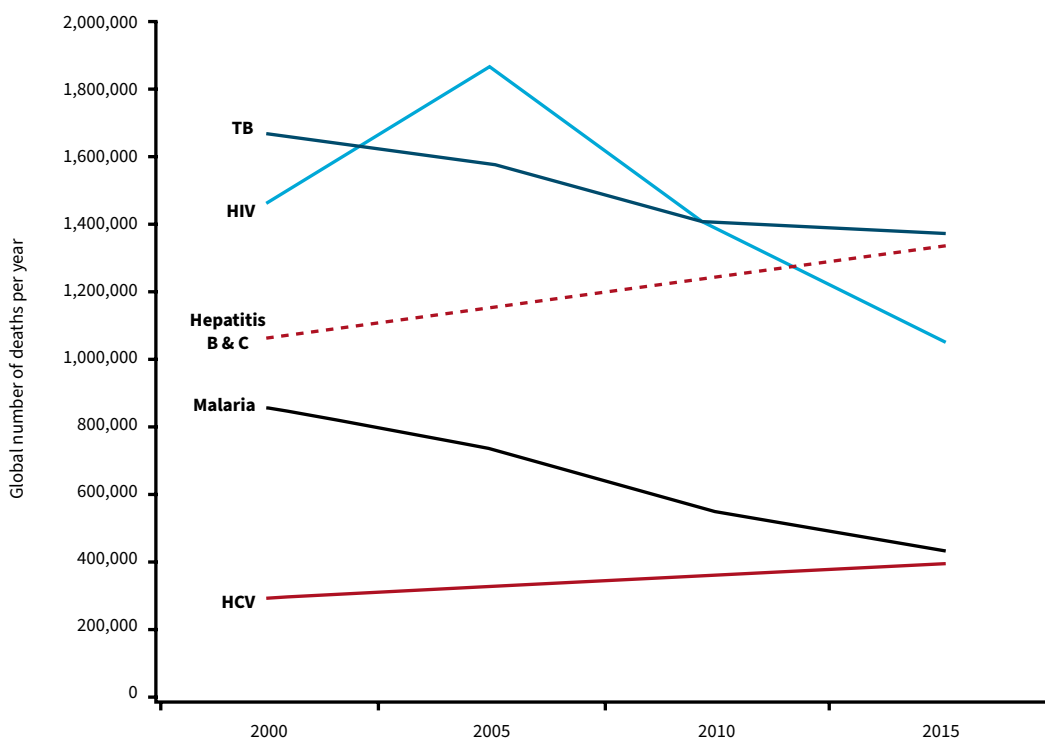
Furthermore, it is estimated that 2.7 million people are coinfecting with HIV and the hepatitis B virus (HBV).<sup>8</sup> Co-infection of HBV and HCV, triple infection (HBV, HCV and HIV) and coinfection of viral hepatitis and TB also occur.

### 2.2 Disease burden

WHO estimates that, in 2015, viral hepatitis led to 1.34 million deaths – a death toll comparable to that of tuberculosis or HIV. The vast majority (96%) of deaths due to viral hepatitis are the result of complications (cirrhosis or liver cancer) due to chronic HBV (66%) and HCV (30%) infections.<sup>8</sup> This corresponds to 400,000 deaths from HCV-related liver disease in 2015<sup>9</sup> – comparable to the number of deaths due to malaria.

Since 2000, the number of deaths from HCV has increased by 22%, while over the same period, the total worldwide number of deaths from HIV, TB and malaria fell (see Figure 1). And WHO expects that the death toll from viral hepatitis will continue to increase.<sup>8</sup>

**FIGURE 1:** Trends in worldwide deaths from HIV, tuberculosis, malaria and viral hepatitis



Source: WHO. Global health estimates 2015: estimated deaths by age, sex and cause.



WHO estimates that, in 2015, 71 million people had chronic HCV infection, with 1.75 million new HCV infections occurring per year. The latter are mostly due to unsafe health care practices that persist in certain countries or settings and to injecting drug use<sup>10</sup>. Meanwhile, in 2015, 257 million people were infected with hepatitis B.<sup>10</sup> In 2017, 1.1 million new HBV infections occurred.<sup>11</sup>

### 2.3 Global goals and targets

On 25 September 2015, world leaders adopted the Agenda for Sustainable Development, including the Sustainable Development Goals. One of the targets for Goal 3 includes a specific reference to combatting hepatitis.<sup>12</sup>

This was followed, at the World Health Assembly in May 2016, by the adoption of the Global health sector strategy on viral hepatitis 2016-2021, which has raised the profile of and increased attention for viral hepatitis. The strategy aims to eliminate viral hepatitis as a major public health threat by 2030<sup>13</sup>. It sets targets that are ambitious but realistic. Some of the key targets for HCV are listed in Table 1.

**TABLE 1:** Selected targets from the *Global health sector strategy on viral hepatitis*

	2015 BASELINE	2020 TARGET	2030 TARGET
<b>Impact targets</b>			
<b>INCIDENCE: NEW CASES OF CHRONIC HEPATITIS B AND C INFECTIONS</b>	6 – 10 million infections reduced to 0.9 million by 2030	30% reduction	90% reduction (80% reduction for HCV and 95% for HBV)
<b>MORTALITY: HEPATITIS B AND C DEATHS</b>	1.4 million deaths due to HBV and HCV reduced to 0.5 million by 2030	10% reduction	65% reduction
<b>Service coverage targets</b>			
<b>HCV DIAGNOSIS</b>	< 5% of chronic infections diagnosed	30%	90%
<b>HCV TREATMENT</b>	< 1% of people with chronic HCV infection receive treatment	3 million people have received HCV treatment	80% of eligible persons with chronic HCV infection treated

The strategy also contains targets on blood safety, injection safety and harm reduction for people who inject drugs. In addition, there are targets specific to hepatitis B. See Annex 1 for an update on progress toward these targets.

### 2.4 Progress and remaining gaps in the HCV response

The 2030 targets for HCV diagnosis and treatment (90% of people with chronic HCV infection diagnosed, and 80% treated) translate to approximately 64 million people diagnosed and 57 million people treated. Achieving these targets will require significant acceleration.

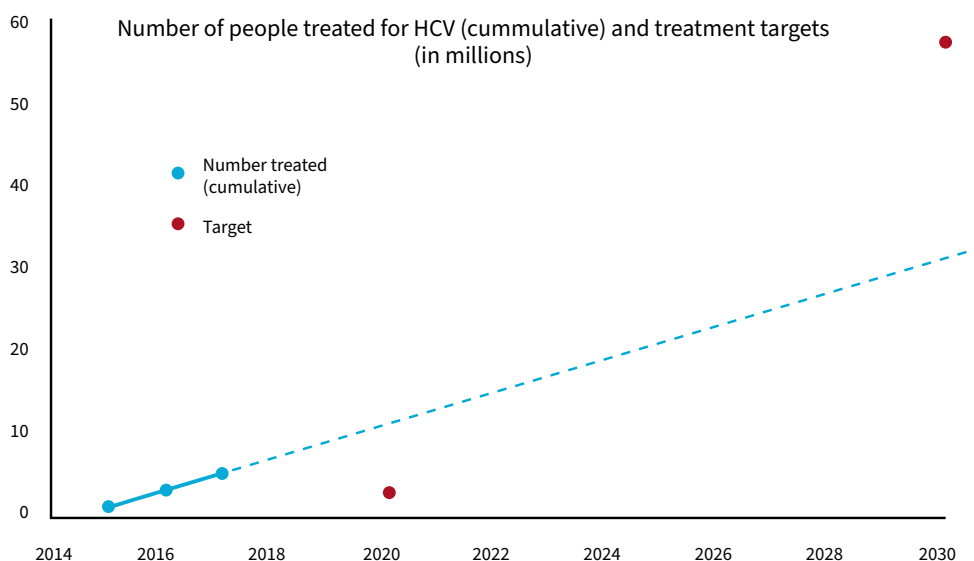
Globally, around 20% of people with HCV infection were diagnosed in 2016. Although this implies that it may be feasible to achieve the 2020 global target for HCV diagnosis, progress is very uneven (varying from 43% of HCV infections diagnosed in HICs to only around 8% in LICs)<sup>15</sup>.

WHO estimates that, in 2015, 1.1 million people were treated for HCV. This increased by 1.76 million people in 2016<sup>15</sup>, and by 2.1 million in 2017<sup>16</sup>, bringing the total number of people that have received HCV treatment (end 2017) to 5 million. Thus, the 2020 treatment target of the Global Strategy has been surpassed – though WHO notes that this achievement can largely be attributed to a small number of countries – with Egypt and Pakistan accounting for half of the people who started treatment in 2016<sup>5</sup>.

Yet this also means that, in the period 2015-2017, only about 7% of people with chronic HCV infection have been treated. Moreover, in 2016, the number of people treated equaled the number of new infections – in other words, the total number of people with HCV infection hardly changed.

Finally, as shown in Figure 2, if the number of people accessing HCV treatment continues to grow at the current rate, the cumulative number of people treated by 2030 will fall significantly short of the target. To achieve elimination, acceleration is therefore warranted.

**FIGURE 2:** Number of people treated for hepatitis C versus treatment targets



## 2.5 Innovation has revolutionized HCV treatment, but access remains limited

Until a few years ago, HCV was difficult to treat. Treatment lasted almost a year, required injections several times per week, was expensive, had severe side effects and offered limited efficacy. Diagnosis, too, was relatively complex and expensive. Available treatments required extensive monitoring (for side effects and efficacy), which further added to the cost and complexity of HCV care. As a result, few low- and middle-income countries (LMICs) were actively screening, diagnosing or treating HCV, and few LMICs had HCV programmes or dedicated budget lines for HCV.

This changed in 2014, when new medicines (direct acting antivirals, or DAAs) were launched. DAAs can cure HCV infection in 12 weeks and have few side effects – thus, they simplify both treatment and monitoring. The more recent advent of pan-genotypic DAA combination treatments (that are effective against all types of HCV virus) furthermore removed the need for genotyping – a complex and costly step in the diagnostic algorithm.

These new HCV medicines therefore revolutionized HCV treatment – but they were launched with very high prices, and arrived, in many countries, in a “vacuum” where diagnosing and treating HCV was not part of mainstream public health services.

Due to actions by several stakeholders, including some Unitaid projects (see section 2.9), nowadays, affordable generic HCV medicines are available in many LMICs, with the cost of a cure currently being reported below US\$ 100 per person – that is, comparable to the cost of a year of HIV treatment.

As several highly effective pan-genotypic combination treatments exist, further innovation is relatively limited. Nevertheless, some innovation is taking place, mostly with a focus on populations that currently are not served/do not have access to the existing DAAs:

- Clinical trials are ongoing with an additional, potentially pan-genotypic combination of sofosbuvir/ravidasvir that could facilitate access to HCV treatment in countries where patent barriers prevent the marketing of generic versions of other DAAs.
- The development of new, long-acting, formulations of existing treatments is being explored; work is still in early stages.

## **2.6 Diagnostic tools are imperfect but improving**

HCV often remains undiagnosed until patients present at health care-facilities with the symptoms of advanced liver disease, including liver cancer. Globally, only one in five people with chronic hepatitis infection know they are infected; in low-income countries this is significantly lower<sup>17</sup>.

A major diagnostic challenge is the lack of suitable, real point-of-care tools for diagnosing HCV. Normally, the first step is a rapid screening test, which identifies the presence of antibodies. If positive, this test needs to be followed by a test to confirm active HCV infection (people who have cleared the infection retain the antibodies, but are no longer infected with HCV and do not require treatment). Confirmation tests are reliable, but require a certain laboratory infrastructure and trained personnel; thus, they can only be undertaken in health facilities of a certain level. In many countries, these facilities are not available everywhere, and not accessible to everyone.

The second test, to confirm active (chronic) HCV infection – and the need for treatment – usually requires a follow-up visit, often to a different facility. Furthermore, before initiating treatment, one or more liver function tests, to assess whether the person has cirrhosis, are required (as cirrhosis may affect the type or duration of treatment). These various tests may require multiple visits, at times to different facilities, which contributes to people not completing the diagnosis (loss-to-follow-up).

Work is ongoing to develop better diagnostic tests for HCV, including through Unitaïd investments.

## **2.7 Prevention: a major gap**

While challenges related to diagnosis and treatment persist, progress is being made (see Figure 2). Unfortunately, this progress is “undone” by the fact that new infections continue to occur, at about the same pace as people being cured. Insufficient prevention is therefore a major weakness in the HCV response.

There are no vaccines or treatments that can prevent HCV infection<sup>18</sup>. Thus, prevention mainly depends on reduction of the risk of HCV infection in high-risk populations (such as people who inject/use drugs), as well as on infection control in health care settings and proper screening of blood transfusion and blood products. Technologies such as auto-disable syringes, low dead-space syringes, and opioid substitution therapy can support such prevention efforts.<sup>19</sup>

Treatment of HCV infected individuals is the other strategy that helps to prevent transmission, especially in populations or settings where the risk of HCV transmission is elevated, notably people who inject/use drugs. Globally, over half of the people who inject drugs have chronic HCV infection. HCV prevalence is also relatively high in HIV-positive men who have sex with men, in prisoners and in some indigenous populations.<sup>19,20,21</sup>

Vaccines that could prevent HCV infection would be a useful additional tool in combating HCV, in particular for high-risk populations. Several candidate vaccines are in early stages of development, but it will reportedly still take many years until they could be ready for use.<sup>19,20,21</sup>

## 2.8 The question of scaling up

There is limited international donor support for HCV elimination; as a result, countries will have to fund the scaling up of HCV testing, treatment and prevention. Until a few years ago, however, hepatitis C care was not part of mainstream public health services in most low- and middle-income countries (due in large part to the limitations of the pre-2015 treatments). Countries therefore have to develop HCV services from scratch. While this offers important opportunities for integration and decentralization, it will be a resource-intensive process.

Some countries with a high HCV burden in the general population, such as Egypt, Mongolia, Pakistan and the State of Punjab in India, were quick to include HCV into their health services<sup>22</sup>. Increasingly, other countries are also starting to take action. For example, in 2012, only 17 countries had a national plan for viral hepatitis. This had increased to 82 countries by 2017, and to 124 countries April 2019.<sup>23,24</sup>

Tools and evidence – developed, in part, by projects Unitaid supported – are available to help countries design their HCV response. Nevertheless, setting up and financing a national HCV response will, in most countries, be a gradual process that will take time.

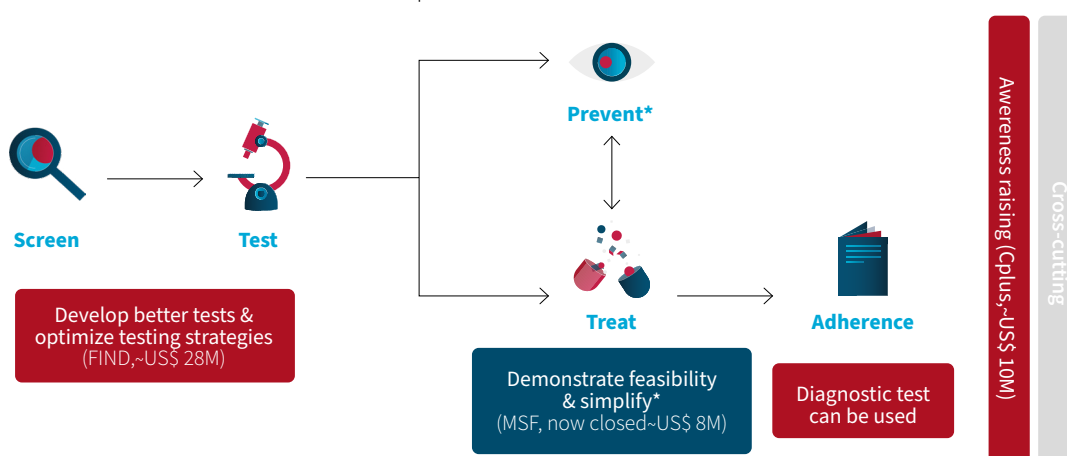
Unitaid could support this process by maneuvering carefully and strategically to catalyze the scaling up of HCV services in countries.

## 2.9 Unitaid's investments to date

Recognizing early on the opportunity presented by the new HCV medicines, as well as the challenges that would hamper access to HCV treatment, Unitaid was among the first to support efforts to eliminate HCV, in spite of the absence of a scaling-up partner other than countries. Unitaid's investments to date, though focused on HIV/HCV coinfection, have also benefitted people with HCV mono-infection.

Figure 3 below represents the sequence from screening to cure, and indicates the area of focus of Unitaid's HCV grants. In addition, several other grants include HCV within their scope, but are not primarily focused on HCV. This is for example the case of the Medicines Patent Pool.

FIGURE 3: Overview HCV portfolio



Note: Red boxes indicate active grants; dark grey indicates closed grant; \* indicates no active or closed grants

Together, Unitaïd's targeted and complementary investments have helped to create many key tools that are necessary for an effective HCV response:

- The MSF project (now closed) pioneered HCV diagnosis and treatment in resource-limited settings. The project developed simplified models of care that allow for task-shifting, demonstrated their feasibility and obtained treatment outcomes that are at par with those in high-income settings. In most project countries, MSF was among the first to provide treatment with the new DAAs<sup>25</sup>. Evidence generated by the project is informing policies in and beyond project countries, including through incorporation in WHO guidelines<sup>9</sup>.
- The project by Coalition PLUS is increasing awareness about HCV among policy-makers and key populations, and generates demand for the new HCV treatments. The project also draws attention to the needs and importance of stigmatized or marginalized populations (such as injecting drug users or prisoners) and advocates for equitable access to HCV care.
- The Medicines Patent Pool and other grants working on intellectual property rights, as well as Unitaïd's grants to MSF and Coalition PLUS, contribute to making HCV medicines more affordable, using a variety of approaches. They also advocate for registration of DAAs in countries.
- The FIND project seeks to accelerate the introduction of new, better and simpler HCV tests, including for diagnosing HCV in HIV/HCV co-infected populations. It also develops appropriate and cost-effective testing algorithms that facilitate task-shifting, explores integration of HCV testing on existing platforms, and devises strategies to reduce the cost of testing. These are crucial elements to enable the expansion of testing, which is one of the major bottlenecks to scaling up and to reaching HCV elimination.
- The WHO enabler project shares knowledge and lessons learned from Unitaïd's HCV projects with stakeholders globally, through its technical assistance and via its policy guidance and guidelines. It also informs the design of certain activities in Unitaïd's HCV projects, to ensure that they can inform its guidelines.<sup>26</sup> WHO furthermore contributes to quality assurance of HCV medicines and tests through the prequalification programme.

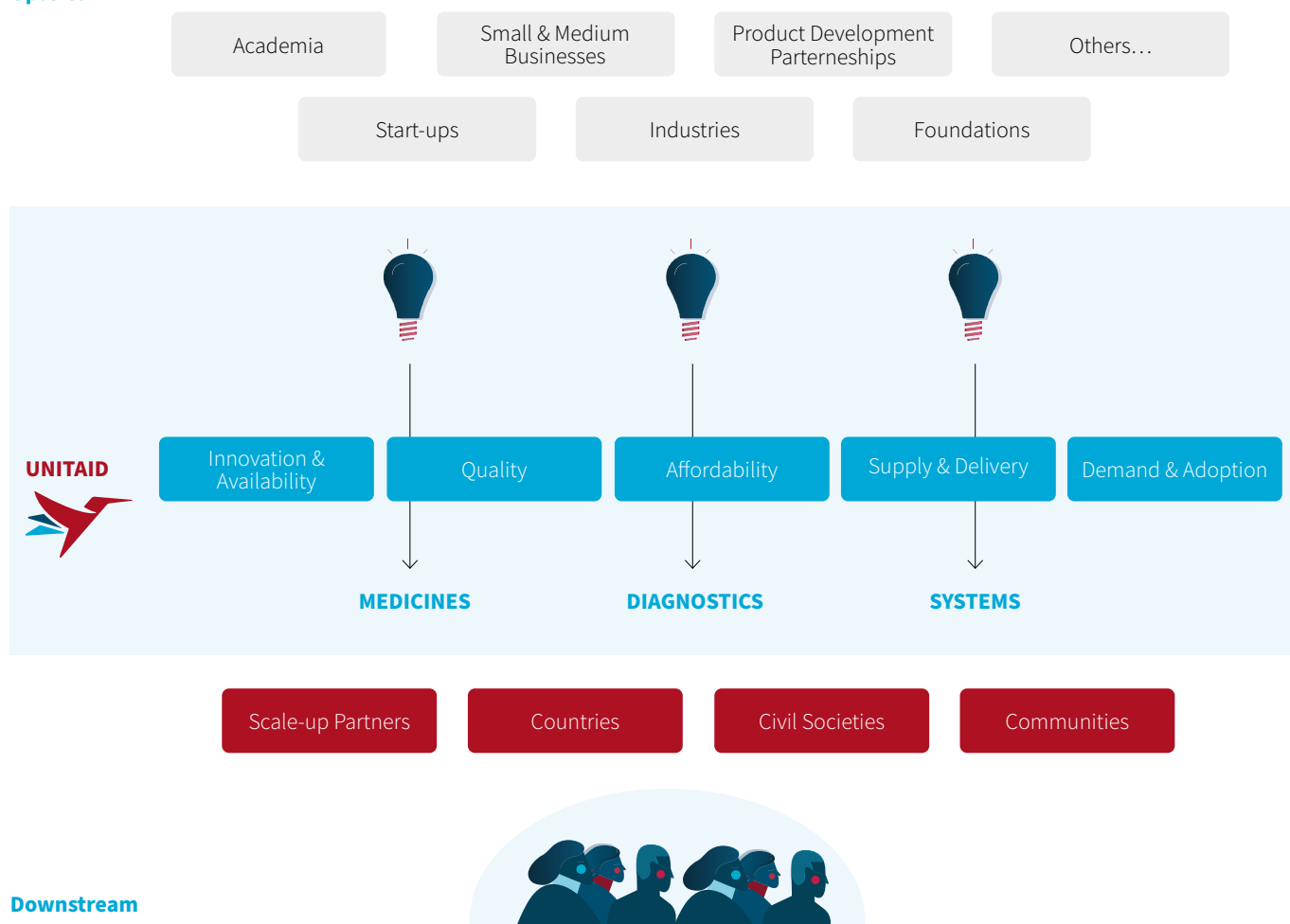
In spite of these achievements and those of other partners, a number of challenges remain or have become more prominent, now that several of the initial challenges are being overcome – see sections 3.1 and 3.2.

## **2.10 Global partners' landscape in HCV**

The number of partner organizations working on hepatitis C, though relatively limited<sup>27</sup>, is increasing. Visibility on their roles is key to identifying critical gaps and to ensuring that Unitaïd's interventions help to optimize the global response. Figure 4 shows Unitaïd's role in the global response vis-a-vis other up-and-downstream actors.

**FIGURE 4:** Unitaid's role in global health

**Upstream**



**Downstream**

Partners focused on upstream innovation are primarily industry, research institutes and academia – though, as noted in section 2, innovation is limited to a number of discrete opportunities. Product Development Partnerships (PDPs) are also playing a role (though there are no PDPs that work exclusively on hepatitis C or viral hepatitis); DNDi is conducting trials on sofosbuvir/ravidasvir, and FIND supports the development of better diagnostic tools.

Further downstream, WHO is working on normative guidance and quality assurance, and several partners work on demand generation and advocacy (World Hepatitis Alliance, Coalition Plus, the International Network of People who Use Drugs and other civil society organizations).

With respect to downstream delivery and scale-up, national Ministries of Health will have to be at the heart of the response – though many are still at the early stages of creating the necessary infrastructure and tools. Several partners are providing support for one or more aspects of delivery, such as programme design, implementation and research – including for instance the Agence Nationale de Recherches sur le Sida et les Hépatites Virales (ANRS), the Center for Disease Analysis (CDA), the Clinton Health Access Initiative (CHAI, through its Quick Start programme), US CDC, Partners in Health (PIH), and the Programme for Viral Hepatitis Elimination (PROVE) of the Task Force for Global Health, as well as WHO and several international, national and local NGOs and civil society organizations. Organizations such as the Global Fund and UNDP can assist countries with procurement.

Several of these actors receive support for some of their work from private foundations, such as the John C. Martin Foundation and the ZeShan Foundation, from funds such as EndHep2030, or from public funders, such as the UK's Department for International Development (DFID). Some pharmaceutical companies also support work to increase awareness and scale up testing for HCV.

Nevertheless, a major difference in HCV compared to HIV, TB and malaria is the more limited role of donors, foundations and funders in scaling up innovations – and, thus, the greater role that countries will have to play with regard to scaling up.

## 3 IDENTIFYING AND PRIORITIZING CHALLENGES

### 3.1 Challenges threatening progress towards global goals

Unitaid identified a comprehensive inventory of challenges that threaten achievement of global goals, as a framework for articulating and refining its focus in potential Areas for Intervention. This analysis was based on input from multiple sources (see box) and consultation with partners.

#### SOURCES USED TO DEVELOP THE LIST OF CHALLENGES

- Unitaid strategic insight and market intelligence resources (e.g. landscapes)
- Countries' implementation experiences and plans
- WHO's Global health sector strategy on viral hepatitis 2016-2021 and other WHO reports and guidelines on viral hepatitis
- Report on accelerating the elimination of viral hepatitis, by the Lancet Commission on Gastroenterology & Hepatology
- Reports by the World Hepatitis Alliance
- Reports and updates by CHAI, DNDi, MSF and TAG
- Learnings from Unitaid-funded projects on HCV
- Innovation pipelines of the private sector

Each input was checked, and partners were consulted, to avoid missing challenges/potential opportunities. Many challenges are interlinked, and there may be many root causes contributing to a single challenge. In some cases, similar challenges have been merged to reach an inventory that can be used as a framework for action.

This comprehensive inventory of challenges was grouped according to key categories:

- Case management: challenges relating specifically to either the diagnosis or treatment of HCV, or to a holistic approach to HCV case management.
- Prevention: challenges relating to preventing new infections, including in the context of health systems (a major route of HCV transmission in the past) or through practices such as injecting drugs use (a major current route of HCV transmission).
- Cross-cutting: Challenges which affect the HCV response as whole. This includes

health system challenges, challenges related to data and financing as well as social and environmental challenges, such as stigma and discrimination.

The inventory of challenges is shown in Figure 5, below. These challenges have evolved since the previous disease narrative, as some of the earlier bottlenecks have been or are being addressed through Unitaid interventions, as well as actions by partners.

**FIGURE 5:** Inventory of challenges related to HCV

**Case management**

<b>TREATMENT</b>	DAA's are not affordable everywhere (though prices are falling)	Key populations (e.g. PWIDs) are not reached or excluded	Restrictions on (re)-treatment	Lack of knowledge about dealing with treatment failure	DAAs not (yet) registered in many countries	No generics for some DAAs	Lack of pediatrics	DAAs not approved in pregnancy		
<b>DIAGNOSTICS</b>	Insufficient scaling up of testing	Tests (AB and confirmatory test) are expensive	Complex (and expensive) Dx algorithms	No clarity on cost-effective testing strategies for elimination	Need multiple/better POC tests	Lack of one-step diagnosis	Lack of demand for testing	Regulatory barriers for Dx	Questionable quality of some AB tests	Lack of POC fibrosis test

**Prevention**

<b>HEALTH SYSTEMS TRANSMISSION</b>	Unsafe injection practices in some countries	Other nosocomial transmissions in some countries	No proper medical waste & sharps management	Unsafe blood transfusions						
<b>TRANSMISSION OUTSIDE HEALTH SYSTEM</b>	Lack of harm reduction programmes	Ongoing sharing injection equipment etc. (PWIDs)	No vaccine	Lack of awareness of HCV and risk factors	Lack of prevention and treatment in prisons	Infection through sexual practices that involve blood, esp. among MSM				

**Cross-cutting**

<b>DATA, PLANNING AND FINANCING</b>	Lack of global collective action / donor funding	Insufficient domestic resources / fiscal space	Lack of solid data to inform planning, prioritization and investment	Lack of data as excuse for inaction	Lack of dedicated national strategy, programs, staff					
<b>HEALTH SYSTEMS</b>	Insufficient simplification / task sharing	Insufficient services for key & vulnerable populations	Lack of knowledge, awareness, capacity among health workers	Weak surveillance systems leading to poor data	LTFU between tests; insufficient linkage to care	Insufficient decentralization / integration eg w HR	Procurement & supply chain challenges Dx & Tx	Lack of forecasting		
<b>SOCIAL / ENVIRONMENTAL</b>	Laws criminalizing certain behavior / products	Stigma; Discrimination	Insufficient political will	Transmission via traditional (medical) practices, tattoos etc	Lack of knowledge where / how to access Dx or Tx					

**3.2 Reviewing challenges for possible Unitaid intervention**

Through a systematic application of four criteria to the inventory of challenges, Unitaid identifies a shortlist of challenges that represent the highest potential for Unitaid interventions. These four criteria are:

- **Potential public health impact:** focus on challenges for which there is strong evidence of high potential public health impact.
- **Feasibility:** focus on challenges for which the necessary technology can be available in the relevant timeframe.



- **Optimized use of resources:** focus on challenges for which critical gaps exist in the global response and where scale-up is possible.
- **Unitaid's expertise:** focus on challenges that affect commodity-access.

The subsequent sections provide a high-level overview/rationale why certain challenges were deprioritized as potential focus areas for Unitaid interventions, followed by the remaining priority challenges. Challenges that Unitaid could potentially address are highlighted in bold. The sections follow the categories of challenges presented in Figure 5.

### 3.2.1 Treatment

As described above, in many LMICs, DAA prices have become much more affordable (with the price of a cure for HCV now being comparable to one year of HIV therapy) due to the availability of generic medicines. While not all MICs can access generic DAAs, work is ongoing to address this, including in and by countries.

Furthermore, many actors are already working to address several of the other gaps; for example, research institutes and industry are conducting trials regarding the use of DAAs in pregnancy and in children, and DAAs are increasingly being registered in countries (sometimes following encouragement by Unitaid projects or other partners).

Remaining priority challenges:

- Contrary to WHO guidance, **key populations, such as people who inject drugs (PWIDs) or prisoners, are often not reached** by testing and treatment programmes, or are intentionally excluded. In addition, in several countries or settings, restrictions on treatment of certain groups may be in force or implemented; this may include restrictions on re-treatment of people who are reinfected. This results in lack of access for some of the most vulnerable populations, and hampers elimination efforts, as the incidence of new HCV cases often is high among these populations.
- A further challenge is the lack of clarity on treatment options for those who do not achieve cure (cases of treatment failure). While, with cure-rates of around 95%, this is a relatively small proportion of patients, it will nevertheless be important that effective second-line regimens/options are identified and included in guidelines.

### 3.2.2 Diagnosis

While the availability of a short and safe cure for HCV infection has galvanized the HCV response, diagnosis has remained a major bottleneck. Multiple challenges hamper access to HCV testing, including the fact that several tests are required and that it is relatively expensive. In some countries, the cost of the required testing surpasses that of treatment. This is partly due to the cost of the various tests, but is at times aggravated by the fact that countries have not yet simplified the diagnostic algorithm as much as they could.

Several partners, including partners funded by Unitaid, are already working on the development of more suitable and affordable tests, on the quality of HCV tests, on addressing regulatory barriers, and on generating demand for testing. Nevertheless, a further boost will be required to overcome some of the interrelated challenges pertaining to diagnosis.

There is no clarity yet on cost-effective testing strategies that would lead to elimination – though it is expected that WHO will develop such strategies, once sufficient country experiences and data will be available.

A point-of-care fibrosis test could, potentially, further facilitate the decentralization of care. Unitaid will monitor this.

Remaining priority challenges:

- **Insufficient scaling up of HCV testing** has been identified as one of main challenges for achieving elimination of hepatitis C<sup>28</sup>. Its underlying causes include insufficient awareness about HCV, a lack of resources, a lack of demand and the relatively high cost of the testing algorithm.
- **The lack of an affordable, one step diagnostic test** for use at the **point of care** is another important challenge, as the multi-step diagnostic algorithm leads to people dropping out (loss to follow-up). Through one of its projects, Unitaid supports the development of such a test; if technically feasible, it will be important to accelerate its launch and maximize the benefits of such a test in helping to address some of the main challenges in HCV<sup>29,30</sup>.

### 3.2.3 Prevention of transmission through the health system

Medical procedures – including, among others, injections or other invasive procedures carried out with poorly sterilized medical or dental equipment and unsafe blood transfusions – used to be a major source of HCV infection. Due to the relatively long time between infection and the development of liver disease, it is likely that many of the current HCV infections can be attributed to past nosocomial infection. However, according to WHO, currently these are no longer major contributors to new HCV infections globally (though there are some notable exceptions, in particular some of the countries in the WHO Eastern Mediterranean region).<sup>31,32</sup>

The lack of proper management of infectious medical waste (e.g. waste contaminated with blood) and sharps (such as needles) can contribute to spreading a range of infections, including HCV.<sup>33</sup> WHO is working with countries to improve the management of such waste, though more could be done. Unitaid will monitor developments in this area.

There are no priority challenges in this category that are immediately relevant for Unitaid.

### 3.2.4 Prevention of transmission outside the health system

While transmission through medical procedures is, in most locations, no longer the main cause of new infections, an estimated 1.75 million new infections do occur every year. High incidence is seen among people who inject drugs, as well as prisoners, people living with HIV and certain indigenous communities. It is generally linked to the sharing or re-use of equipment for injecting, piercing or cutting skin. Low awareness of the risks and the lack of access to sterile equipment are fueling this.

Partners such as the World Hepatitis Alliance and its member organizations, the World Health Organization, and projects funded by Unitaid are already working on the low awareness about HCV, its mode of transmission and risk factors, though their focus on key populations varies.

An effective vaccine to prevent infection, or re-infection, would be a very useful additional tool to reducing HCV incidence, especially among high risk groups. Unfortunately, no such vaccine is expected in the foreseeable future<sup>34</sup>.

Remaining priority challenges:

- The **lack of harm reduction programmes** perpetuates the ongoing high rates of transmission and new infections among people who use drugs. Even where harm

reduction programmes exist and are accessible, the number of needles and syringes provided is often insufficient<sup>35,36</sup>; this may contribute **to ongoing sharing of injection equipment – and HCV infection – among PWIDs**. It is noteworthy that the sharing of other paraphernalia (e.g. spoons, filters, inhalation equipment) also can result in transmission of HCV infection.<sup>37,38</sup>

- Generally, HCV prevalence and incidence is also high in prisons – yet **few prisons have programmes for HCV prevention, treatment and awareness raising**. This is a missed opportunity, because case-finding should be relatively easy/effective in prison-settings, and curing HCV-positive inmates would prevent that they, unwittingly, transmit the infection upon release.
- Sexual transmission of HCV, though uncommon, is seen among MSM. Though previously believed mainly to affect HIV+ MSM, reports are starting to emerge about increasing numbers of sexually transmitted illnesses – including HCV infections – in HIV-negative MSM on PrEP<sup>39</sup> (when they engage in sexual practices that involve blood).

### 3.2.5 Data, planning and financing

Several donors and partners support work on HCV; however, major external or donor funding – comparable to that provided through the Global Fund and PEPFAR for HIV, TB or malaria – is unlikely to materialize within the next few years. Scaling-up will therefore mostly have to be funded from countries' domestic resources.

Partners such as WHO and CHAI are assisting countries with the development of national strategies and plans. They are also helping countries to develop better estimates of the disease burden and realistic cost estimates. Partners, including Unitaid projects, have also assisted some countries with the development of an investment case.

Remaining priority challenges:

- The lack of major, external funding for viral hepatitis means that **countries will have to fund the scaling up** of HCV diagnosis, treatment and testing from domestic resources. While the momentum is growing, and the number of countries that provide funding and dedicated staff for viral hepatitis/HCV is increasing, the process **will take time**.
  - By implication, for Unitaid's HCV investments to achieve their full potential and be scaled-up/rolled out, Unitaid may have to provide some support for the initial uptake or roll-out in some countries.

### 3.2.6 Health systems

Multiple challenges relate to the provision of HCV diagnostic and treatment services, reflecting the fact that, until recently, these were complex and only available in tertiary hospitals but were not part of mainstream public health services. Unitaid already funds projects that, working in tandem with partners such as WHO and CHAI, aim to increase knowledge and capacity among health workers. These and other partners are also working with countries to strengthen surveillance, address supply-chain challenges and improve forecasting.

Integration of HCV diagnosis and treatment with existing services, though challenging, can help to optimize the use of resources and lead to overall efficiencies. Examples include integration with ART services, which has been pioneered/demonstrated by Unitaid with MSF and with FIND.

Remaining priority challenges:

- **Insufficient** implementation of simplified algorithms (as recommended by WHO) that enable **task sharing, decentralization and integration**, including **insufficient**

**integration with harm reduction services**, limits the number of people with chronic HCV infection that are reached, diagnosed and cured.

- **Loss to follow-up** between different tests that are required, as well as insufficient linkage to care, poses an important challenge in many countries. As a result, a proportion of the people that are accessing screening, miss out on getting cured.
- As mentioned earlier, the provision of **services to key and vulnerable populations** (including prison populations) has remained **insufficient**.

### 3.2.7 Social and environmental factors

Social and environmental factors significantly affect the risk of HCV infection. For example, the criminalization of injecting drug use leads to people hiding their behavior and hampers (or makes impossible) the provision of harm reduction services. It makes it harder for PWIDs to access clean needles and syringes and thus increases the likelihood of re-use and sharing injection equipment – which entails a significant risk of contracting or spreading HCV. Criminalization also means PWIDs may face incarceration, and is probably a factor that contributes to relatively high HCV prevalence in prison populations.

Stigma and discrimination – including because of the association with drug use – affect individuals and their care seeking behavior. They also contribute to hepatitis not being talked about much, thus contributing to the lack of knowledge and awareness. Furthermore, all of these factors contribute to a lack of political will to address HCV.

A further compounding factor is the potential for HCV infection to spread through a broad range of “traditional” medical or non-medical practices that do or can involve contact with blood, if the utensils used are not or not sufficiently sterilized. Examples include injections by traditional healers, circumcision practices, tattoos and body piercings.

The above issues and challenges are fundamental to HCV transmission. Partners are working, both within countries and at international level, to try to address these, though more could be done.

Unitaid can help address or mitigate some of these challenges, through its projects, though the primary focus would be on increasing demand for and access to innovative tools and approaches for testing, treatment or prevention of HCV infection.

### 3.3 Priority challenges for possible Unitaid intervention

Through the prioritization process described in section 3.2, a number of outstanding challenges that potentially fit with and that could be addressed by Unitaid have been identified. These are shown in Figure 6.

**FIGURE 6:** Overview of outcome of the filtering process

**Case management**


<b>TREATMENT</b>		Key populations (e.g. PWIDs) are not reached or excluded	Restrictions on (re)-treatment	Lack of knowledge about dealing with treatment failure				
<b>DIAGNOSTICS</b>	Insufficient scaling up of testing	Tests (AB and confirmatory test) are expensive		No clarity on cost-effective testing strategies for elimination		Lack of one-step diagnosis	Lack of demand for testing	Lack of POC fibrosis test

**Prevention**

<b>HEALTH SYSTEMS TRANSMISSION</b>			No proper medical waste & sharps management					
<b>TRANSMISSION OUTSIDE HEALTH SYSTEM</b>	Lack of harm reduction programmes	Ongoing sharing injection equipment etc. (PWIDs)			Lack of prevention and treatment in prisons		Infection through sexual practices that involve blood, esp. among MSM	

**Cross-cutting**

<b>DATA, PLANNING AND FINANCING</b>			Lack of solid data to inform planning, prioritization and investment					
<b>HEALTH SYSTEMS</b>	Insufficient simplification / task sharing	Insufficient services for key & vulnerable populations		LTFU between tests; insufficient linkage to care	Insufficient decentralization / integration eg w HR			
<b>SOCIAL / ENVIRONMENTAL</b>								

 To monitor

Note: 'Monitor' refers to cases where there may be potential for a market-based approach, but further exploration is needed.

## 4 POTENTIAL OPPORTUNITIES

Based on the prioritization process described in section 3.2 and 3.3 and validated with key partners, a number of outstanding challenges have been identified that are high priorities for the HCV response and that Unitaid could potentially contribute to (see Figure 6). As most of these challenges relate to a few common themes, they have been combined into the following broader potential opportunities/areas for further investigation<sup>40</sup>:

- **Demonstrate feasibility of treatment and prevention of HCV among key populations**, notably PWIDs and prisoners. Through HCV testing, treatment and harm reduction services tailored to their needs, these populations can be reached. Eliminating HCV among key populations, in whom prevalence and risk are high, would also be an important step in reducing the number of new infections.
- **Integrate HCV testing and treatment** in other services, including harm reduction services. This can help reach more people and make HCV testing and treatment more efficient and cost-effective. This, in turn, can facilitate action, and the allocation of resources, by countries. It can also help Unitaid to develop and pioneer new models of scaling-up.
- **Expand HCV testing** to find people with chronic infection. Tools for diagnosing HCV exist and better tools that allow for testing closer to the point of care or interaction are being developed. Accelerating their introduction and supporting countries to make optimal use of them and to tackle HCV, will both support HCV elimination and help prevent future deaths from liver cancer<sup>41</sup>.
- **Retain people in care** by ensuring that those with chronic HCV infection can complete the testing algorithm and be linked to treatment. Unitaid is already working on this, including through its support for the development of a HCV cAg RDT test and a potential long-acting treatment (a ‘one-shot cure’). Together, these tools could help reduce loss to follow-up.

It should be noted that these opportunities are subject to change in light of the dynamic nature of commodity markets, changes in partner activities, or other factors.

# ANNEX I

The table below presents those service delivery targets not included in table 1 (section 2.3), together with the current status, as per WHO's progress report on HIV, viral hepatitis and sexually transmitted infections, 2019.<sup>42</sup>

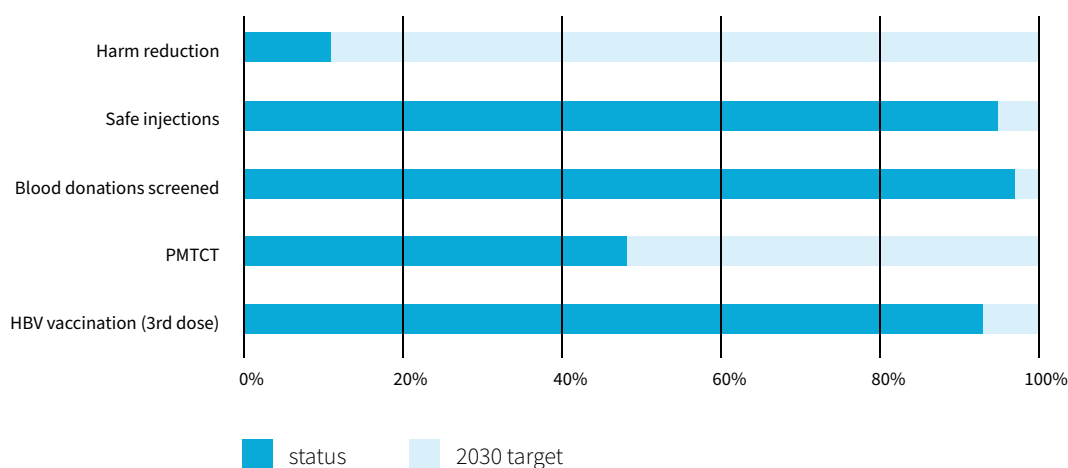
	DESCRIPTION OF TARGET	CURRENT STATUS	2020 TARGET	2030 TARGET
MOSTLY HCV	Harm reduction number of (sterile needles and syringes provided per person who injects drugs per year)	33	200	300
	Safe injections	86%*	50%	90%
HBV & HCV	Blood safety (% of donations screened)	97%	95%	100%
HBV	Prevention of hepatitis B virus mother-to-child transmission (birth dose or other approach)	43%	50%	90%
	Hepatitis B virus vaccination (childhood vaccine coverage (third dose coverage))	84%	90%	90%

\*Estimate, based on 3.9% reuse of injection equipment in 2017.<sup>45</sup>

The graph below shows the current status versus the 2030 target, based on the data above. Clearly, there is a major gap with regard to harm reduction (which mostly affects HCV).

In addition, progress is lags behind regarding the prevention of mother to child transmission of HBV.

## Progress toward 2030 service delivery targets for HBV and HCV



## ENDNOTES

1. WHO. What is hepatitis? July 2018.
2. Hepatitis D also spreads in this way. By contrast, hepatitis A and E are typically caused by ingestion of contaminated food or water. Hepatitis B can also be transmitted from mother to child.
3. Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG et al. Global distribution and prevalence of hepatitis C virus genotypes. *Hepatology*. 2015;61(1):77-87.
4. Platt et al., Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. *Lancet Infect Dis*. 2016. 16(7):797-808.
5. WHO Global Hepatitis Report, 2017
6. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3035774/>
7. Unitaid/WHO Technology and Market Landscape for Hepatitis C Medicines. August 2017
8. WHO Global Hepatitis Report, 2017
9. WHO. Global health estimates 2015: estimated deaths by age, sex and cause.
10. WHO Global Hepatitis Report, 2017.
11. WHO. Progress report on HIV, viral hepatitis and sexually transmitted infections, 2019. Accountability for the global health sector strategies, 2016–2021.
12. Target 3.3 reads “By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases”.
13. Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis. WHO, 2016.
14. Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis. WHO, 2016.
15. WHO. Progress report on access to hepatitis C treatment. Focus on overcoming barriers in low- and middle-income countries, March 2018.
16. WHO Global Hepatitis Programme and Center for Disease Analysis.
17. WHO. Progress report on access to hepatitis C treatment. Focus on overcoming barriers in low- and middle-income countries, March 2018.
18. Several candidate vaccines are in early stages of development, but it will reportedly still take many years until they could be ready for use. See Cooke et al., Accelerating the elimination of viral hepatitis: a Lancet Gastroenterology & Hepatology Commission. *Lancet Gastroenterol Hepatol*. 2019. 4: 135–84.
19. Cooke et al., Accelerating the elimination of viral hepatitis: a Lancet Gastroenterology & Hepatology Commission. *Lancet Gastroenterol Hepatol*. 2019. 4: 135–84.
20. WHO. Progress report on HIV, viral hepatitis and sexually transmitted infections, 2019. Accountability for the global health sector strategies, 2016–2021
21. Cunningham C. Accelerating the elimination of viral hepatitis for Indigenous peoples. *Lancet Gastroenterol Hepatol*. 2019. 4: 93–94.
22. Due to the high burden, hepatitis C became a political priority in these countries.
23. Smith et al. Global progress on the elimination of viral hepatitis as a major public health threat: An analysis of WHO Member State responses 2017.
24. WHO. Access to hepatitis C testing and treatment for people who inject drugs and people in prisons — a global perspective. April 2019.
25. The project used Unitaid funding for treatment of the target population (HIV/HCV co-infected people), complemented by MSF-funding for the treatment of those with HCV mono-infection.
26. Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. WHO, 2018.
27. At least in comparison to the partner landscape in HIV, TB or malaria.
28. World Hepatitis Alliance. Overcoming the Barriers to Diagnosis of Viral Hepatitis: The Role of Civil Society and the Affected Community in Finding the Missing Millions. 2018.
29. It can help find more people with chronic HCV (including people who do not have easy access to health facilities with laboratory infrastructure) as well as reduce the loss to follow-up. This would be particularly relevant for people who inject drugs.
30. In addition, the technology pioneered to develop this test can probably be adapted for other diseases. Of particular interest would be the potential development of a simple HBeAg RDT for use in antenatal clinics, where it could play a role in preventing mother-to-child transmission of HBV – currently the main gap in the prevention of hepatitis B (see Annex 1). A positive HBeAg result indicates active replication of HBV and high infectivity. The risk of vertical transmission of HBV is therefore greatest in pregnant women that are HBeAg+, but currently there is no simple, rapid point-of-care test for the HBeAg to identify these women. The technology can also potentially be adapted to an RDT for the HIV p24 antigen (to facilitate early infant diagnosis of HIV).
31. Injection safety has significantly improved in many countries, but remains important in some countries, notably in the Eastern Mediterranean region. [WHO Global Hepatitis report 2017]
32. Unsafe blood transfusions still are a concern in some countries, mostly due to irregular supply of test kits [WHO Global Hepatitis report 2017].



33. Medical waste is however not known to be a major cause of HCV infection. WHO GHP, verbal communication.
34. In the absence of a vaccine that prevents HCV infection, treating and curing people with chronic HCV is an important prevention measure.
35. WHO. Progress report on HIV, viral hepatitis and sexually transmitted infections, 2019. Accountability for the global health sector strategies, 2016–2021.
36. Larney S, et al. Global, regional, and country-level coverage of interventions to prevent and manage HIV and hepatitis C among people who inject drugs: a systematic review. *Lancet Glob Health*. 2017;5:e1208–20.
37. WHO. Guidance on prevention of viral hepatitis B and C among people who inject drugs, 2012.
38. WHO. Guidelines for the screening, care and treatment of persons with chronic hepatitis C virus infection. WHO, 2016.
39. See for example Hoornenborg et al. MSM starting pre-exposure prophylaxis are at risk of hepatitis C virus infection. *AIDS*, July 2017 and Price et al. Sexually acquired hepatitis C infection in HIV-uninfected men who have sex with men using pre-exposure prophylaxis against HIV. *J Infect Dis*, Nov 2018.
40. Please note: Further analysis and partner consultation is needed before these exploratory areas can be presented to the Board of Unitaid for funding-decisions.
41. In addition, a specific opportunity, that builds on Unitaid's work in HCV diagnostics, has been identified: the potential development of an HBeAg RDT, see endnote 30.
42. WHO. Progress report on HIV, viral hepatitis and sexually transmitted infections, 2019. Accountability for the global health sector strategies, 2016–2021.

