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**Adapted from pre-read for Agenda item N° 11**

## **HIV/HCV co-infection strategic narrative**

**For Information**  **For Review and Advice**  **For Decision**

## Executive summary

Until recently, diagnosis and treatment of HCV was complex. Suitable tools for screening and diagnosis were lacking, and treatment was hampered by limited efficacy and severe side effects.

New medicines for the treatment of HCV have revolutionized HCV treatment. Combinations of these new medicines, which are generally well-tolerated and effective, can cure HCV in 12 weeks. This offers a huge opportunity to address HCV, in particular among HIV/HCV co-infected people, who are more vulnerable as they progress faster to serious disease than HCV mono-infected people.

Nevertheless, these new treatments do not reach people, due to their high costs and because services to diagnose and treat HCV are limited or non-existent in many countries. In addition, there is a lack of reliable point-of-care HCV tests. The lack of suitable tests contributes to a lack of surveillance and epidemiologic data, which hamper planning and allocating resources for HCV services.

But though there are no accurate data on the magnitude of the HCV epidemic, it is clear that millions are affected. The number of deaths due to HCV is increasing and reached 700 000 in 2013.

Increasing awareness about the scale of the problem and the rising death toll, as well as of the fact that effective cures now exist have led WHO to propose an ambitious goal: elimination of viral hepatitis as a public health problem. The adoption of this goal, and the targets and milestones to reach it, is expected to take place at the World Health Assembly in May 2016.

UNITAID has identified a comprehensive list of challenges the response is facing to reach global goals. These challenges were identified through the following steps:

- Analysis of partners' strategies
- Review of relevant UNITAID's landscapes
- Engagement with partners

Based on this list UNITAID has identified preliminary indications of potential Areas for Intervention (AfIs), or areas to consider, using the following criteria:

- a. UNITAID's expertise: focus on challenges that are inherently commodity access issues
- b. Potential public health impact: focus on challenges for which there is strong evidence of high potential public health impact
- c. Feasibility: focus on challenges for which the necessary technology can be available in the relevant timeframe
- d. Optimized use of resources: focus on challenges for which critical gaps exist in the global response and where scale up is possible

These areas to consider will be refined with partners and developed into Areas for Intervention to be presented to the Board for endorsement in 2016. At this stage, these are intended to be directional only and are subject to change.

Four areas to consider were identified:

### 1. Address the lack of epidemiological data and guidelines

The lack of epidemiological data and the absence of clear guidance for screening, diagnosing and treating hamper the ability of governments to develop effective strategies and plans to address HCV. The lack of clarity on how many people to screen and treat also makes it difficult to allocate resources to HCV diagnosis and treatment.

Better epidemiological data and guidance would mean more clarity on the needs, ability to plan for the provision of services and allocate resources. As a result, services to diagnose and treat HCV infection at the national level become available.

## **2. Find innovative ways to unlock funding for HCV**

To date, international donors offer limited support for HCV treatment; the primary funders of HCV treatment are likely to be national governments. Several low- and middle-income countries are exploring ways to fund treatment for hepatitis C.

By unlocking funding for HCV, innovative funding options would enable the provision of services to diagnose and treat HCV infection at the national level. As a result, the market for HCV commodities will expand. Larger volumes would enable economies of scale and make price reductions feasible.

## **3. Increase affordability and adaptability of HCV medicines**

Medicines to cure HCV are expensive. Price reductions and voluntary licenses are in place for some medicines but not for all components of the pan-genotypic regimen.

Increased affordability would mean more people will be able to access HCV treatment and get cured. Purchases of HCV medicines will increase; the larger volumes will enable economies of scale and make further price reductions feasible.

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# 1 Analysis of disease context

## 1.1 Disease introduction

Hepatitis C is a blood-borne disease currently widely under-diagnosed and untreated, especially in low- and middle-income countries<sup>1</sup>. According to the WHO, between 130 and 150 million people globally suffer from chronic HCV infection<sup>2</sup>. One third of those who become chronically infected are predicted to develop liver cirrhosis or hepatocellular carcinoma.<sup>3 4</sup> According to the Global Burden of Disease Study, an estimated 700 000 persons died in 2013 from HCV-related liver disease.<sup>5</sup>

Hepatitis C is caused by a virus; there are six major genotypes of the hepatitis C virus (HCV). HCV is primarily transmitted through exposure to infected blood, such as through transfusion with infected blood or blood products, contaminated needles used in medical procedures, and sharing of needles among injecting drug users. Through bloodborne routes, transmission is 10 times more efficient for HCV than for HIV.<sup>6</sup>

Hepatitis C is found worldwide. Though data are limited, the prevalence and burden of HCV varies considerably between regions; the most affected regions appear to be Africa and Central and East Asia.<sup>7</sup> Depending on the country, hepatitis C infection can be concentrated in certain populations (for example, people who inject drugs or prisoners).<sup>8</sup>

Worldwide, approximately 2.3 million people are co-infected with HIV and HCV<sup>9</sup>; HIV+ people are nearly 6 times more likely to be infected with HCV than people who are not HIV+<sup>10</sup>.

People living with HIV (PLHIV) who also contract HCV suffer increased rates of liver diseases, increased risk of mortality, and increased treatment complications due to liver damage and toxicity. For example: cirrhosis of the liver is as much as three times higher in co-infected versus mono-

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<sup>1</sup> WHO, Hepatitis: Frequently Asked Questions

[http://www.who.int/csr/disease/hepatitis/world\\_hepatitis\\_day/question\\_answer/en/](http://www.who.int/csr/disease/hepatitis/world_hepatitis_day/question_answer/en/) Accessed 29 January 2015.

<sup>2</sup> WHO Hepatitis C Factsheet, <http://www.who.int/mediacentre/factsheets/fs164/en/> Accessed 29 January 2015. However, see also section 4.1.1.5.

<sup>3</sup> WHO Hepatitis C Factsheet, <http://www.who.int/mediacentre/factsheets/fs164/en/> Accessed 29 January 2015.

<sup>4</sup> Guidelines for the screening, care and treatment of persons with hepatitis C infection. Geneva: World Health Organization; 2014 (<http://www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en>, April 2014).

<sup>5</sup> GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;385(117-71).

<sup>6</sup> Global policy report on the prevention and control of viral hepatitis. Geneva: World Health Organization; 2013.

<sup>7</sup> Gower E et al.(2014); Hepatitis C. Fact sheet No 164 (updated). Geneva: World Health Organization; 2015.

<sup>8</sup> The Gap report, UNAIDS (2015), Hepatitis C. Fact sheet No 164 (updated). Geneva: World Health Organization; 2015.

<sup>9</sup> Platt L et al. Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. *Lancet Infect Dis*. February 2016.

<sup>10</sup> 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*. February 2016.

infected HCV.<sup>11</sup> Co-infected people also have increased risk of kidney diseases, including acute renal failure, and of cardiovascular illnesses.<sup>12</sup>

## 1.2 Global goals

While there are no specific goals or targets related to co-infections, there is a need to address them to both meet the targets the international community has set for treating HIV and HCV separately, as well as to meet UNITAID's strategic objectives.

UNAIDS has already set an ambitious target of achieving 90% of people living with HIV diagnosed, 90% of diagnosed people on treatment, and 90% of those on treatment virally suppressed by 2020<sup>13</sup>. The World Health Organization is proposing similar goals– 90% diagnosed, 90% of eligible people treated, and 90% of those cured by 2030 – for hepatitis C; it is expected that these goals will be adopted by the World Health Assembly in May 2016.

On 25 September 2015, world leaders adopted an Agenda for Sustainable Development, including the Sustainable Development Goals, which include combatting hepatitis in one of the targets.<sup>14</sup>

## 1.3 New breakthroughs but large gaps in commodity access

### 1.3.1 Treatment

Until recently, the standard treatment for HCV involved ribavirin plus weekly injections of pegylated interferon (Peg-IFN). Treatment lasted 24-48 weeks depending on the genotype. This treatment has suboptimal efficacy, poorer efficacy among patients with certain genotypes, and among HIV/HCV co-infected people. It often has severe side-effects that make the treatment intolerable for many patients. Diagnosis of HCV and treatment monitoring were also complex, requiring multiple different tests, though this was in part attributable to the limited efficacy and serious side effects of treatment with Peg-IFN and ribavirin.

HCV can now be cured with a combination of direct-acting antiviral medicines (DAAs). The development of DAAs is a breakthrough for HCV treatment. These medicines can be taken orally, are generally well-tolerated and effective, and cut treatment time to 12 weeks. Cure rates are around 90%, including in people living with HIV.

The price of DAAs is high and beyond what people and health systems in LMICs can afford. Sofosbuvir is emerging as the backbone of HCV treatment; Gilead's best price for sofosbuvir in low- and middle-income countries is US\$900 in Egypt for a 12-week treatment course (US\$300 per one month box).

### 1.3.2 Diagnostics

HCV often remains undiagnosed until patients present at health care-facilities with the symptoms of advanced liver disease, including liver cancer. A major diagnostic challenge is the lack of suitable

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<sup>11</sup> <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3035774/>

<sup>12</sup> <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3035774/>

<sup>13</sup> [http://www.unaids.org/sites/default/files/media\\_asset/90-90-90\\_en\\_o.pdf](http://www.unaids.org/sites/default/files/media_asset/90-90-90_en_o.pdf)

<sup>14</sup> 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”.

point-of-care tools for diagnosing HCV/HIV co-infection. The current diagnostic tools, which are a prerequisite for accessing HCV treatment, are sub-optimal. The options are reliable tests that require expensive equipment that is usually only available in centralized laboratories that are not accessible to many people, or rapid tests whose quality and reliability is often unclear. Existing rapid screening HCV tests perform less well in patients co-infected with HIV and HCV. This makes it challenging to identify, diagnose and treat HCV infection in people living with HIV.

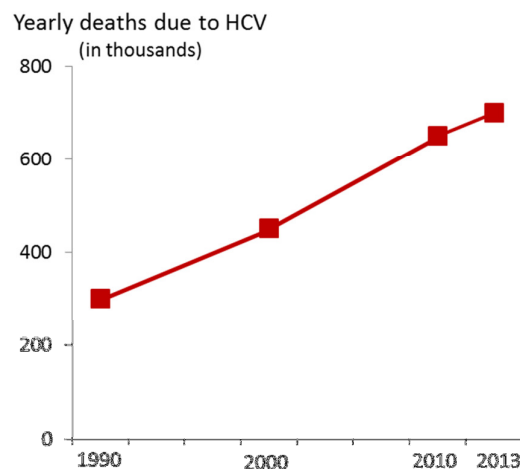
#### 1.4 Lack of data on the epidemiology

The lack of suitable tests also is one of the factors that perpetuates the lack of accurate information as to the extent of the epidemic. This, in turn, hampers adequate planning, response and resource allocation, as well as market visibility. Indeed, one of the key challenges is the lack of accurate epidemiological information. Recent publications estimate that:

- Between **115 and 180 M** people are infected with HCV;
- Between **80 and 150 M** of them are suffering from chronic HCV infection.<sup>15</sup>

However, one thing is clear: the number of people dying from HCV each year is increasing as shown in figure 1:

**Figure 1.** Deaths due to HCV<sup>16</sup>



Source of data: the Global Burden of Disease

This increasing mortality contrasts with a general trend of decreasing mortality that is seen in most of the major infectious diseases.<sup>17</sup>

<sup>15</sup> Mohd Hanafiah et al. (2013), Lavanchy et al. (2011), Gower et al. (2014)

<sup>16</sup> Source of data: The Global Burden of Disease.

<sup>17</sup> Based on Stanaway et al (2015).



## 1.5 Innovation

The main challenge is not that we don't have the tools but that we are not able to reach the people who need them:

- The lack of reliable epidemiological data means it is often not well-known who is most at risk of HCV infection and where HCV-infected people are. This, combined with the lack of systems and suitable tools to screen for and diagnose HCV, results in many people not being diagnosed.
- Among those diagnosed with chronic HCV infection, it is not clear who is eligible for treatment, due to a lack of guidance.
- Because of the lack of systems or programs for HCV treatment and care as well as the high cost of medicines, many eligible people cannot access treatment.
- However, a high percentage (> 90%) of those that manage to access treatment do get cured. This even applies to HIV/HCV co-infected people – who in the pre-DAA era had significantly lower rates of successful treatment than HCV mono-infected people.

### Key messages:

- The scale of the HCV epidemic is not well-known, but the number of deaths is increasing
- HCV is concentrated in certain vulnerable populations
- It is estimated that approximately 2.3 million HIV+ people are co-infected with HCV; they progress faster to serious liver disease
- New treatments are available that can cure HCV in 12 weeks, but treatment is expensive
- Pan-genotypic treatments will decrease the complexity of testing
- Services to diagnose and treat HCV are lacking in many countries
- Moreover, HCV is under-diagnosed due to lack of suitable tools
- This contributes to the lack of data on who to treat, where and when

## 2 Partner landscape in HCV

Until recently, there was limited attention for hepatitis C. However, this is changing due to a growing awareness about the increasing HCV-related mortality and the launch of new treatments that can cure HCV; partners are increasingly developing strategies and planning actions to contribute to the fight against HCV. For example, DNDi intends to advance the development of combinations of medicines from different companies to optimize treatment, FIND has started exploring the HCV diagnostic pipeline, and CHAI is assisting several countries with planning and the identification of resources for diagnosis and treatment of HCV (as shown in figure 2).

Brazil and Egypt have already set up national HCV treatment programs. A growing number of governments in other low- and middle-income countries is considering or starting the implementation of treatment at national level. However, unlike HIV, treatment for HCV will not be able to rely on significant donor funding; rather, countries will have to identify and rely on their own resources fund the response to HCV.

**Figure 2.** Partners mapping

### 3 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 consultation with partners and input from multiple sources, as mentioned in the Box below.

**List of sources used to develop list of challenges:**

- UNITAID strategic insight and market intelligence resources (e.g. landscapes, dashboard)
- Countries strategies and plans
- Prevention & Control of Viral Hepatitis: Framework for Global Action (2012) and the Draft Global Strategy on Viral Hepatitis 2016-2021 by WHO
- The Global Fund reports on hepatitis C and co-infections/co-morbidities, Board Meeting, November 2014 and March/April 2015.
- FIND strategy 2015-2020
- A public health approach to hepatitis C using direct acting antivirals (DAAs) by DNDi
- MSF Diagnosis and treatment of hepatitis C: A technical landscape. April 2014
- Innovation pipelines of the private sector

Each input was checked, and partners consulted, to avoid missing potential opportunities. Many challenges are interlinked, and there may be many root causes contributing to a single challenge. In

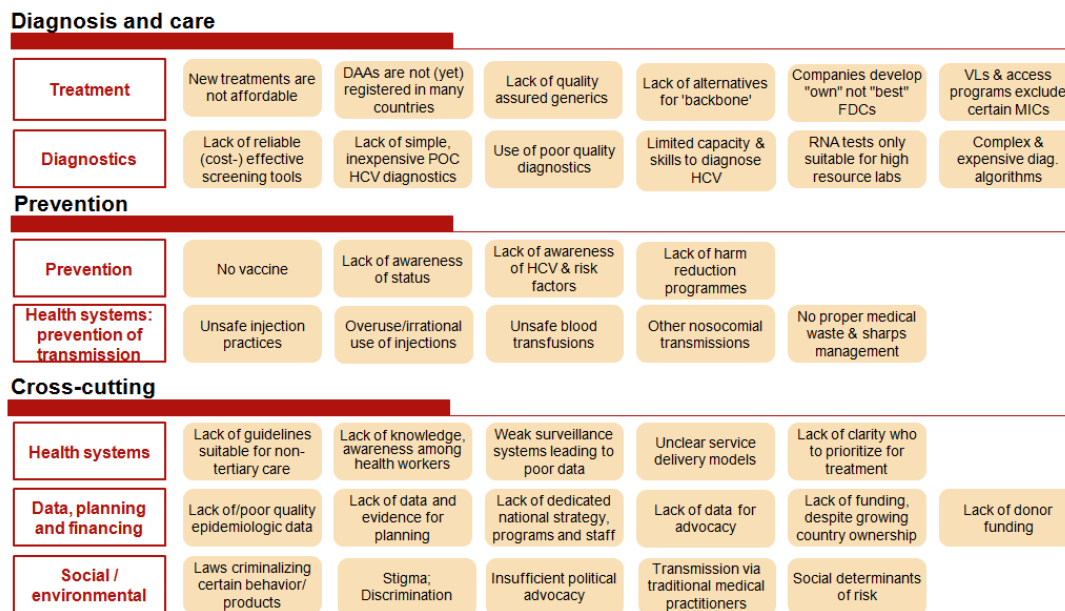
some cases, similar challenges have been merged to reach an inventory that can be used as a framework for action.

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

- **Diagnostics and care:** A holistic, patient-centered approach to diagnosis and care is essential to optimize individual patient outcomes and reach overall public health goals. Challenges related to treatment (medicines), diagnosis and screening (screening and diagnostic tools) are described here.
- **Prevention:** As health systems can play a major role in the spread of HCV, a separate sub-category was created for health-system-related prevention.
- **Cross cutting:** Those health system challenges that are not related to prevention were listed under cross-cutting – and as many of them related to (the lack of) data, planning and financing, these were combined in a separate sub-category.

The complete inventory of challenges is shown in figure 3. Description of challenges is available in appendix 1.

**Figure 3.** Challenges inventory



Four criteria were then applied to the inventory of challenges with the aim of focusing on challenges:

1. UNITAID's expertise: focus on challenges that are inherently commodity access issues
2. Potential public health impact: focus on challenges for which there is strong evidence of high potential public health impact
3. Feasibility: focus on challenges for which the necessary technology can be available in the relevant timeframe
4. Optimized use of resources: focus on challenges for which critical gaps exist in the global response and where scale up is possible

These criteria were used as filters to identify a shortlist of challenges that represent the highest potential for UNITAID intervention. This final list of challenges provided the basis for the identification of Areas for Intervention for UNITAID.

## 4 Priority challenges to be addressed by UNITAID

The objective of this section is to describe the results of the filtering process through which challenges were prioritized as potential focus areas for UNITAID, leading to potential Areas for Intervention.

### 4.1 Challenge prioritization process

#### 4.1.1 UNITAID's expertise: focus on challenges that are inherently commodity access issues

This first criterion is designed to ensure UNITAID focuses on areas where it has expertise and strength in addressing gaps in access to products used to test, treat, and prevent disease. By doing that, UNITAID will leverage its market-shaping experience.

This criterion aims to focus on challenges that are directly linked to commodity access issues. As such, challenges that do not relate directly to commodity access or are primarily programmatic and/or funding related challenges, have been removed at this stage:

- Lack of awareness of status
- Lack of awareness of HCV and risk factors
- Unsafe injection practices
- Overuse / irrational use of injections
- Unsafe blood transfusions
- Other nosocomial transmissions
- No proper medical waste and sharps management
- Lack of data for advocacy
- Laws criminalizing certain behavior / products
- Stigma; discrimination
- Insufficient political advocacy
- Transmission via traditional medical practitioners
- Social determinants of risk

These challenges, though of major importance, are therefore not UNITAID's focus.

#### 4.1.2 Potential public health impact: focus on challenges for which there is strong evidence of high potential public health impact

The second criterion is designed to focus UNITAID on those areas where its action will have the greatest impact on the global response. The following challenges have been removed but still need to be closely monitored:

- Use of poor quality diagnostics

Lack of reliable epidemiological data is a major challenge in HCV. It hampers, among others, efforts to assess the magnitude of challenges or assess the impact of interventions, as there is no reliable baseline against which they can be measured. Thus, while there frequently is information and evidence related to specific settings and/or anecdotal evidence, the lack of basic epidemiological information is a key constraint, that makes this filter hard to apply. Yet the lack of evidence should not be confused with or equated to evidence of non-effectiveness.

#### 4.1.3 **Feasibility: focus on challenges for which the necessary technology can be available in a relevant timeframe**

The third criterion is largely pragmatic, focusing UNITAID intervention on challenges for which the necessary technology is available, or can be expected to be available, in the timeframe needed. Under this criterion, the following challenges have been removed:

- No vaccine: HCV vaccines are still in early stages of development, and it seems unlikely that any would be launched in the next two years.

The following challenges are removed, but still need to be closely monitored:

- Lack of alternatives for backbone
- Companies develop "own" not "best" FDCs

#### 4.1.4 **Optimize use of resources: focus on challenges for which critical gaps exist in the global response**

The fourth and final criterion is the most critical in ensuring UNITAID's added value in the global response. Pending further discussions with partners, no challenges have yet been eliminated with this filter.

## 4.2 **Priority challenges and recommended themes to be addressed by UNITAID**

UNITAID is being recognized as a pioneer in this area by many partners, and many have expressed hope and expectations that UNITAID will continue, within the limits of its mandate, to play an active and constructive role in the emerging global response.

The list of challenges remaining following the above prioritization process still seems quite daunting. This is a reflection of the fact that the global response is still in its early stages, and that multiple challenges contribute to the commodity access issues but are much broader in scope.

The next step in the prioritization process therefore consisted of relooking at the remaining challenges and regrouping them, in order to identify key issues that can break the commodity access gridlock. A simpler picture then emerges – but one that contains multiple vicious cycles:

- Epidemiologic data and clear guidelines are instrumental to plan a national response, advocate for resources and set up programs that enable health facilities to provide services; guidelines and services are also a prerequisite for obtaining better data on the epidemiology;
- Service provision requires that reliable diagnostics and quality treatments are available and affordable;
- Diagnosis is a precondition for accessing treatment, and diagnostic tests are needed to confirm cure;
- Screening, diagnosing and treating can help generate epidemiological data and evidence on impact, and are a key input into guidelines, which are needed to provide services.

Potential Areas for Intervention are listed below. This list of areas to consider will be refined in the coming months, therefore, at this stage, its purpose is to provide Board members an indication of the expected direction.

#### 4.2.1 **Existing Area for Intervention: Development of better tools to diagnose HCV, in particular in case of HIV/HCV co-infection.**

This AFI has been approved at EB22 in June 2015. A call for proposals was launched; currently the proposal screening process is ongoing.

#### 4.2.2 **Area to consider 1: Address the lack of epidemiological data and guidelines**

The lack of epidemiological data and the absence of clear guidance for screening, diagnosing and treating hamper the ability of governments to develop effective strategies and plans to tackle HCV. The lack of clarity on how many people to screen and treat and where these people are also makes costing of implementation plans difficult. This, in turn, makes it very difficult to allocate resources to HCV diagnosis and treatment.

Work may be needed to:

- Bring existing but scattered epidemiological data together and ensure a more comprehensive data set is developed and available to all stakeholders.
- Develop an optimum epidemiological model based on agreed and sound assumptions. The model should be constructed to enable refinement as additional or better data become available.
- Improve surveillance systems to generate better epidemiological data.
- Develop guidance on the best approaches to screening, diagnosis and treatment: The guidance should be detailed and specific enough to facilitate planning for and implementation of HCV surveillance, diagnosis and treatment at national level.

Better epidemiological data and guidance would mean:

- More clarity on what the needs are and where the needs are greatest; thus the ability to plan for the provision of services at national level.
- Better understanding of resource implications; the ability to allocate resources for the provision of services.
- Services to diagnose and treat HCV infection at the national level become available.

#### 4.2.3 **Area to consider 2: Find innovative ways to unlock funding for HCV**

To date, international donors have offered limited support for HCV treatment; the primary funders of HCV treatment are likely to be national governments. A few countries, most notably Brazil and Egypt, have already started to fund and provide access to HCV treatment. A range of other low- and middle-income countries – including Cameroon, Ethiopia, Indonesia, Mongolia, Myanmar, Nigeria, Rwanda, Uganda and Viet Nam – are developing national plans and are exploring ways to fund them.

Work may be needed to facilitate the identification of new/untapped financial resources, at national or international level, that can be used to finance commodities and/or services for HCV.

Innovative funding options would mean:

- Services to diagnose and treat HCV infection are being made available and can be scaled up at the national level.
- The market for HCV commodities (screening and diagnostic tests and medicines) will expand.
- Purchases of HCV medicines will increase. The larger volumes will enable economies of scale in production and make price reductions feasible.

#### 4.2.4 Area to consider 3: Increase affordability and adaptability of HCV medicines

Medicines to cure HCV are expensive. Even though one company offers significantly lower prices and has issued voluntary licenses that enable generic production for eligible low- and middle-income countries, treatment of HCV requires a combination of several medicines. The most affordable combination (sofosbuvir+ledipasvir) is priced at US\$ 1200 for 12 weeks treatment – however, this price does not apply outside the 101 eligible countries and the combination is not recommended for genotypes 2 and 3.

The optimum, pan-genotypic regimen combines medicines from different companies (sofosbuvir and daclatasvir from Gilead and BMS respectively). No voluntary licenses have been issued for daclatasvir, and no generic versions are available.

Work may be needed to:

- Negotiate voluntary licenses (MPP) with companies that have not yet issued any licenses and/or seek to improve the existing voluntary license, in order to enable generic competition.
- Use TRIPS flexibilities in order to enable generic competition in low- and middle-income countries that are not eligible for voluntary licenses or discounts.

Increased affordability would mean:

- Prices of HCV medicines and regimens will be more affordable due to generic availability and competition.
- More people will be able to access HCV treatment and get cured.
- National treatment programs can treat and cure more people with the financial resources available to them.
- Purchases of HCV medicines will increase. The larger volumes will enable economies of scale in production and make further price reductions feasible.

### 4.3 Next steps including further partner engagement

The themes described above (and depicted in dashed outlines in figure 4) will be developed and refined in close collaboration with stakeholders and partners, with Areas for Intervention planned for Board endorsement in 2016.

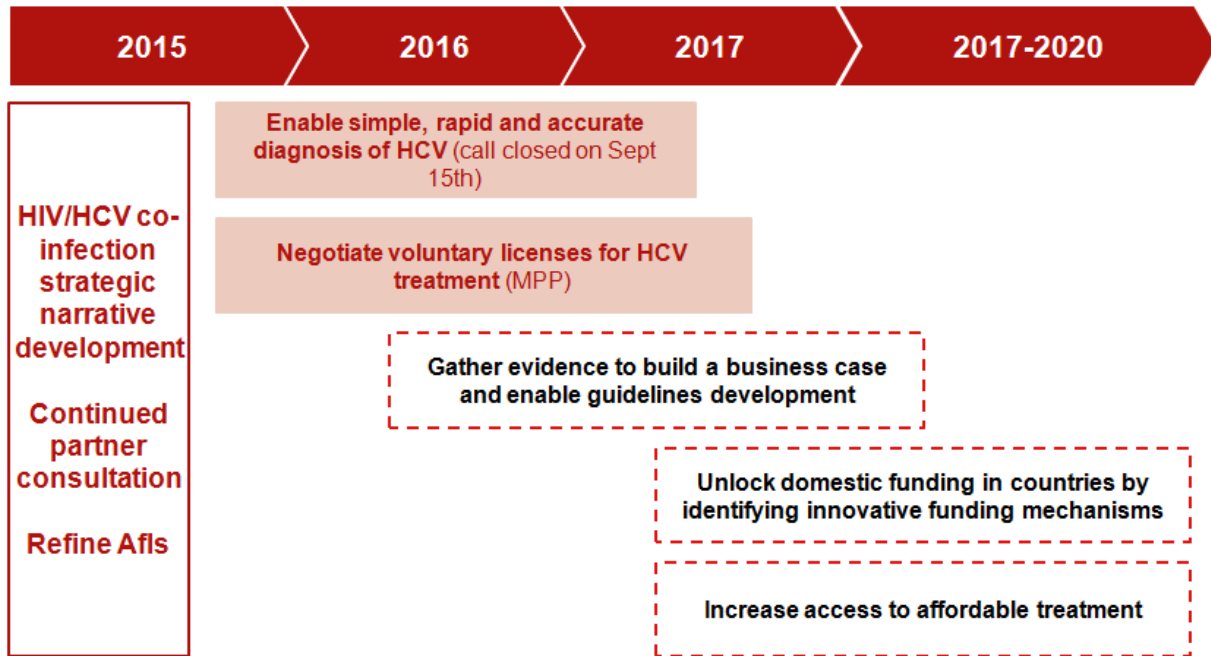
Partner engagement is already underway, with consultations including interactions alongside participation in technical fora and strategic meetings and in-person targeted strategy discussions to gain perspectives on critical challenges and high-priority areas of intervention for improving the markets for HCV commodities and, ultimately, improving access.<sup>18</sup>

Further work will be undertaken, including further, in-depth consultations with a widening range of stakeholders and partners.

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<sup>18</sup> E.g. discussions with participants at the World Hepatitis Summit (2-4 September 2015) and with experts and members of the WHO Guideline Development Group (30 Sept.-2Oct. 2015). These discussions include representatives from WHO, CDC, CHAI, MSF, Government officials from low- and middle-income countries, industry representatives, civil society representative and academia/researchers.

**Figure 4.** Potential timing





## 5 APPENDIX: Description of challenges

### 5.1 Challenges related to integrated diagnosis and care

#### 5.1.1 Treatment

##### ***New treatments are not affordable***

The price of DAAs is high: Gilead's best price reported for sofosbuvir in LMICs is US\$900 in Egypt for 12-week treatment cure (US\$300 per one month box).

Studies estimate that the production cost for a 12-week treatment of sofosbuvir is \$101, and that for 12 weeks of ledipasvir+sofosbuvir is US\$193.<sup>19</sup> Steep price decreases are therefore possible but will require a greater involvement of generic producers. Generic competition will require there being demand for the product and overcoming patent obstacles to producing and accessing the generic medicines.

##### ***Lack of alternatives for 'backbone' of treatment***

Four of the five currently used interferon-free regimens contain sofosbuvir, which is the only NS5B nucleotide polymerase inhibitor on the market. The fifth regimen is only recommended for genotypes 1 and 4, and has a more complex dosing schedule that makes it less suitable for use in resource limited settings. Sofosbuvir is therefore de facto emerging as the backbone of interferon-free treatment of HCV.

##### ***New treatments are not (yet) registered in many countries***

As of August 2015, sofosbuvir is registered in one low income country and in seven middle-income countries. Its registration is pending in two low-income countries, six lower-middle-income countries and three upper-middle-income countries.<sup>20</sup> This means sofosbuvir is not yet registered in most low- and middle-income countries. Similarly, the other DAAs are not yet registered in the vast majority of low- and middle-income countries.

##### ***Companies develop "own" not "best" FDCs***

The combination that looks most promising for use in resource limited settings (i.e. that comes closest to being pan-genotypic) is sofosbuvir with daclatasvir. However, its development has been relatively slow, partly due to the commercial focus on in-house regimens which has effectively limited collaborative approaches.

##### ***Voluntary licenses & access programs exclude certain MICs***

Gilead has announced steep price reductions for sofosbuvir and sofosbuvir+ledipasvir, and has issued voluntary licenses covering 101 low- and middle-income countries. Bristol-Myers Squibb has

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<sup>19</sup> Hill et al. Minimum costs for producing hepatitis C direct acting antivirals, for use in large-scale treatment access programs in developing countries. *Clinical Infectious Diseases*. 2014; Van de Ven et al. Minimum target prices for production of direct acting antivirals and associated diagnostics to combat hepatitis C virus. *Hepatology*. 2015

<sup>20</sup> UNITAID. Hepatitis C Medicines Technology and Market landscape. Update (forthcoming).

announced its intention to issue voluntary licenses covering 90 countries. This however leaves out a number of middle-income countries, including several that have large numbers of HCV-infected people, such as Brazil, Thailand and Ukraine.

### ***Lack of quality assured generics***

Meanwhile, generic versions of sofosbuvir are starting to become available. They are produced by holders of a voluntary license, or in countries where no patents are in force.<sup>21</sup> To date, none have been prequalified by WHO – though it is understood that several are currently in the process of WHO prequalification.

## **5.1.2 Diagnostics**

### ***Lack of reliable (cost-) effective screening tools***

The performance of most point-of care serological screening tests is poor in low-income settings, especially in HIV co-infection. The most reliable serological rapid test reportedly costs over \$10 per test, meaning it is unaffordable in resource limited settings.<sup>22</sup>

### ***Lack of a simple, inexpensive POC HCV diagnostic***

Although point-of-care diagnostic serological tests exist, no test meets all the criteria (including affordability, sensitivity, specificity, user-friendliness, being rapid, of assured quality and equipment-free) that make its use suitable and practical in resource limited settings. Moreover, in many African settings and in HIV-HCV co-infected patients, false-positive and false-negative results are common.<sup>23</sup>

### ***Use of poor quality diagnostics***

Poor quality diagnostics for viral hepatitis enter markets in resource-limited settings because of substandard or nonexistent regulatory controls.<sup>24</sup> When used, these tests can lead to unreliable and wrong results.

### ***Limited capacity to diagnose HCV***

In many low-and middle-income countries, facilities such as laboratory infrastructure and equipment to diagnose HCV are inadequate or absent. In addition, staff may not have the necessary training and expertise.

### ***RNA tests only suitable for high resource labs***

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<sup>21</sup> UNITAID. Hepatitis C Medicines Technology and Market landscape. Update (forthcoming).

<sup>22</sup> MSF. Putting HIV and HCV to the test. 2015.

<sup>23</sup> Cohn et al. Simplified diagnostic monitoring for hepatitis C, in the new era of direct-acting antiviral treatment. Current Opinion, 2015.

<sup>24</sup> WHO. Prevention & Control of Viral Hepatitis: Framework for Global Action (2012).

There are several molecular tests on the market, but all operate on costly platforms designed for centralized, high-resource settings. The price of HCV RNA tests currently is higher than that for HIV RNA tests running on the same platform.<sup>25</sup> Molecular tests that target low-resource, decentralized settings are in development.<sup>26</sup> However, all HCV RNA tests, including those in development, are prohibitively expensive (US\$ 18-80 per test). In addition, they are largely unavailable in LMICs.

### ***Complex and expensive diagnostic algorithms***

A complex, five-step diagnostic paradigm—screen, test for active disease, stage for treatment, monitor treatment, and test for cure—has evolved over time as a consequence of safety concerns and limited efficacy of interferon-based treatment and to make the most efficient use of healthcare resources. While there is agreement that this algorithm can be significantly simplified due to the much better safety and efficacy profile of the new treatments, there is a lack of clarity and consensus on the extent of simplification that is feasible and desirable. WHO guidance on this would be very much welcomed – and very much needed – by countries.<sup>27</sup>

As a result, just two in five people live in countries where testing is accessible to more than half of the population, and only 4% of low income countries report that testing is accessible.<sup>28</sup>

## **5.2 Challenges related to prevention**

### **5.2.1 Prevention**

#### ***No vaccine***

There is currently no vaccine against HCV, and while research is ongoing, there are no vaccine candidates in late-stage development; the only vaccine candidates are still in phase I or II.<sup>29</sup>

#### ***Lack of awareness of status***

Due to the fact that acute HCV infection is usually asymptomatic, as well as the lack of access to testing and diagnosis for HCV (see above), the majority of HCV-infected people are unaware of the fact that they are infected. For instance, in the United States, reportedly 75% of individuals infected with HCV are unaware of their infection – a percentage that is “significantly larger” than the percentage of undiagnosed HIV or HBV infections.<sup>30</sup> This not only means people will not seek treatment, but also that they may inadvertently transmit the disease to their family members and others.

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<sup>25</sup> MSF. Putting HIV and HCV to the test. 2015; UNITAID. Hepatitis C Diagnostics Technology landscape. 2015.

<sup>26</sup> One has recently entered the market.

<sup>27</sup> Presentations and discussions at the World Hepatitis Summit, 2015.

<sup>28</sup> World Hepatitis Alliance, Viral Hepatitis: Global Policy, 2013.

<sup>29</sup> Li et al. Hepatitis C virus vaccine development: old challenges and new opportunities. 2015

<sup>30</sup> The Joint Center for Political and Economic Studies, The “Secret” epidemic: Disparities in Hepatitis C Incidence, Treatment, and Outcomes, 2010.

***Lack of awareness of hepatitis C and risk factors***

Transmitted through blood-to-blood contact, HCV is 10 times more infectious than HIV and the HCV virus can survive on surfaces outside the body for a few days. Thus, HCV can be transmitted by sharing needles, but also razor blades or even toothbrushes.

Unfortunately, lack of knowledge on HCV transmission is still common.<sup>31</sup> Good, easily understandable and accessible information about hepatitis C will not prevent all infections or stop all high-risk behavior; however, the absence of information and awareness leaves those at risk much more vulnerable.

***Lack of harm reduction programmes***

In all regions, HCV is prevalent among people who inject drugs; it is estimated that, globally, approximately 60-70% of people who inject drugs have been infected with HCV.<sup>32</sup> As the majority of intravenous drug users become infected by repetitive exposure to contaminated injection equipment,<sup>33</sup> harm reduction programs and needle exchange facilities can contribute to containing the risk; however these are absent or woefully inadequate in many countries.

**5.2.2 Health systems: prevention of transmission*****Unsafe injection practices and blood transfusion, other nosocomial infections, lack of proper medical waste and sharps management***

The transmission of HCV infection occurs via blood-to-blood contact. In resource-poor countries, the primary source of HCV infection is the use of unsterilized, or insufficiently sterilized, equipment for injections, the use of unsterilized or insufficiently sterilized equipment for other medical and dental procedures, and infusion of inadequately screened blood or blood products.<sup>34</sup>

For example, throughout the world an estimated 16 000 million injections are administered every year. Not all needles and syringes are properly disposed of, creating a risk of injury and infection and opportunities for re-use. WHO estimates that, in 2000, injections with contaminated syringes caused, among others, two million HCV infections and 260 000 HIV infections worldwide. Many of these infections would have been avoidable if the syringes had been disposed of safely.<sup>35</sup>

In thirty-nine countries, donated blood is not routinely screened for transfusion transmissible infections, such as HCV and HIV.<sup>36</sup> In forty countries there is heavy dependence on a system of family/replacement and paid donors for blood, which increases the risk of infected persons donating blood.<sup>37</sup>

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<sup>31</sup> See for example: Saleh et al., Knowledge and perceptions of hepatitis c infection and pesticides use in two rural villages in Egypt, BMC Public Health 2014.

<sup>32</sup> Nelson et al. The epidemiology of viral hepatitis among people who inject drugs: Results of global systematic reviews Lancet. 2011. 378(9791): 571–583.

<sup>33</sup> Tibbs, Methods of transmission of hepatitis C, Journal of Viral Hepatitis, 2007.

<sup>34</sup> MSF. Diagnosis and treatment of hepatitis C: A technical landscape. 2014; Prati D. Transmission of hepatitis C virus by blood transfusions and other medical procedures: A global review. J Hepatol. 2006.

<sup>35</sup> WHO. Waste from health-care activities. Fact sheet N°253, 2011.

<sup>36</sup> WHO. Key global facts and figures in 2011, Fact Sheet no 279, 2011.

<sup>37</sup> WHO. Prevention & Control of Viral Hepatitis: Framework for Global Action (2012).

### 5.3 Cross-cutting challenges

#### 5.3.1 Health systems

##### ***Lack of guidelines suitable for non-tertiary care***

Tertiary hospitals in low-and middle income countries may be able to rely on guidelines developed by and for high income countries, such as those from the American Association for the Study of Liver Diseases or the European Association for the Study of the Liver. Lower level facilities will not be able to follow such complex and sophisticated guidance. WHO has been proactive in including the new HCV medicines early on in its guidelines; however, these guidelines need to be complemented with practical guidance on implementation.

##### ***Lack of knowledge and awareness among health workers***

Knowledge about HCV and its modes of transmission among health care workers is crucial for two reasons. Firstly, because health care workers have a relatively high risk of becoming infected. According to a survey in the UK “of healthcare workers reporting a significant occupational exposure, half were exposed to hepatitis C (HCV), a third to HIV and one in ten to hepatitis B (HBV)”.<sup>38</sup> Secondly, insufficient knowledge and awareness among health workers increases the risk that their practices contribute to the spread of HCV (see 5.1.2.2). Unfortunately, health care workers knowledge and awareness is not always sufficient.<sup>39</sup>

##### ***Weak surveillance systems leading to poor data***

About 80% of WHO Member States report having a national surveillance programme that regularly collects data regarding hepatitis incidence. However, only approximately half of those surveillance systems monitor chronic hepatitis B and C, which are responsible for most hepatitis-related morbidity and deaths.<sup>40</sup>

##### ***Unclear service delivery models***

There is a lack of clarity on optimum testing approaches, preferred regimens for treatment and the need to confirm cure. Decisions will also need to be made about the level at which services are to be provided, whether to integrate HCV services into other programs (e.g. HIV programmes), and how this can be implemented. To date, experience with HCV treatment in low- and middle-income countries is limited, and suitable service delivery models have not yet clearly emerged.

##### ***Lack of clarity who to prioritize for treatment***

Most countries prioritize patients with more advanced fibrosis and cirrhosis (METAVIR F3 and F4 stages) for treatment. Traditionally, the rationale for this prioritization of the sickest patients related

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<sup>38</sup> Public Health England, Eye of the Needle: United Kingdom Surveillance of Significant Occupational Exposures to Bloodborne Viruses in Healthcare Workers, Dec. 2014.

<sup>39</sup> See for example Setia et al., Attitudes and Awareness Regarding Hepatitis B and Hepatitis C Amongst Health-care Workers of a Tertiary Hospital in India, *Ann Med Health Sci Res.* 2013; Knowledge And Awareness About Chronic Hepatitis B and C, in Colvin and Abigail (eds.), *Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C*, Institute of Medicine (USA), 2010.

<sup>40</sup> WHO Global policy report on the prevention and control of viral hepatitis in WHO Member States, 2013.

to costs, concerns regarding the safety and efficacy of treatments, and the complexity of treatment monitoring. In case of the new HCV medicines, due to significantly better safety and efficacy profiles, the cost of treatment appears to be the predominant justification for this approach. A public health argument could however be made for different approaches that focus on those that are most likely to transmit HCV infection and/or for a “treatment as prevention” approach.<sup>41</sup>

### 5.3.2 Data, planning and financing

#### ***Lack of/poor quality epidemiological data***

The lack of reliable epidemiological data is a major challenge in HCV. It is illustrated by the wide variation in the HCV prevalence estimates in section 1.4. As a result, the magnitude of the disease is not well-known and has been underestimated.

#### ***Lack of data/evidence for planning***

The lack of data, or of reliable data, hampers planning of effective programs to diagnose and treat HCV. It also hampers efforts to monitor or evaluate the effectiveness of interventions. The lack of accurate prevalence data on hepatitis is widely recognized as inhibiting more effective prevention and control at both international and national levels.<sup>42</sup>

#### ***Lack of dedicated national strategies, programs and staff***

According to a survey conducted by WHO, only 37.3% of WHO Member States have a written national strategy or plan for addressing viral hepatitis. Even fewer (28.6%) have a governmental unit dedicated to addressing hepatitis prevention and control. Furthermore, the number of government staff working full-time on hepatitis-related activities is small; more than half of the countries reported having no more than two employees.<sup>43</sup>

#### ***Lack of data for advocacy***

The lack of reliable epidemiological data and estimates weakens advocacy – including advocacy by health officials for the resources required to set up or expand effective programmes for screening, diagnosing and curing HCV infection.

#### ***Lack of domestic funding, despite growing country ownership***

A growing number of governments of LMICs are considering or already starting implementation of treatment for HCV with new DAAs and allocating resources to do so. These countries include: Brazil, Cameroon, Egypt, Ethiopia, Georgia (national elimination plan), India, Indonesia, Mongolia, Thailand, Rwanda, Ukraine, and Viet Nam. Existing treatment programs, in some of these countries, that use pegylated interferon based treatment are also seeking to transition to the more effective and better tolerated DAAs.

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<sup>41</sup> Suthar and Harries, A Public Health Approach to Hepatitis C Control in Low- and Middle-Income Countries, PLoS Med. 2015; Hagan et al., Treatment as prevention and cure towards global eradication of hepatitis C virus, Trends in Microbiology, Dec. 2013.

<sup>42</sup> World Hepatitis Alliance, Viral Hepatitis: Global Policy, 2013.

<sup>43</sup> WHO Global policy report on the prevention and control of viral hepatitis in WHO Member States, 2013.

***Lack of donor funding***

Donor funding for HCV is virtually non-existent, though the Global Fund has opened the door to buying products for HIV/HCV co-infection, subject to conditions.<sup>44</sup>

**5.3.3 Social / environmental*****Laws criminalizing certain behavior or products***

Laws criminalizing certain behavior or the use of certain products (e.g. injecting drug use) may undermine, or preclude, harm reduction activities. They may also discourage people to access health services. As a result, some of the key affected populations may have very limited access to prevention and care/may be very hard to reach in some countries.

***Stigma and discrimination***

The link between (illicit) injecting drug use and HCV transmission has affected perceptions about HCV, even in some countries where injecting drug use is not the main route of transmission.<sup>45</sup> Persons with HCV infection can face stigma and discrimination; for example they may risk loss of employment and health benefits, or they may face travel restrictions. People may be reluctant to access screening and diagnostic services or to seek treatment and care due to fears of stigma and discrimination.

***Insufficient political advocacy***

Though the inclusion of hepatitis in target 3.3 of the Sustainable Development Goals is a significant step in raising awareness about hepatitis, including hepatitis C, among politicians and policy makers, in many countries the level of awareness is still low compared to infectious diseases such as HIV or TB.

***Transmission via traditional (medical) practitioners***

The use of traditional healers and medical practitioners is high in some settings. These practitioners may lack knowledge about infection control and may contribute to HCV transmission, for instance by providing injections with inadequately sterilized equipment or using other unsterile equipment. Transmission may also take place in the context of other cultural, religious or traditional practices, for example traditional circumcision practices.<sup>46</sup>

***Social determinants of risk***

Poverty often results in lack of access to clean water and to proper sanitation facilities. It is a factor contributing to many infectious diseases, and though this issue has not been explored enough (and thus evidence is limited), it is unlikely that hepatitis C would be an exception to this rule.

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<sup>44</sup> The Global fund. Decision Point GF/B33/DP08. Policy on co-infections and co-morbidities. April 2015.

<sup>45</sup> Economist Intelligence Unit. The silent pandemic.

<sup>46</sup> See for example Kenyon et al., Female Genital Cutting and Hepatitis C Spread in Egypt, *Hepatology*, 2013