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Hepatitis C Medicines and Diagnostics in the Context of HIV/HCV Co-Infection: A Scoping Report

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List of abbreviations

Note: The term "interferon" refers to pegylated interferon, unless otherwise stated.

AASLD	American Association for the Study of Liver Diseases
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
ARV	Antiretrovirals
CD4	Lymphocyte white blood cells
CI	Confidence interval
DAA	Direct-acting antivirals
EASL	European Association for the Study of the Liver
ELISA	Enzyme-linked immunosorbant assay
ESLD	End-stage liver disease
FDA	Food and Drug Administration (United States)
HAART	Highly active antiretroviral therapy
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IFN	Interferon
NGO	Nongovernmental organization
PCP	pneumocystis jiroveci (carinii) pneumonia
PCR	Polymerase chain reaction
PI(s)	Protease inhibitor(s)
POC	Point of care
RIBA	Recombinant immunoblot assay
Peg-IFN	Pegylated interferon
Peg-IFN + RBV	Pegylated interferon + ribavirin
RBV	ribavirin
RNA	Ribonucleic acid
SVR	Sustained virologic response
TB	tuberculosis
WHO	World Health Organization

Executive summary

The UNITAID 2013-2016 Strategy includes the treatment of HIV/AIDS and co-infections as one of six strategic objectives. This scoping report focuses on issues, challenges and opportunities related to one of the most important HIV co-infections—Hepatitis C virus (HCV)—and represents UNITAID's first effort to gather market intelligence on products for the diagnosis and treatment of HCV in individuals co-infected with HIV and HCV.

Though preliminary in nature, this scoping report gives an overview of the prevalence and impact of HCV and HIV co-infection, existing medicines and diagnostics as well as those in the pipeline, commodity access issues, and market shortcomings.

Preliminary estimates suggest that approximately 5.5 million people may be co-infected with HCV and HIV, of whom approximately 2.5 million live in low- and lower-middle-income countries.[1] This represents ~16% of the total HIV-infected population. In recent years, the increasing efficacy of antiretroviral therapy (ART) has increased the life expectancy of HIV-positive individuals. As a result, HCV infection can now reach advanced stages in HIV-positive individuals, and end-stage liver disease (ESLD) has become a leading cause of death for co-infected populations. HCV also is a major health burden in itself, currently infecting approximately 150 million people worldwide, the majority of whom live in resource-limited settings. 500,000 HCV-related deaths occur each year. (1)

The current HIV/HCV diagnostic and treatment paradigm is inappropriate for resource-limited settings due to unaffordable products that are complex to use. The diagnostics required to screen for HCV and monitor treatment effectiveness cost ~$300-1,400 per patient.[2] Interferon, the cornerstone of current treatment protocols, is priced at ~$2,000-20,000 per treatment course. The current interferon (IFN)-based treatments have relatively low efficacy rates and high toxicity/side effects, all of which are exacerbated for HIV/HCV co-infected individuals. Furthermore, screening for HCV and the administration of IFN (requiring subcutaneous injections over 24-48 weeks) are complex procedures; they require trained medical staff to treat and monitor patients, and advanced healthcare delivery systems to manage side effects.

New oral-based treatments could revolutionize the treatment of HCV. Eleven HCV drugs are in Phase III clinical trials, with very promising cure rates and better side effect profiles. These direct acting antivirals (DAAs) are expected to come to the market from 2014 onwards. A number of these drugs show very high efficacy across HCV genotypes, appear to be well-tolerated, and have shorter regimens. The cost of production is likely lower than that of IFN, although the ultimate affordability of these treatments in resource-limited settings remains unclear.

The approach to HCV diagnosis will also change. Upcoming point-of-care (POC) rapid diagnostic tests could increase access to HCV testing in resource-limited settings, while new pan-genotypic drugs might eliminate the need for genotyping and liver scans. New treatments and diagnostics have the potential to increase access to treatment for the millions of HIV/HCV-infected individuals in resource-limited settings.

1 Estimates by Center for Disease Analysis. See Section 4.5.1 for more detail. WHO estimates are expected by end 2013.
2 This does not include the cost of a liver biopsy. Including the biopsy, the cost is $700-2,700.

Despite these promising signs, questions remain regarding the affordability of these new medicines and diagnostics in resource-limited settings. Moreover, it is anticipated that the launch of these new treatments in low- and lower-middle-income countries will significantly lag behind that in developed countries.

In order to optimize scale-up of HCV diagnosis and treatment in HIV/HCV co-infected individuals in resource-limited settings, shortcomings in these markets must be addressed.

Examples of possible interventions include:[3]

- Increase the affordability of medicines, notably the new DAAs, and/or diagnostics in resource-limited settings, through approaches such as aggregating demand, price negotiations, voluntary licensing or tiered pricing;
- Facilitate the uptake of new medicines and/or diagnostics, through approaches such as demand forecasting or support for the development of country roll-out plans, including updating national guidelines and programmatic integration;
- Accelerate/streamline the approval process for new medicines and/or diagnostics in low- and middle-income countries;
- Develop new diagnostic and/or treatment approaches tailored for resource-limited settings and demonstrate their feasibility.

3 This list is not comprehensive, nor are interventions listed in any order of priority.

1 Foreword

This report is a contribution to the implementation of UNITAID's 2013-2016 Strategy, which calls for *"Increase[d] access to emerging medicines and/or regimens as well as new formulations, dosage forms, or strengths of existing medicines that will improve the treatment of HIV/AIDS and co-infections such as viral hepatitis"*.

HIV/HCV co-infection is a looming public health problem. As access to treatment for HIV infection expands, more and more people co-infected with HCV live long enough to experience the manifestations of HCV disease. Indeed, liver disease has become a leading cause of death in HIV/HCV co-infected patients.(2) To address this problem, a drastic scale-up in HCV screening and treatment is needed. Unfortunately, currently available HCV treatments and diagnostics have notable shortcomings in terms of their affordability, complexity, efficacy, and toxicity; they are far from ideal tools required for scale-up. Moreover, the safety and efficacy of these treatments are of particular concern for HIV/HCV co-infected individuals as compared to those infected with HCV alone.

Fortunately, there is hope that profound improvements may come from new oral drugs that are expected to come to the market in the coming years. These treatments offer promise for greater acceptability, improved safety and efficacy, simplification of the diagnostic paradigm, and, potentially, decentralization of care. In addition, new and improved diagnostic tools are expected to come to market in the coming years.

This scoping report presents an initial, high-level overview of the HCV medicines and diagnostics landscape. It introduces HCV and HIV/HCV co-infection, discusses the burden of disease, and characterizes the landscape for current and pipeline products.[4] The report is intentionally forward-looking; it focuses on the likely future options for diagnosis and treatment, notably for the much anticipated—and much needed—oral treatments. It therefore focuses less attention on describing markets around the current standard of care. It also details some of the main market shortcomings and suggests interventions that could accelerate availability and ensure affordability of new tools as rapidly as possible in resource-limited settings.

This scoping report will help guide priority setting for UNITAID. In addition, it is hoped it will be helpful for other stakeholders and organizations considering market-based approaches to improving access to treatments and diagnostics for HIV/HCV co-infection.

4 For more detailed information, see *Diagnosis and treatment of hepatitis C: A technical landscape*, MSF Access Campaign, April 2013 (5) and *2013 Pipeline Report*, i-Base and TAG, June 2013.

2 Introduction

UNITAID's framework for the strategic prioritization of investments aims to maximize UNITAID's public health and market impact. The strategic framework includes, among other things, landscape analyses to map current and future trends in disease burden, product development, and market evolution for preventatives, diagnostics, and medicines used in HIV/AIDS, tuberculosis (TB), and malaria.

As a first step, this scoping report provides an initial overview of the challenges and opportunities in treating HIV/HCV co-infection in resource-limited settings. It provides a description of HIV/HCV co-infection and HCV infection, current and future diagnostics and treatments, challenges related to treating HCV, and potential opportunities for UNITAID to address market shortcomings in order to improve access in this domain.

This report begins with an overview of the epidemiology and disease burden of HCV and HIV/HCV co-infection around the world. Sections 3 and 4 map the landscape of currently available HCV diagnostics and medicines, as well as products that are expected to enter the market in the near future. Following this, Sections 5 and 6 summarise the HIV/HCV-related initiatives of global public health players and the shortcomings in the market for HCV diagnostics and treatments, respectively. The report concludes by exploring potential opportunities for market-based intervention.

In addition to the report's authors (see Methodology), UNITAID gratefully acknowledges the insights and suggestions of those who contributed to the development of this report, especially: Jennifer Cohn, Philippa Easterbrook, Nathan Ford, Charles Gore, Khalil Elouardighi, Brian Kaiser, Isabelle Meyer-Andrieux, Anton Ofield-Kerr, Teri Roberts, Philip Rosenthal, Tracy Swan, Sheena Talwar, and Stefan Wiktor.

3 Methodology

This scoping report was prepared by Wouter Deelder, James Eustace and Priya Pingali of Dalberg Global Development Advisors, and by Chris Estes, Erin Gower, Sarah Hindman, Andrew Levitch and Homie Razavi of the Center for Disease Analysis with support from the UNITAID Secretariat. Final editing and framing of the report was undertaken by the UNITAID Secretariat.

From a methodological perspective, there are several distinct components of the report:

The discussion of **HCV and HIV/HCV co-infection epidemiology, disease progression and disease impact** were compiled through desk research and literature review, taking into account published and unpublished reports and articles, peer-reviewed journals, and websites. In addition, a select number of expert interviews were conducted.

The section on the **quantification of the disease burden** of HIV/HCV co-infection was informed by recent analysis by CDA (publication forthcoming). This analysis was informed by desk research, expert interviews, and prior studies by CDA. For more detail on the methodology, see Annex 1.

The analysis of **existing and new treatments and diagnostics** for HCV (including pipeline technologies) was informed by desk research (with a focus on analyst reports, clinical trial reports, and company publications) and conversations with companies and experts. The majority of these interviewees preferred not to be named or quoted.

Finally, the sections on **market shortcomings and potential interventions** were informed by the analyses and sources described above, as well as additional interpretation and analysis.

Although additional data is slowly becoming available, there are significant data limitations in the HCV and HIV/HCV space. There is little data available on the overall funding, volumes, and prices for current HCV treatments and diagnostics—particularly in resource-limited settings. At the time of this report, there was no public information available on the launch schedule, pricing and potential differentiated access provisions (e.g. in low- versus high-income countries) for the new oral drugs. Furthermore, given these drugs are still in late-stage clinical development, data on efficacy—including across genotypes—and general acceptability is still preliminary and may be subject to change.

4 Epidemiology and disease burden

This section focuses first on HCV, including a description of the disease and its transmission, symptoms, outcomes and burden. The second half of this section is dedicated to HIV/HCV co-infection.

4.1 What is HCV?

Hepatitis C is a virus that infects liver cells, resulting in severe inflammation. (3) Although HCV itself does not directly damage the liver, the immune system's attempt to rid the liver of infected cells causes inflammation. This inflammation can lead to cirrhosis—a hardening of the liver—which makes it difficult for blood to flow through the liver. (4) Cirrhosis reduces the liver's ability to clear the blood of waste products, toxins and infections. Once it infects an individual, HCV may either be naturally cleared by the body within six months (the "acute" phase), or develop into a chronic condition.[5]

To date, 11 different HCV genotypes have been identified, as well as several subtypes. (5) Whereas Genotype 1 is the most common form of HCV in developed countries, Genotypes 1, 3, 4, 5, and 6 are all widely prevalent in low- and lower-middle-income countries. (4)[6] HCV has been observed to respond differently to treatment according to its genotype. See Annex 2 for the distribution of HCV prevalence and Annex 3 for a map illustrating the geographic distribution of the various HCV genotypes.

4.2 How is HCV contracted?

HCV is mainly spread through blood-to-blood contact, with different patterns of transmission in high versus low- and lower-middle income countries.[7] In high-income countries, HCV is typically spread nosocomially (e.g., through dialysis equipment and endoscopy equipment) and through contaminated needles used for injecting recreational drugs.(6)[8] Men who have sex with men, especially if HIV-positive, constitute another high-risk group for contracting HCV infection.(7) In resource-limited settings, HCV is additionally spread through contaminated blood transfusions.[9,10] Transmission linked to injection drug use[11] and among men who have sex with men is also increasingly observed in resource-limited settings.

4.3 How does the disease progress?

HCV infection starts with an acute phase that is asymptomatic for approximately 85% of patients.(8) If symptoms do occur within the first six months of infection, they are similar to those caused by the flu and are therefore easy to overlook. Therefore, most infected people will not seek screening and remain unaware of their condition.

Approximately 80% of HCV-infected people fail to clear the virus during the acute phase and develop a chronic infection. (9) As shown in Figure 1, over time chronic HCV can lead to cirrhosis and, in some cases, to liver cancer.[12] Only a subset of patients respond successfully to currently available treatments; in the remaining cases, treatment does not eliminate HCV from the body. It is estimated that each year 1-5% of cirrhosis patients develop hepatocellular carcinoma (HCC).(3)[13] Without treatment, HCV-associated cirrhosis may lead to liver failure and death.

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5 HCV is spontaneously cleared by the body in only 10-30% of cases; 70-90% of the time, it develops into a chronic illness.

6 Genotype 2 is found across the world (with the exception of Northern Africa and the Middle East), but its prevalence in each region is relatively low. It is most prevalent in Europe.

7 Vertical mother-to-child transmission of HCV is also possible, though the exact nature of this transmission is not yet clearly understood.

8 The hepatitis C virus is very resilient. Studies have shown that HCV can survive in the environment for at least 16 hours in dried plasma and be a source of new infections (122).

9 To a lesser extent, infection is spread through unsterilised non-medical tools, such as barber tools and those used during traditional circumcision practices

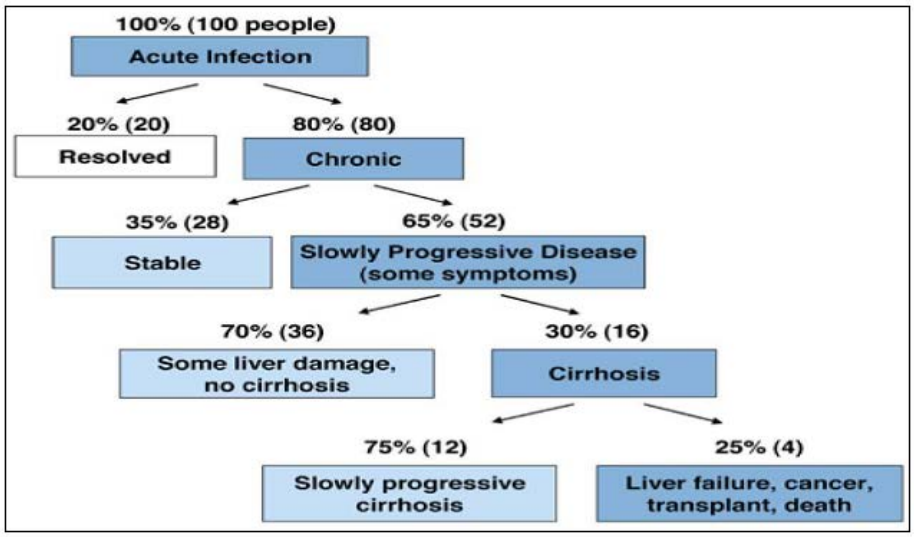
10 Heterosexual transmission of HCV appears to be very rare, although data on this topic is limited. One interviewed expert estimated that HCV is rarely transmitted sexually. Another expert described a discussion among a group of hepatologists on the topic of sexual transmission of HCV, which concluded that it is a very unlikely mode of transmission (it is likely only possible with a significant transfer of blood). Furthermore, in their study titled *Lack of evidence of sexual transmission of hepatitis C among monogamous couples: results of a 10-year prospective follow-up study*, Vandelli et al. argue that "the risk of sexual transmission of HCV within heterosexual monogamous couples is extremely low or even null. No general recommendations for condom use seem required for individuals in monogamous partnerships with HCV-infected partners".

11 The presence of HCV antibodies is very high among injecting drug users, across geographies.

12 Patients with chronic HCV infection are also at an increased risk of developing comorbidities, including cardiovascular, renal and central nervous system conditions

13 HCV accounts for 27% of liver cirrhosis cases and 25% of hepatocellular carcinoma cases worldwide

Figure 1. HCV disease progression over 10–15 years (mono-infection)



Source: *http://www.correlation-net.org/hep_c_trainers_manual/Module03/3_3_liverdamage.html*

4.4 What is the burden of HCV?

Approximately 150-184 million people are currently infected with HCV.(8) (10) According to a CDA-conducted analysis of HCV prevalence, around 40% of the HCV-infected population globally—approximately 60 million people—live in low- and lower-middle-income countries.(10)[14,15]

An estimated 500,000 deaths occur annually due to all HCV-related causes.(1) (10)[16] The majority of these deaths occur in low- and lower-middle-income countries.

The burden of HCV is expected to grow dramatically, especially in resource-limited settings. Estimates indicate that 3-4 million people are newly infected with HCV each year.(10) The WHO calculates that unsafe healthcare practices account for 2.3 million of these new infections.(8) In 2008, the WHO found that for low-income countries where data is available, only 53% of blood was screened for HCV in a quality-assured manner; in 39 countries, blood was not routinely screened at all.(8) (11)[17]

4.5 HIV/HCV co-infection and its significance

4.5.1 Estimated incidence of HIV/HCV co-infection

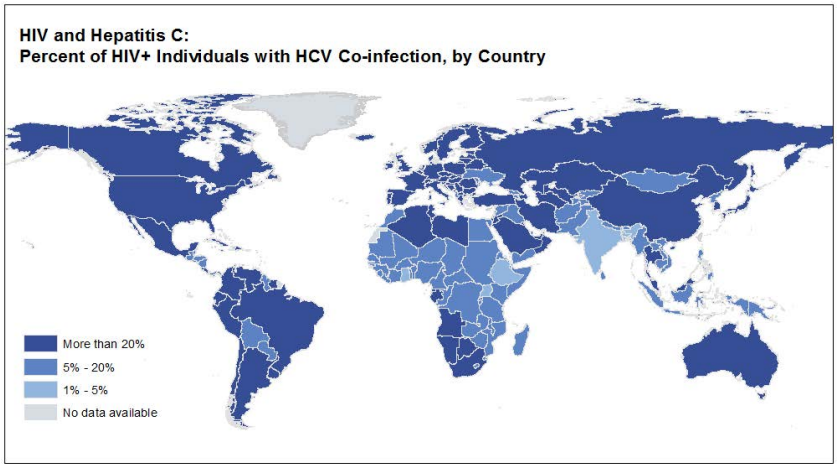
HCV is one of the most common co-infections among people living with HIV. (12) Though data is limited, it is generally estimated that 4 to 5 million people are co-infected with HIV and HCV. (13) WHO estimates of HIV/HCV co-infection are expected by end 2013.

According to estimates by the CDA, derived from a review of 45 published studies, the number could be as high as 5.5 million people—or 16% of the world's 34 million HIV-infected people.[18]

The estimated burden of HIV/HCV co-infection across the world is shown in Figures 2 and 3. As depicted in these maps, HIV/HCV co-infection is a significant problem. In North America, Australia, and most of South America and Europe, more than 20% of HIV-positive individuals are co-infected with HCV. In most African and Asian countries this rate is lower, but varies considerably by risk group.

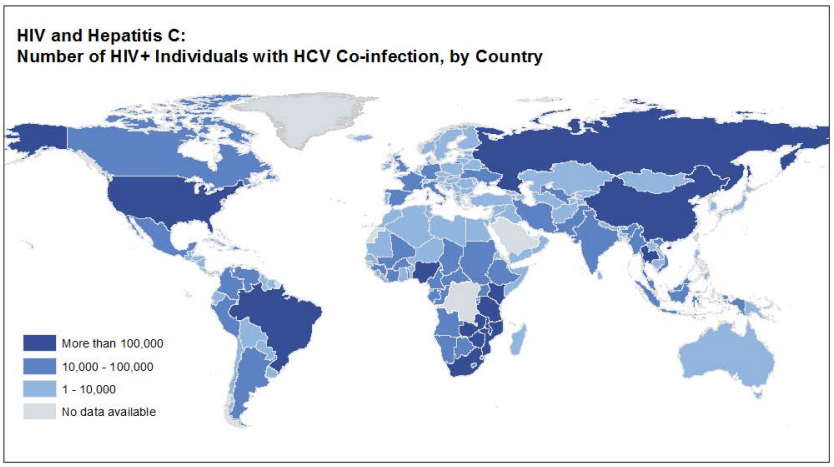
14 According to the World Bank classification, 2011
15 Countries in Asia and Africa have the highest reported prevalence (of anti-HCV)
16 The exact number is 0.9%
17 WHO estimates that about 40% of injection-related equipment is reused in developing countries
18 Center for Disease Analysis, unpublished data. See Annex 1 for more details.

Figure 2. Estimated percentage of HIV population co-infected with HCV[19]



According to the estimates depicted in Figure 3, the highest absolute numbers of HIV/HCV co-infected individuals reside in the United States, Brazil, China, Russia, and Southeast Africa.

Figure 3. Estimated number of HIV/HCV co-infected persons by country[20]



The co-infection rate in high income countries is estimated to be ~20%, in upper-middle-income countries it is ~25%, in lower-middle-income countries it is ~10%, and in low-income countries it is ~15%[21], with prevalence varying widely by risk group. Low- and lower-middle-income countries account for almost half of the world's co-infected population (45%), as a result of their higher HIV burden (approximately two-thirds of HIV-infected persons live in low- and lower-middle-income countries).(5)[22]

HIV/HCV co-infection rates tend to be correlated with countries' overall overlapping risk factors for HIV and HCV. Countries where the main risk factors for HIV acquisition are the same as for HCV, for example, injecting drug use or men who have sex with men, will tend to have high rates of co-infection.(14) (15) (16) Nevertheless, even in countries with low average co-infection rates, vulnerable groups such as injecting drug users, prisoners and men who have sex with men can be dramatically affected.(17)

Figures 4 and 5 present HIV/HCV co-infection estimates as a proportion of HIV and HCV mono-infection, respectively.[23]

19 Based on CDA analysis. See Annex 1 for methodology.
20 Based on CDA analysis. See Annex 1 for methodology.
21 Center for Disease Analysis study of country-level co-infection rates to be published in 2013.
22 Some estimate the total number of co-infected individuals to be as high as 7 million.
23 Based on CDA estimates. See Annex 1 for methodology.

Figure 4. Total number of HIV/HCV co-infected and HIV mono-infected individuals

Total number of infected people (in millions), by country income categories.

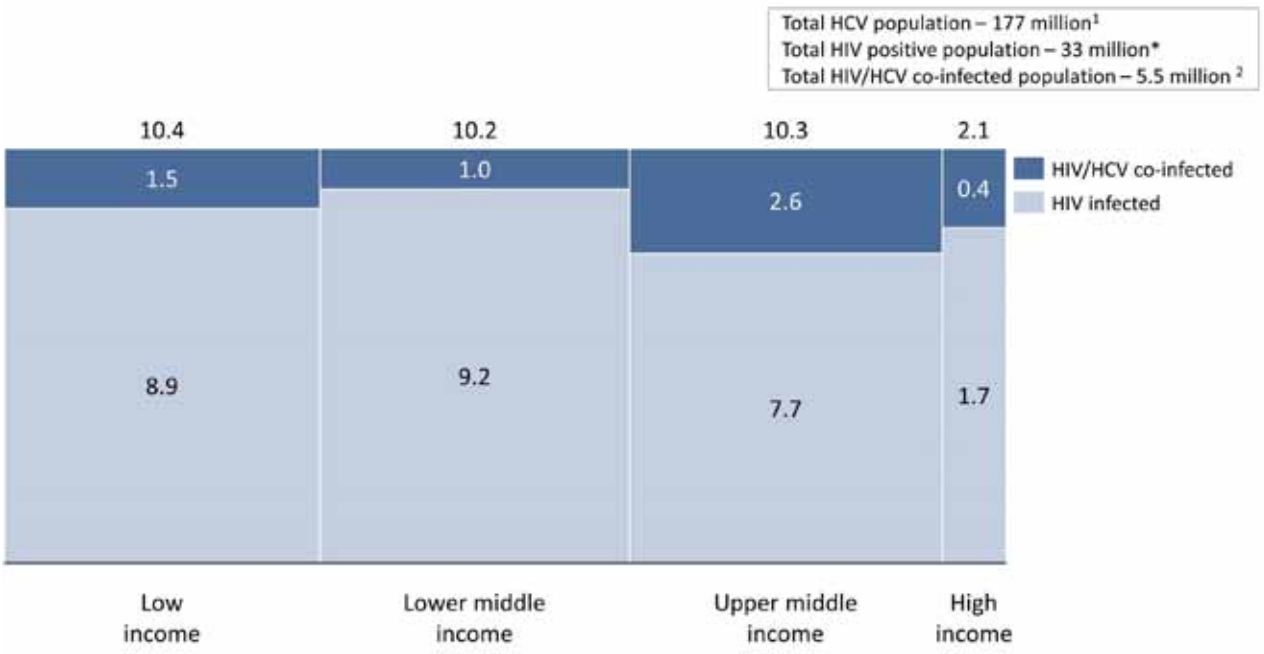
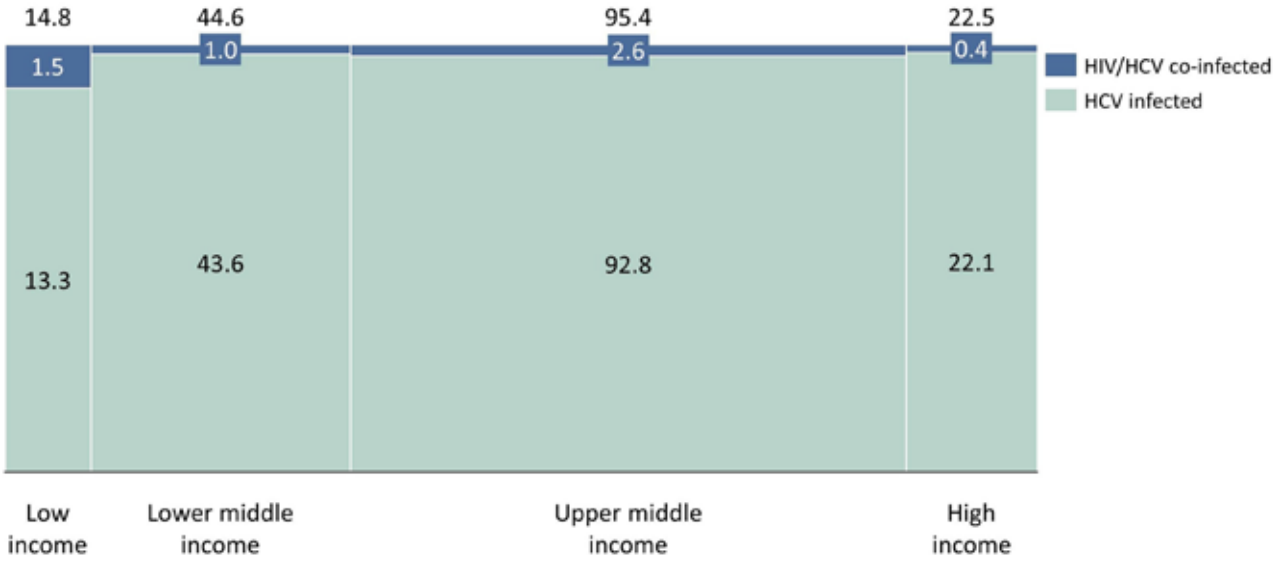


Figure 5. Total number of HIV/HCV co-infected and HCV mono-infected individuals

Total number of infected people (in millions), by country income categories.



**Based on total sum of country-wise HIV population data from CIA World Fact Book (this is slightly less than global estimates of 34 million, due to slight discrepancies in CIA data).*

1 - Based on Dalberg's and Center for Disease Analysis' calculations, using country-wise HCV rates (from WHO, 2007) and country-wise total population figures (based on World Bank data, 2011)

2 - Based on global estimates of approximately 4-7 million people and CDA analysis

Note: Analysis is based on the assumption that the global HIV/HCV co-infected population is approximately 5.5 million;

Source: *Central Intelligence Agency, The World Factbook, People Living with HIV/AIDS; World Bank country classification, 2011;World Bank population statistics, 2011; World Health Organization HCV prevalence rates, 2007*

4.5.2 Clinical impact of HIV/HCV on progression of HCV

HIV infection accelerates the progression of HCV. There is strong evidence that HIV/HCV co-infection accelerates the progression of cirrhosis and fibrosis, driven by increased inflammation and immune dysfunction.(5) (18) (19) (20) (21) (22) (23)[24,25] A number of studies have explored the effect of HIV on HCV, as shown in Annex 4. In 2010, a compilation of systematic reviews of HIV comorbidity studies concluded that HIV accelerates HCV.(24)[26] It included a systematic review by Deng, et al.(25), which found that HIV accelerates HCV disease progression, including death, histological fibrosis/cirrhosis, and decompensated liver disease. An additional systematic review led by Bonacini concluded that HCV infection leads to earlier and more severe liver disease. (26) Co-infection with HIV has also been shown to increase the rate of vertical, mother-to-child transmission of HCV. Compared to the rate of vertical transmission among mono HCV-infected mothers of 2-5%, the rate of vertical transmission in cases of HIV/HCV co-infection is 20%.(3) (27) (28) (29)[27]

There remains uncertainty regarding the causal relationship between HCV co-infection and progression of HIV. A 2008 meta-analysis led by Chen found that in the highly active antiretroviral therapy (HAART) era, HCV co-infection (compared with HIV infection alone) accelerates the risk of mortality, but not the risk of AIDS-defining events.(24)[28] Further, a study by Dorrucci et al found that HCV infection does not affect progression to AIDS.(30) In addition, three separate studies from Scotland, Spain and the United States found no difference in the progression to AIDS in HIV-infected patients, whether HCV-positive or HCV-negative.(31) (32) (33)[29]

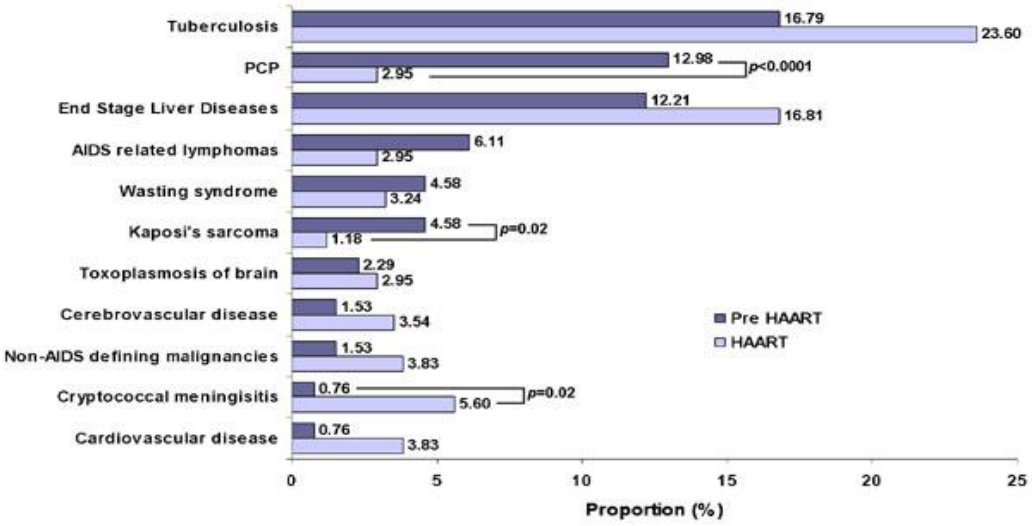
Conversely, some investigations have concluded that under specific conditions HIV/HCV co-infection can lead to faster progression of HIV to AIDS.(26) A 1998 study led by Piroth demonstrated that clinical progression is more rapid in HIV/HCV co-infected patients than in HIV seropositive patients not infected by HCV.(34) Another study led by Miller observed that HIV-infected patients are likely to have a better immunological response to ART if they are not co-infected with HCV.(35) Similarly, a 2012 analysis found that HCV co-infection increases the risk of HIV- and/or AIDS-related mortality in the cART era.(36) More research is needed before conclusions on this interaction can be made.

There is evidence that increased and earlier ART treatment has drastically increased the impact of HCV. Based on a small-scale, 10-year study in Georgia, Figure 6 depicts the 'before and after' incidence of various opportunistic infections after the widespread introduction of HAART. The proportion of deaths studied that were caused specifically by ESLD increased from 12% in 1989 to 17% in 2009. Counter-intuitively, this development is a result of the success of ART; the survival gains made possible by ART have unmasked the severity of HCV co-infection. Whereas patients would mostly succumb to AIDS-related events in the pre-ART era, the increase in life expectancy resulting from current ART therapy has allowed HCV infections to reach advanced stages, causing significant liver damage and death from ESLD or HCC.

24 Compared with HIV un-infected women, HIV-infected women have markedly higher levels of CD4+ and CD8+ T cell activation ($P<0.1$).
25 One of the drivers of this is that HIV/HCV co-infection is associated with a reduced rate of spontaneous HCV RNA clearance.
26 It also concluded that HCV increases the risk of mortality for people with HIV.
27 Approximately 5 out of every 100 infants born to HCV-infected women become infected at the time of birth.
28 AIDS-defining events are defined by a limited number of specific co-infections that result in an HIV-infected individual developing AIDS. Increased mortality of HIV-infected individuals will not necessarily lead to AIDS.
29 It should be noted that a number of the studies mentioned in this paragraph and the next were conducted in the pre-ART era.

Figure 6. Causes of death among HIV-infected persons in Georgia, 1989-2009. (37)

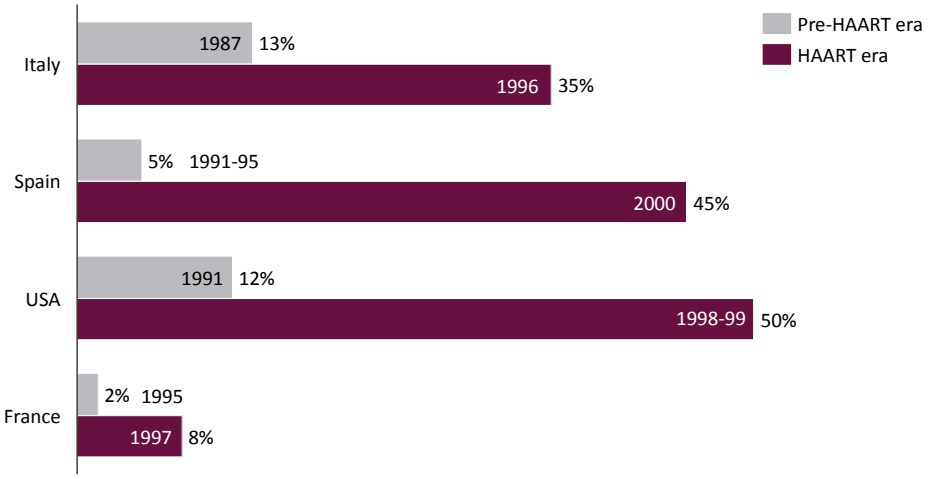
(% of overall deaths among 470 HIV patients)



A growing body of surveys show increased morbidity and mortality rates among HIV/HCV co-infected individuals in developed countries. As shown in Figure 7, the incidence of ESLD has increased drastically in Europe and the US after the introduction of HAART. In addition, a study conducted in France in 2000 concluded that 10% of all deaths among a group of HIV-positive individuals were caused by HCV.[30] In Boston, clinicians found that, from 1998-1999 (before the advent of Peg-IFN), 50% of all deaths of HIV-positive people were due to liver disease.(38) These, and additional studies on the mortality and morbidity of HIV/HCV co-infection, are provided in Annex 5.

Figure 7. Mortality caused by ESLD among HIV/HCV co-infected patients, 1987-2000.(18)

Deaths attributed to ESLD across various studies



30 Conference on Retroviruses and Opportunistic Infections, 2013 (Poster by National Institute of Health and Medical Research [INSERM], France)

Though limited data is available on HIV co-morbidities in low- and lower-middle-income countries, a similar trend of increased morbidity and mortality rates is expected to occur as access to ART is expanded. Studies conducted to date on this subject are scarce, and those that have been conducted typically have small sample sizes. Therefore, there is little conclusive evidence on the exact cause of ESLD among HIV-positive patients in resource-limited settings. Currently, ART coverage rates in low- and lower-middle-income countries are overwhelmingly lower than in high-income countries, and ART is also initiated at lower CD4 levels than in high-income countries. Together, these increase the likelihood of AIDS-related death from opportunistic infections other than HCV. However, HCV-related mortality is expected to rise as access to ART treatment expands and ART is initiated earlier on. As survival rates and life expectancy improve among HIV-positive populations in low- and lower-middle-income countries, co-infected individuals will be at an increased risk of HCV-related liver disease.

4.6 Treatment guidelines

Although currently there are no WHO treatment guidelines for the management of HCV infection, these guidelines are under development. In the absence of WHO guidelines, guidelines from the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) are widely used. See Annex 9 for more information.

The WHO 2013 Consolidated HIV Guidelines (39) recommend that the initiation of ART among people co-infected with HIV and HCV follows the same principles as for people with HIV mono-infection. The consolidated guidelines refer to the forthcoming WHO guidelines for the management of HCV for detailed guidance on HCV screening and treatment.

Meanwhile, in April 2013, WHO has added Peg-IFN to the Model List of Essential Medicines.(40)

4.7 Commodity access issues

There are significant commodity access issues for HIV/HCV treatment and screening. While there is a paucity of data on access to treatment and screening in low- and lower-middle-income countries, it is clear that there is little to no public funding for HIV/HCV screening or treatment programs in these settings (see Section 7). This gap is driven by the lack of affordability and complexity of diagnosis and IFN-based treatment (see Section 8), which also drastically limits out-of-pocket purchases in the private sector.

5 Treatment for HCV, including pipeline

5.1 Introduction

HCV infection can be cured with anti-viral drugs.[31] The primary goal of treatment for chronic HCV infection is the elimination of viral infection, and a secondary goal is the prevention of progression to liver disease.[32] Treatment success is measured by the absence of HCV, defined as the patient being HCV RNA negative 12 to 24 weeks after the end of treatment.(41)

The bulk of HCV treatment sales take place in developed countries. In 2012, the total global market for HCV drugs was estimated at $5 billion, with Peg-IFNs accounting for $2.5 billion, ribavirin (RBV) for $1 billion, and the new protease inhibitor therapies (boceprevir and telaprevir) accounting for the remaining $1.5 billion.[33] Approximately 70% of the Peg-IFN sales were in high-income countries, due to greater volumes and higher prices in these countries.[34] Detailed data on the geographic presence of new therapies was not available at the time of this publication; however, it is widely understood that low- and lower-middle-income countries remain vastly underserved.

5.2 HCV treatment—current and future therapies

The current and future medicines to cure HCV are shown in Table 1. The cure rates and duration of treatment of current treatments vary by HCV genotype: Genotypes 2 and 3 exhibit higher cure rates, while Genotypes 1, 4, 5 and 6 require longer treatment and exhibit lower cure rates.(41) (42) In addition, cure rates within the HIV/HCV co-infected population are typically lower than those among HCV mono-infected persons.

31 Currently, there are no vaccines on the market for HCV. Please see Annex 7 for an overview of the HCV vaccine pipeline

32 HCV can exist as either an acute (first six months of infection) or a chronic disease. Unfortunately, few acute cases are treated as most individuals are unaware of their infection at this stage of the disease. The treatment for acute HCV is the same as for chronic HCV as described below. Curing acute HCV will prevent progression to a chronic infection.

33 Merck, Roche and Vertex 10K reports.

34 Based on the Center for Disease Analysis' study of Peg-IFN sales in high-income countries.

Table 1. Current and future treatments to cure HCV

		2001	2001-2011	2011-2014	Estimated 2014-2015	Estimated 2014-2016	Estimated >2016
		Unpegylated IFN + RBV (3/wk Injec. + 1-2/day pill)	**Peg-IFN + RBV** (1/wk Inject. + 1/ day pill/s)	**PI + Peg-IFN + RBV** (3/day oral pill + 1/wk Inject. + 1/day pill/s)	**2-3 DAAs + Peg-IFN + RBV** (1/day oral pills + 1/wk Inject. + 1/day pill)	**2-3 DAAs + RBV** (1/day oral pill/s)	**2-3 DAAs** (1/day oral pill/s)
	Daily Pill Burden	**RBV** (2-6/day)	**RBV** (2-6/day)	**PI** (8-12/day) **RBV** (2-6/day)	**DAA** (2-3/day) **RBV** (2-6/day)	**DAA** (2-3/day) **RBV** (2-6/day)	**DAA** (1-2/day)
Genotype 1	Treatment Duration	48 wks	48 wks	24-48 wks	12-24 wks	12-24 wks	≤12 weeks
	Cure Rate (HCV)	~30% (43)	~40% (44)	~70% (45)	85-90% (46) (47) (48)	85-100% (49) (50) (51) (52) (53) (54) (55) (56) (57) (58)	>90% (53) (54) (56) (59) (58)
	Cure Rate (HIV/ HCV)	~8-19% (60) (61) (62)	~30% (61)	60-75% (63) (64) (65)	~80% (66) (67)	TBD	TBD
	Est. Price/Patient	$2-14K	$2-27K	$20-55K	TBD	TBD	TBD
Genotype 2	Treatment Duration	24 wks	24 wks	N/A	12-24 wks	12-24 wks	≤12 weeks
	Cure Rate (HCV)	~60% (67) (43)	~70% (68) (69)	N/A	~85% (70)	~95% (48) (71)	>90%* (56)
	Cure Rate (HIV/ HCV)	~20% (61)	~60% (61)	N/A	TBD	TBD	TBD
	Est. Price/Patient	$1-7K	$1-13K	N/A	TBD	TBD	TBD
Genotype 3	Treatment Duration	24 wks	24 wks	N/A	12-24 wks	12-24 wks	≤12 wks
	Cure Rate (HCV)	~60% (45)	~60% (68) (69)	N/A	~70% (70)	~60% (48) (71)	>90%* (56)
	Cure Rate (HIV/ HCV)	~20% (61)	~60% (61)	N/A	TBD	TBD	TBD
	Est. Price/Patient	$1-7K	$1-13K	N/A	TBD	TBD	TBD
Genotype 4–6	Treatment Duration	48 wks	48 wks	N/A	12-24 wks	12-24 wks	≤12 wks
	Cure Rate (HCV)	~30% (43)	~40% (44)	N/A	80-95% (46) (48)	TBD	TBD
	Cure Rate (HIV/ HCV)	~8-19% (60) (62)	~30% (72)	N/A	TBD	TBD	TBD
	Est. Price/Patient	$2-14K	$2-27K	N/A	TBD	TBD	TBD

Only the most common genotypes are listed. Patients who are already cirrhotic, or have not responded to previous therapies may have a lower cure rate. All prices are in thousand US dollars. Ranges for duration of treatment are due to uncertainty in the duration of future treatment. Ranges in price reflect pricing in different countries. The high end of the price range typically represents prices in the United States. Studies in multiple genotypes were excluded unless noted otherwise.

*N/A: not applicable; TBD: to be determined; *Study in combined genotypes 2 and 3.*

5.2.1 Current therapies

Standard (unpegylated) IFN + RBV

IFN alpha 2a and 2b (IFN) have been commercially available since 1986. IFN proteins defend the body against HCV by activating an immune response. IFN has to be injected three times a week and can cause flu-like symptoms, such as muscle ache and low-grade fever. RBV is another drug that interferes with viral replication. In combination with RBV, IFN has been shown to cure twice as many patients as IFN alone.(43) However, RBV can lead to anaemia (low red blood cell levels). Thus, patients taking IFN and RBV therapy should be closely monitored. Standard unpegylated IFN plus RBV is still used in some countries in patients with low viral load to manage the overall cost of treatment.

A number of generic products for HCV treatment are already in the market. Generic RBV is available for $0.30 per day. In comparison, branded RBV can cost $35 per day in the United States. Follow-on versions of unpegylated IFN are available for $8-30 per day.[35]

Peg-IFN + RBV

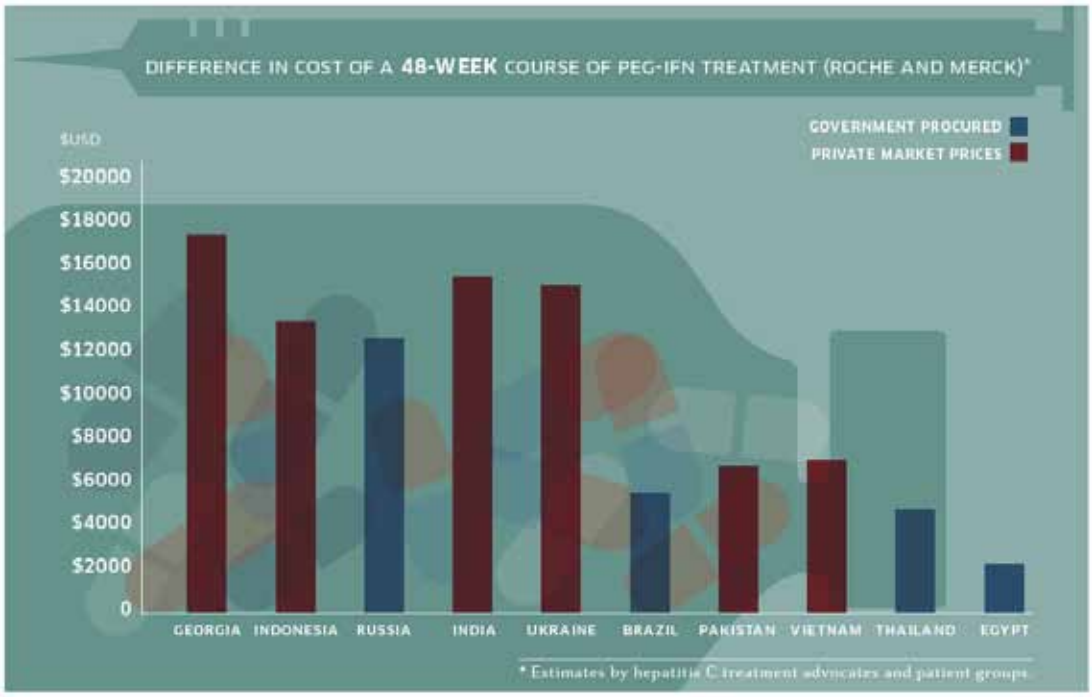
In 2001, the first Peg-IFN was launched. The addition of polyethylene glycol to the molecule allowed IFN to last longer in the body, thereby reducing the number of injections to one per week. In addition, patients are required to take a daily dose of RBV; Peg-IFN + RBV is the current standard of care in most countries. Peg-IFN is sold in pre-filled syringes. The average daily cost of Peg-IFN ranges from $6-45 per day. As shown in Figure 8, the price of a 48-week Peg-IFN + RBV treatment varies widely from $2,000 to $18,000 in middle-income countries.(73)

Follow-on versions of Peg-IFN have been adopted in a few markets, notably Egypt, where Peg-IFN is procured for a daily cost of $6 (including a weekly supply of RBV). This was accomplished by a combination of an Egyptian manufacturer offering follow-on versions of Peg-IFN, and subsequent price concessions from branded manufacturers. As a result, the 48-week treatment course costs less than $2,000 per patient. This uniquely low treatment cost, therefore, is a reflection of both the active efforts by the Egyptian government to provide large-scale treatment for its HCV-infected population, and of competition in the market.

Nevertheless, Peg-IFN produced in Egypt, and in some other middle-income countries, has not been approved by a stringent regulatory authority, nor has it been WHO prequalified; in fact, biosimilars are currently beyond the scope of the WHO prequalification progamme.

35 Price estimates using IMS Health data.

Figure 8. Peg-IFN 48-weeks price (US dollars)



Source: *Momenghalibaf, A. Hepatitis C Treatment: Price, Profits, and Barriers to Access. New York, Open Society Foundations, 2013.*

Unfortunately, not everyone can tolerate Peg-IFN + RBV treatment. It is estimated that 17% of a patient population in the United States had at least one condition (e.g., depression) that may be a contraindication for Peg-IFN + RBV therapy.(74) Among eligible patients, adverse events are common, and a substantial number of patients are intolerant of the drug therapy. Data from 1,920 patients enrolled in four clinical trials indicate that approximately 24% of all participants experienced intolerance to Peg-IFN + RBV therapy.(74) A recent survey of 697 physicians, from 29 countries, identified fear of side effects and concerns regarding treatment duration and cost as critical barriers to treatment.(75)[36]

HCV Protease Inhibitors + Peg-IFN + RBV

The launch of HCV protease inhibitors (PIs) in 2011 has improved the efficacy of treatment regimens for Genotype 1-infected individuals. In countries where HCV PIs have launched, the standard of care for Genotype 1 patients includes treatment with one of two protease inhibitors (telaprevir or boceprevir). The triple therapy (PI + Peg-IFN + RBV) has improved cure rates, as shown in Table 1, but it has also increased the number of adverse events and the complexity of treatment monitoring. The product labels for the PIs report 35-50% anaemia among treated patients in clinical trials (as compared to 15-30% with Peg-IFN + RBV alone), and state that skin rash is observed in 15-55% of the patients (as compared to 5-35% with Peg-IFN + RBV alone).(76) (77)

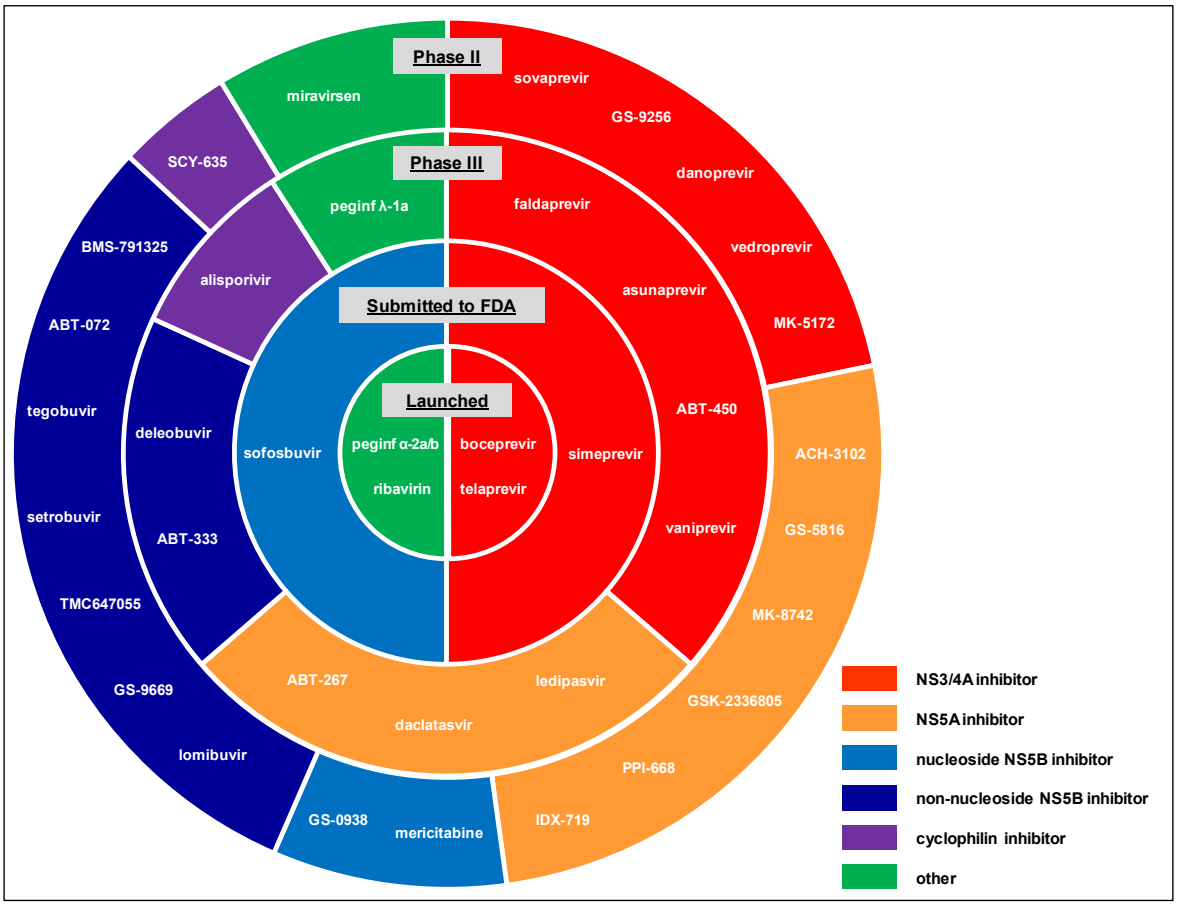
According to a recent survey by WHO, nearly 20% of member states reported that the HCV protease inhibitors (boceprevir and/or telaprevir) are on their national Essential Medicines List or are subsidized. (102) HCV PIs are taken as pills, three times per day, in addition to the weekly injections of Peg-IFN and daily oral doses of RBV. These new drugs come at a sizeable cost (up to $55,000 for a course of treatment), although some suppliers are providing large discounts and rebates (e.g., at a 50% discount) in select countries to promote their use before the launch of future therapies.

36 Nevertheless, new orals (see Section 5.2.2) may result in new treatment regimens with higher cure rates and a shorter duration (3 months versus 12 months) of Peg-INF, which may be better tolerated.

5.2.2 Future therapies

There are currently 11 drugs in phase III clinical development for HCV (see Annex 6 for more details). Behind these are another 22 compounds in phase II of clinical development for the treatment of HCV. However, not all of these compounds are expected to reach the market. Historically, only half of all compounds in phase II and 70% of compounds in phase III have reached the market. The first of these future products will launch in 2014 with expected higher cure rates, shorter duration of treatment, and fewer side effects, compared to the current Peg-IFN + RBV treatment. The new DAAs target enzymes essential to viral replication as compared to IFN-based therapy. The latter activates the host's defences leading to the death of the infected hepatocytes. As a result, it is expected that DAAs could be used with a lower risk of hepatic decompensation in patients with more advanced liver damage.(78)

Figure 9. Compounds in development for treatment of HCV, phase II to launch



Though these future products have been added to Peg-IFN + RBV in a number of studies, it is anticipated that regimens combining one or two DAAs with RBV will emerge as the preferred treatment options. Such all-oral therapies would eliminate the need for Peg-IFN injections, as well as the corresponding side effects. These therapies would also increase the number of patients eligible for treatment. By 2016, RBV could potentially be eliminated as well by using multiple DAAs. This could reduce the number of individuals experiencing anaemia and increase the population eligible for treatment even further.

All-oral drug combinations that work across all genotypes could work well in resource-limited settings, as they would allow all patients to be treated with a single therapy, without the need to determine the genotype of patients.

In March 2013, two compounds (sofosbuvir by Gilead and simeprevir by Janssen Pharma) were submitted to the US Food and Drug Administration (FDA) for approval. Before the end of 2013, similar applications by Abbott, Roche, Boehringer-Ingelheim, and Bristol-Myers Squibb are also expected to be filed. Numerous clinical trials are underway due to the number of potential variations for each drug, such as combinations with different DAAs, with or without Peg-IFN or RBV, variation in HCV genotype, differences in patients' prior exposure to treatment (treatment naive, relapse, or null responder), liver disease stage, and HIV/HCV co-infection (see Box 1). A comprehensive summary of recent clinical trials in different populations has recently been published.(87)

Multiple launches are expected for each individual compound, because regulatory agencies will only approve their use as a component of a specific combination when data from clinical trials demonstrate efficacy of that combination. To illustrate, the projected launch dates for Gilead's sofosbuvir in Genotype 1 are shown in Figure 10 (these launch dates have been projected without guidance from Gilead). Gilead has filed with the US FDA for use of sofosbuvir in combination with Peg-IFN + RBV for Genotypes 1, 4, 5 and 6, and for use with RBV in Genotypes 2 and 3; this could be approved and launched in 2014. By 2014, Gilead is expected to file for a Peg-IFN-free combination for other genotypes, with an expected launch date of 2015. By 2016, some RBV-free regimens could be available in the US and EU. However, the launch of these combinations is expected to be delayed in certain geographies. For example, launches in several high-income countries are projected to be delayed by a year or more, while the launch of these therapies in low- and lower-middle-income countries could be delayed by 3-5 years, relative to the drug's initial launch. In the meantime, the current Peg-IFN-based treatments would remain important for patients in these countries.

Figure 10 is a simplified projection of first launch dates for sofosbuvir in HCV Genotype 1 mono-infections in different parts of the world. Within each group, the timeframe for approval and launch may nevertheless vary among countries.

Box 1: Clinical trials

To date, most clinical trials for new HCV treatments have focused on Genotype 1 mono-infected patients. These trials have demonstrated higher cure rates for new DAAs used in combination with Peg-IFN + RBV, as well as the ability of these regimens to shorten overall duration of treatment to 12-24 weeks.(79) However, a few of the compounds (for example, sofosbuvir by Gilead, daclatasvir by BMS, and ABT-450 by AbbVie) are being studied across multiple genotypes.(53) (51) (56) (70) (80) (81) (82)

In the case of Genotype 2 and 3, a combination of Peg-IFN + RBV has been shown to result in a 60-75% cure rate with 24 weeks of treatment. In these genotypes, sofosbuvir plus RBV has been shown to be non-inferior (71) (48), though Genotype 3 may be more difficult to cure with the new therapies as compared to Genotype 2 (cure rate ~60% versus 90%, respectively).(71)

The current trials with DAAs are conducted in the adult population. Once optimal drug combinations that provide superior efficacy over the standard of care have been identified, and the safety and optimal dosing of these combinations have been determined, clinical trials may be conducted in paediatric patients. In return for studying a drug in the paediatric population, companies are awarded additional exclusivity and protection in the US and EU.(83) (84)

It remains to be seen how suitable the DAAs are for HIV/HCV co-infected people due to possible drug-drug interactions with WHO-recommended antiretrovirals (ARVs). Moreover, cure rates within the HIV/HCV co-infected population have been historically lower than those of mono-infected persons (see Table 1); however, this difference may decline with the new therapies. Recent studies with direct-acting antivirals (DAAs) + Peg-IFN + RBV showed comparable cure rates in both mono- and co-infected populations.(66) (67) A proof-of-concept study with a single DAA showed a nearly identical drop in HCV RNA in Genotype 1 and Genotype 2/3 mono-infected patients and HCV/HIV co-infected patients.(85) Nevertheless, all published studies to date relate to combinations with peg-IFN + RBV.

Currently, only one phase III clinical trial using an all-oral treatment (sofosbuvir plus RBV) is underway in Genotype 1, 2, and 3 HCV/HIV co-infected individuals.(86)

Figure 10. Projected first launch dates for sofosbuvir in Genotype 1

	2014	2015	2016	2017	2018	2019
US, France, Germany, & UK	sofosbuvir + Peg-IFN + RBV	sofosbuvir + RBV	sofosbuvir + other DAAs			
Other high-income & upper-middle-income countries		sofosbuvir + Peg-IFN + RBV	sofosbuvir + RBV	sofosbuvir + other DAAs		
Low- & lower-middle-income countries				sofosbuvir + Peg-IFN + RBV	sofosbuvir + RBV	sofosbuvir + other DAAs

5.2.3 Patents

With the exception of RBV, which is already available in generic form, the above compounds generally are patented. Key US patents for PegIntron®[37] will expire between 2015 and 2020 (88), while Pegasys'®[38] patents will expire in 2019.(89) Boceprevir has patent coverage in the US until 2027 and telaprevir is patented until 2025.(89) The patents for the future therapies are not expected to expire until between 2026 to 2031.(90)

37 Pegylated interferon alfa-2b, marketed by Merck.
38 Pegylated interferon alfa-2a, marketed by Roche.

Table 2. Expected expiration dates of key patents in the US and western Europe

Compound/s	US & Western Europe Patent Expiration Date
RBV	Generic
Peg-IFN	2015-2020
New Protease Inhibitors	2025-2027
Future DAAs	2026-2031

Based on limited available information, Pegasys® appears to be more widely patented in middle-income countries than PegIntron®. Specifically, key patents on Pegasys® have been granted in seven of eight (88%) middle-income countries for which information is available, and are pending in the remaining country. PegIntron® is under patent in one of eight (13%) middle-income countries for which information is available, while applications are pending in three of those countries (38%). These patents are expected to expire between 2016 and 2020.(91)

6 HCV diagnostics—current and future diagnostics

Current diagnostic algorithm

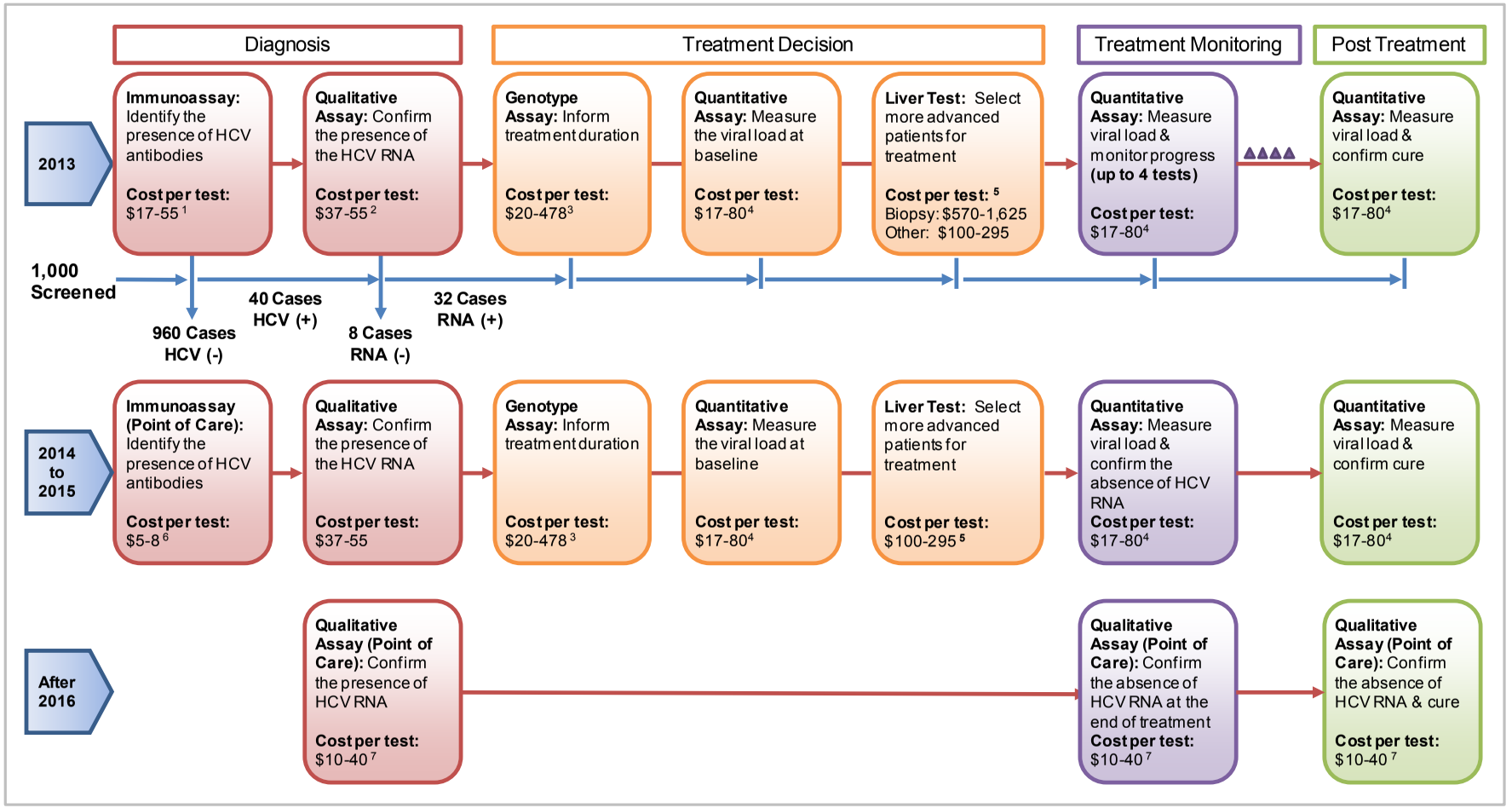
Currently, the first step in diagnosing HCV is an immunoassay screening test, which determines the presence of anti-HCV antibodies. The presence of such antibodies means that the person has been exposed to HCV, but it does not mean there is active infection (antibodies remain after the infection has been cleared or cured). Most tests for HCV antibodies use whole blood or serum/plasma, though new tests that screen saliva are available. Unfortunately, since active HCV disease is often asymptomatic, many patients who screen positive receive no additional follow up. In general, only patients exhibiting symptoms are referred to a specialist for further evaluation. The next step involves a molecular assay to test for the presence of active virus in circulation, measuring either HCV RNA or HCV proteins.

The population with active HCV disease is defined by patients with detectable HCV RNA. For such patients, physicians may choose to send additional samples to test if the patient should be treated, and how. These tests extend beyond HCV diagnostic tests to general medical tests such as liver tests, to inform clinical decision making. Tests may include: 1) a viral load assay to measure the viral count or confirm diagnosis, 2) a genotype assay to determine the HCV genotype, and/or 3) liver tests to determine the stage of liver damage. Patients who begin treatment also need several viral load tests to determine their response to the drugs. More viral load tests are required for Genotype 1 patients (who undergo treatment for 48 weeks with current regimens) as compared to patients with Genotypes 2/3 (who currently receive shorter-duration regimens). This complex monitoring paradigm is largely a consequence of safety concerns and limited efficacy of the current treatment options.

Each treated patient undergoes a final viral load test, generally six months after completion of treatment, to confirm a true cure (since some patients will relapse after the end of treatment).

This five-step diagnostic paradigm—screen, test for active disease, stage for treatment, monitor treatment, and test for cure—has evolved over time to make the most efficient use of healthcare resources. In a country with an HCV prevalence rate of 4%, only 40 people will test positive for HCV antibody after screening 1,000 individuals, and only 28 to 35 of those will prove to have active HCV disease. (In populations with large numbers of HIV patients, where the co-infection rate is much higher than the general population, 150-600 patients may screen positive.) Thus, the majority of the population can be screened using low-cost HCV antibody tests, before the more expensive molecular assays are used to identify active HCV infection.

Figure 11. Simplified HCV diagnostic paradigm, today and in the future in a resource-limited settings



The above figure illustrates a simplified evolution of diagnostic technologies in a resource constraint setting. After 2016, the focus of the analysis was to illustrate the preferred technologies in regions where testing at a central laboratory is not feasible or it is more efficient to test patients locally rather than send samples away to a central laboratory.

1. Rein et al., 2012 estimated a range of $17-$55 (92); Medicare/Medicaid 2013 reported $27-37 per test (93); point-of-care OraSure test was estimated at €14 or $19 according to MSF report.(5)

2. Medicare/Medicaid 2013 reported $37 per test (93); MSF reported a range of $49-$55 for Roche COBAS test; for future therapies, MSF reported a cost $20 per test for the reagents for the Wave 80 test.(5)

3. Medicare/Medicaid 2013 reported $478 per test (93); MSF reported a cost of $20 for the reagents for Sacace test which is not approved in the US and a cost of $50 for the reagents for the reagents for the Wave80 test.(5)

4. Medicare/Medicaid 2013 reported $80 per test (93); MSF reported a cost of $42-64 for the reagents for the Roche COBAS tests, $22 for the reagents for the QIAGEN test, and $17 per test for the reagents for the Sacace test; it also reported a reagent cost of $40 per test for Wave80, which is a pipeline product.(5)

5. McGarry et al., 2012 reported an average biopsy cost of $570 (94); in other studies, liver biopsy cost was estimated at $974-1,623 per patient and Fibrotest cost was estimated at $100-295.(95) (96)

6. Point-of-care CD4 tests were used as an analogue for point-of-care immunoassay test for HCV with a cost of $5-8 per test (97). Test prices for Daktari, MBio, and Zyomyx CD4 tests were included in this analysis. The cost per test would be as low as $2 if flow cytometers were considered. Qualitative RNA test are more complex.

7. HIV tests were used as an analogue for HCV. Cepheild's GeneXpert's price per cartridge is estimated at $10, bioMérieux's nucliSenS HIV Solution average price was estimated at $24, and Abbott RealTime's price was estimated at $25-40.(97)

Near future diagnostic paradigm (2014-2015)

In the near future, two developments are expected that could have a large impact on HCV diagnostics in resource-limited settings: the availability of point-of-care (POC) HCV assays to complement existing central lab technologies, and future oral therapies.

POC assays will enable on-site diagnosis and monitoring. This will be an important benefit in settings where patients have to travel long distances for access to care, where blood samples have to be transported to central laboratories for testing, and where patients are expected to return to the clinic days or weeks later to obtain their results (since many patients never return for their results).

The future oral therapies will require fewer viral count tests due to simpler treatment regimens and a shorter duration of treatment. In addition, so-called 'pan-genotypic' drugs—drugs that are equally effective across all HCV genotypes—would eliminate the need for a genotype assay and simplify the number of diagnostics required.

Future diagnostic paradigm (2016+)

POC tests that can measure the presence of HCV RNA or HCV proteins may reach the market by 2016.[39] These tests can be used to determine the presence or absence of HCV before the patient leaves the clinic—effectively combining screening and testing for active viral infection into a single POC test. With safer, more effective treatments, the need for staging liver damage could also be reduced in resource-limited settings by making all patients potentially eligible for treatment, regardless of disease stage. This will simplify physicians' decision process as well as limit the number of diagnostic tests required to initiate treatment. Pan-genotypic drugs are also expected to reach the market by then, eliminating the need to determine patients' genotype.

Diagnosis and confirmation testing could take place in the clinic with POC testing. Patients could then be put on an 8-12 week all-oral treatment regimen before leaving the clinic. An RNA test at the conclusion of treatment could test for the absence of the virus, followed by another test three to six months afterwards to confirm that the patient is cured. Staging of liver damage may only be required for patients with advanced stages of the disease, who require treatment by a specialist and liver tests before and after treatment to track the potential progression of the damage, and, in cirrhotic patients, the development of HCC.

The future diagnostic paradigm presented in Figure 11 (i.e., after 2016) is focused on resource-limited settings. Where access to specialists is more feasible, the 2013 and 2014-2015 paradigm is expected to remain in place with fewer viral load tests required due to the shorter duration of treatment.[40]

Manufacturer landscape

As shown in Table 3, a number of manufacturers offer diagnostics for HCV and/or are developing future diagnostics that can perform faster and at lower costs at the point of patient care.

39 Based on CDA interviews with manufacturers and analysis of product pipelines.

40 An immunoassay followed by an RNA assay will be used to screen and diagnose patients with HCV RNA. Viral load and liver tests will also be performed to monitor the progress.

Table 3. Current and future providers of diagnostics

Type of Assay	Description/Price	Manufacturers		
		2013	2014-2015	After 2016
Immuno- Assay	Identifies the presence of HCV antibodies **Estimated Price:** **2013:** $17-55 **2014-2015:** $5-8 **After 2016:** N/A	1. ELISA *Abbott* *Acon Labs, Inc* *Bio-Rad* *Dialab* *Human Diagnostics* *Innogenetics* *J.Mitra* *MP Biomedicals* *Ortho-Clinical* *Roche* *Siemens* 2. Point of Care *Alere** *Alfa Scientific** *Axiom Diagnostics** *CORE* *Dialab** *Fujirebio Inc* *Green Cross Medical Science* *Human Diagnostics** *J.Mitra* *MedMira** *MP Biomedicals* *OraSure* *Standard Diagnostics** 3. RIBA *Innogenetics* *MP Biomedicals*	1. Point of Care *Chembio* *MedMira*	1. Point of Care *MBio*
Qualitative	Confirms the presence or absence of HCV RNA above a certain threshold **Estimated Price:** **2013:** $37-55 **2014-2015:** N/A **After 2016:** $10-40	1. PCR *Roche* 2. TMA *GenProbe* *Novartis Hologic* *Siemens*		2. Point of Care *Daktari* *MBio* *Wave 80*
Genotype	Determines the genotype of hepatitis C virus **Estimated Price:** **2013:** $20-478 **2014-2015:** N/A **After 2016:** Not Determined	1. Line Probe *Siemens* 2. Linear Array *Roche* 3. RT-PCR *Abbott* *Sacace* *Siemens*		1. Point of Care *Celera* *Wave 80* 2. RT-PCR *Cepheid*

Type of Assay	Description/Price	Manufacturers		
		2013	2014-2015	After 2016
Quantitative	Measure the viral count/load **Estimated Price:** **2013:** $17-80 **2014-2015:** Not Determined **After 2016:** $15-50	1. bDNA *Siemens* 2. RT-PCR *Abbott* *Qiagen* *Roche* *Sacace* *Siemens*	1. RT-PCR *Cepheid*	1. Point of Care *Alere* *Daktari* *IQuum* *Wave 80* 2. RT-PCR *Cepheid* 3. TMA *Hologic Gen-Probe*
Liver Tests	Evaluates the extent of liver damage/fibrosis **Estimated Price:** **Biopsy:** $570-1,625 **FibroTest:** $100-296+ **FibroSure:** $161-269+ **FibroSpect:** $263-438+ **Fibroscan:** $98-164+	1. Liver biopsy 2. Biomarker Tests *BioPredictive (FibroTest, ActiTest)* *BioLiveScale (Fibrometer)* *LabCorp (FibroSure)* *Quest (Hepascore)* *Prometheus (FibroSpect)* 3. Transient Elastography *Echosens (Fibroscan)*		

** Point-of-care tests currently on the market that are not CE-Marked, FDA Approved, or WHO tested*

+ Pricing estimates from Carlson et al., 2009 (96) and Liu, et al, 2011.(95)

ELISA: enzyme-linked immunosorbant assay; RIBA: recombinant immunoblot assay; PCR: polymerase chain reaction; RT-PCR: reverse transcription polymerase chain reaction; TMA: transcription-mediated amplification; bDNA: branched DNA assay

7. Funding activities by major public health players

Public players (including governments, NGOs and multilateral organisations) have historically not identified either HCV or HIV/HCV co-infection as a priority funding area, especially in low- and lower-middle-income countries. It should be noted that a shortage of published information limits visibility on the funding landscape;[41] however, the absence of evidence in this case likely equates to evidence of absence.

Multilateral institutions have so far committed limited financial resources to address HCV and HIV/HCV co-infection in low- and lower-middle-income countries. The Global Fund to Fight AIDS, Tuberculosis, and Malaria is likely one of the few institutions that have financed HIV/HCV activities. Even so, its projects are limited, reaching an average of 100-200 beneficiaries each.(98)[42,43] Other major global health funders have not yet made large-scale investments.

Though there are notable exceptions, many national governments have so far not identified HCV and HIV/HCV as a strategic priority. In May 2010, the World Health Assembly adopted a resolution on viral hepatitis.(99) The resolution urges Member States, among others, to increase surveillance, prevention, control and management of viral hepatitis. Yet in many middle-income countries, HCV and HIV/HCV policies are still under discussion, or have only recently been finalised.(100) Several government programs in middle-income countries have not yet established specific treatment targets or measurement indicators.(100) For example, in the majority of middle income countries in eastern Europe and central Asia, patients are expected to independently finance their own HCV treatment.(101)[44] Annex 8 provides more information on HCV and HIV/HCV treatment and funding in a number of eastern European countries. The lack of public funding in middle-income countries suggests that the situation in low- and lower-middle income countries will be of even greater concern. For example, more than 70% of countries in Sub-Saharan Africa that responded to a recent survey reported that no public funding is available for treatment of HCV.(102)[45]

A lack of awareness of HCV's burden and prevalence, combined with a lack of appropriate and affordable treatment options, has likely limited funding for HCV and HIV/HCV screening and treatment. Partly due to the paucity of available data on the prevalence and sequelae of HCV on a national and regional level, it is potentially difficult for local and global policy makers to grasp the extent of the epidemic, and might lead to a lack of recognition of the magnitude of HCV and HIV/HCV as major public health problems.

Few foundations and NGOs are funding HCV or HIV/HCV programs. Médecins Sans Frontières (MSF) has indicated an interest in starting several HIV/HCV co-infected patients on treatment and has done surveillance in several HIV treatment sites. Other foundations are programming small-scale HCV interventions. For example, in 2011, the Bristol-Myers Squibb Foundation awarded four grants (totalling nearly $1 million) to fund HCV treatment in China and India. In the same year, the US Centers for Disease Control and Prevention launched the Viral Hepatitis Action Coalition, a public-private partnership to address viral hepatitis.

41 As funding for Hepatitis B and C is jointly described in a number of publications, it is challenging to accurately calculate how much funding is dedicated solely to HCV programs.

42 Past projects include providing HCV diagnostics and treatment services to HIV/HCV co-infected individuals in Georgia and Macedonia.

43 Ukraine's Global Fund Round 10 project will include hepatitis C testing for most at risk populations and integration of hepatitis C prevention education into existing harm reduction programs.

44 Full or partial government funding for HCV treatment is available in 33% of low-income countries. However, this calculation includes funding for Hepatitis B as well.

45 Of the countries that responded.

8. Market shortcomings and reasons

The following section provides an overview of market shortcomings for HCV treatment and diagnosis.[46] After a short discussion of the vaccine pipeline, IFN-based treatment is first explored, followed by future oral medicines. Finally, market shortcomings in diagnostics are discussed.

Table 4. Market shortcomings

Category	Market shortcoming
Vaccine	• Lack of availability
IFN-based treatments	• Lack of affordability • Lack of acceptability/adaptability • (Negative feedback cycle between lack of screening and lack of access to treatment)
Future oral drugs	• Possible lack of affordability • Acceptability/adaptability yet to be confirmed • Possible delay in delivery
Diagnostics	• Lack of affordability • (Negative feedback cycle between lack of affordable treatment and lack of screening)

8.1 Vaccines

There is currently no HCV vaccine available or in late-stage development. This is due to the technological complexity of developing an efficacious vaccine, rather than the lack of a market opportunity.(3)[47] A vaccine is not expected in the near future. (See Annex 7 for an overview of the vaccine pipeline.)

8.2 Current treatments

IFN-based treatments suffer from a lack of affordability, and from a lack of acceptable/adaptable products. Finally, the lack of appropriate diagnostics reduces the demand for treatment.

8.2.1 Lack of affordability of products.

IFN-based treatments are not affordable for people living in low- and lower-middle-income countries. IFN constitutes the key element in current HCV treatments.(103)[48] As shown in Section 5, the average treatment price across 10 middle-income countries is approximately $9,500, with significant variation (see Figure 8).

A number of reasons explain the lack of affordability of current IFN-based treatments.[49] Table 5 provides a summary, with further explanation in the following paragraphs.

46 For details on how UNITAID categorizes market shortcomings, see UNITAID Strategy 2013-2016, p. 32-33.

47 The genome of HCV is highly mutable, which makes it difficult to create a vaccine that gives widespread immunity. Furthermore, due to the fact that there are over six different HCV genotypes, vaccine antigens from multiple HCV serotypes would probably be necessary for a universally effective vaccine. Because HCV is a continuously replicating RNA virus and evolves over time as it infects humans, it is believed to persist as a collection of virus quasispecies. By constant mutation, HCV may be able to escape host immunologic detection and elimination, which complicates the development of an effective vaccine.

48 Ribavirin is a generic, and available at relatively low costs (as low as $0.03 per 100 mg pill).

49 The current treatment for HCV is either pegylated interferon, pegylated interferon and ribavirin, or pegylated interferon and ribavirin with a protease inhibitor (boceprevir or telaprevir).

Table 5. Market shortcomings summary—IFN

Symptoms	Category	Reasons (I)	Reasons (II)	Reasons (II)
Lack of affordability of IFN	Supply-side	Production costs	IFN is biological	• Relatively high upfront investment
		Profit margin	Lack of competition/ barriers to entry	• Lack of clear regulatory pathway for biosimilars • Intellectual property barriers (patents, manufacturing know-how/trade secrets)
	Demand-side	Profit Margin	Lack of buyer bargaining power	• Low volumes

IFN is a biological; upfront investment in production facilities for biologicals is relatively high. Biologicals are produced not through chemical syntheses like small-molecule drugs, but through biological processes in living cells.[50,51] Since production and filling of biologicals has to take place under completely sterile conditions, upfront investments in facilities and equipment tend to be higher than those for small-molecule drugs (24).[52]

Profit margins may be high, and contribute to high prices for IFN. IFN-based treatment costs up to $18,000 in some middle- and high-income markets, but cost $2,000 in others. Though details of the cost structure are not known, this price variation is likely driven by differences in costs and in fixed cost allocation across markets, as well as differences in profits/operating margins.[53] In general, a market with two dominant manufacturers[54] and significant barriers to entry (see below) is likely to have limited price competition and above-average profits. (104)[55]

There is no clear regulatory pathway for biosimilars.[56] Biologicals made in different cell lines or manufacturing plants are unique and cannot be assumed a-priori to be identical or similar.[57] Moreover, regulatory pathways for follow-on biologicals are not as well-established, and are more complex than the pathway for small-molecule drugs. Thus, second-to-market/follow-on manufacturers usually cannot fully rely on comparability studies with incumbents, and may also have to undertake clinical trials. Thus, development costs for biologicals are relatively high. This, combined with the uncertain pathways[58], might deter entry and reduce competition.[59]

Intellectual property barriers may deter or delay market entry of follow-on products. Peg-IFN is still under patent in the two major markets (US and EU). There is no comprehensive data on the extent of patenting of Peg-IFN in low- and middle-income countries; however, available data indicate that patents have been granted in several middle-income countries with high HCV prevalence. These patents are likely to deter manufacturers of follow-on products; at least one manufacturer in India (Virchow Biotech Ltd) is reportedly involved in a patent dispute over Peg-IFN.(91)

There is no strong concentration of buyer bargaining power to create price pressure. Funding and procurement of HCV diagnostics and treatments by/for low- and lower-middle-income countries has been limited and fragmented. To date, there have been no efforts to consolidate or coordinate procurement through global or regional procurement or price negotiation mechanisms.

50 Biologics are significantly larger in size and of greater complexity than small molecule drugs.
51 The average production length of biologicals is usually longer than for small-molecule drugs, although there are notable exceptions.
52 This however depends on the plant's size, complexity and location.
53 Operating margins may be used to cover fixed costs, however such upfront investments (in clinical trials and production capacity, for example) were most probably earned back and depreciated in the last decade.
54 One manufacturer (Minapharm) sells a follow-on version of interferon in Egypt at a cost of $2000. However, it does not appear to have regulatory approval in other markets.
55 As shown in the MSF publication *Medécins Sans Frontières—Untangling the Web*, the number of players in the ARV market has a strong correlation with price decreases over time.
56 Biosimilars are biological products which are similar in terms of quality, safety and efficacy to a biological product that is already registered.
57 Biological drugs include antibodies, blood components and vaccines.
58 Clearly, success in clinical development and regulatory approval cannot be taken for granted. Recently, biomedical companies' new products have been rejected, due to insufficient clinical evidence of efficacy and comparability of the biosimilar.
59 Lack of "know how" can pose further challenges.

8.2.2 Lack of acceptability and adaptability of products

IFN-based treatments are difficult to use, especially in resource-limited settings. Most of their limitations are exacerbated in HIV/HCV co-infected patients.

The efficacy of current HCV treatments is low, particularly for HIV/HCV co-infected patients. The efficacy of the Peg-IFN + RBV therapies in curing HCV infection is only 40% in Genotypes 1, 4, 5, and 6 (as shown in Table 1).[60] These Genotypes are common in low- and lower-middle-income countries. The addition of protease inhibitors increases the efficacy in Genotype 1 patients to 70% but the associated increase in adverse events requires close monitoring of patients. The current duration of treatment in Genotypes 1, 4, 5 and 6 is 48 weeks. The long duration of treatment negatively affects adherence. HIV/HCV co-infected patients have a lower cure rate than HIV-negative patients (as shown in Table 1). For example, Genotype 1 co-infected patients have a cure rate of 30% as compared to 40% in HCV mono-infected patients, while Genotype 2 co-infected patients show a cure rate of 60% versus 70% in HIV-negative individuals.

IFN-based treatment causes serious side effects. IFN + RBV therapy has serious adverse events (e.g., decrease in red blood cells and platelets) in 10-20% of patients. In addition, patients experience fatigue and headache (65%), fever (50%), injection site reaction (20-75%), anxiety (30-50%), muscle pain (50%), nausea and vomiting (30%), and loss of hair (30%).(105) (106) (107) Addition of protease inhibitors increases the adverse side effects to 50% of patients.(108) (76)

In addition, HIV/HCV co-infected patients respond differently to some of the current therapies. In clinical trials, 19% of HIV/HCV co-infected patients experienced serious adverse events as compared to 10% of the HCV mono-infected patients.(105) The most serious adverse event was bacterial infection (5% in co-infected population vs. 3% in HCV infected). In addition, co-infected patients typically have higher discontinuation (16% vs 11%) and dose modification rates due to side effects.(105)

There is interaction between ARVs and HCV medicines. IFN + RBV interacts with certain ARVs, which must be taken into consideration before treating a co-infected patient. For example, RBV cannot be used with didanosine and requires close monitoring for patients on zidovudine. Also, currently available PIs have interactions with some ARVs.(63) (108) (109) It should be noted that drug-drug interactions with future DAAs may also limit options for HCV/HIV co-infected patients.

8.3 Future oral treatments

The pipeline and potential of future drugs is uncertain, but looks very promising.[61] However, as these treatments are not yet on the market, and critical information on pricing and effectiveness is still unknown, this section will focus on *potential* shortcomings.

8.3.1 Possible lack of affordability of products

Future oral treatments are likely to be expensive. The costs of production of the future oral DAAs are not yet known, and are likely to vary among different drugs; but since they are small molecules, the long-term cost of production is expected to be lower than that of Peg-IFN. In fact, according to some estimates, in 15 years, the price of a 12-week treatment course of two generic DAAs plus RBV could be as low as $100-$200.(110) Nevertheless, manufacturers have made large upfront investments, and are expected to have applied for patent protection, at least in the main markets and in countries with manufacturing capacity.

To date, no manufacturer has made its pricing strategy public.[62,63] Nor has any provided details regarding possible price differentiation schemes or made firm commitments on affordable pricing for low- and middle-income countries. Nevertheless, some DAA manufacturers reportedly are considering possible strategies for providing access to these drugs in low-income countries. Manufacturers may be willing to explore access strategies similar to those used for HIV and malaria medicines. This may be feasible, since the global prevalence

60 Genotype 4 is found mostly in North Africa, genotype 5 is prevalent in South Africa, while genotype 6 is concentrated in South East Asia.

61 Though there are a number of competing producers and products, many anticipated drugs are still undergoing late-stage clinical trials. Significant uncertainty remains regarding which drugs will ultimately receive approval, and whether these new drugs will be able to fully substitute current medicines (e.g. cover all genotypes).

62 In 2011, Gilead purchased Pharmasset, a pharmaceutical company that created PSI-7977 (a DAA used in HCV treatment) for $11.1 billion.

63 Dalberg-conducted interviews with HCV experts.

of HCV is much higher than HIV and companies typically recover their investment in drug development in the US and Western Europe.

8.3.2 Acceptability and adaptability of products yet to be confirmed

Although the overall efficacy and safety profiles of future oral drugs look promising, further studies are needed. Clinical trials with DAAs suggest much higher cure rates (80-95%) as compared to current treatments. In addition, though data is very limited, DAAs may have the same cure rate in HIV-positive and HIV-negative patients. (45) (64) (51) (56) (111) (112) (85) (113)[64] The duration of treatment will be reduced with the future therapies—i.e., $\leq$24 weeks of treatment versus 24-48 weeks for current treatments—possibly resulting in improved adherence. However, further studies in genotypes common in low-income countries (Genotypes 3-6) are needed to demonstrate the universal effectiveness of DAAs.

8.3.3 Possible delay in delivery of products

Market entry of future oral treatments in low- and lower-middle-income countries may be delayed relative to launch in the EU and US. Manufacturers are likely to focus initially on launching their products in the more profitable markets of developed countries, where there is a considerable demand for these products. This could delay the use of DAAs in resource-limited settings by several additional years.

8.4 Current diagnostics

As described in Section 6, screening for HCV and monitoring of HCV treatment requires a suite of diagnostic tests. The following section explores the market shortcomings, notably the affordability, of the "total package" of diagnostics, looking at both the number of diagnostics required and the price per diagnostic test.

8.4.1 Lack of affordability

The current diagnostic protocol has low affordability, driven by both the quantity and price of diagnostics. As depicted in Table 6, and as described earlier, diagnosing HCV and monitoring HCV treatment requires a number of complex and expensive tests. In addition, the overall length of treatment increases the number of viral load tests required.

Table 6. Current HCV diagnostic requirements

Stage of diagnosis	Type of diagnostic	Number required	Price per test (USD)	Total price (USD)
Confirmation of HCV	Immunoassay	1	~20-50	~20-50
	Qualitative assay	1	~40-50	~40-50
Treatment duration decision	Genotype test	1	~20-500	~20-500
Baseline (1), monitoring (3-4), and post-treatment (1)	Quantitative assay (viral load)	5-6	~20-80	~100-480
Treatment decision	Liver function test	1	~100-300 (Biopsy: ~500-1,600)	~100-300 (Biopsy: ~500-1,600)
			TOTAL PRICE	**~300-1,380** ~700-2,680 (with biopsy)

For source of cost estimates, see Figure 11. Figures were rounded off.

64 SILEN-C1 study arm of 240mg QD FDV plus pegIFN/RBV in HCV GT1 treatment-naïve monoinfected patients without cirrhosis.

8.4.2 Lack of appropriateness and adaptability

The current diagnostic paradigm is not suitable on a large scale for low-income countries, and is challenging for middle-income countries. HCV-infected individuals currently undergo multiple diagnostic steps. These include a primary screening (serological assay), a confirmatory test (molecular assay), a genotype assay, a viral load test, and liver disease progression tests. In low- and lower-middle-income countries, the sheer number of tests and resources required to conduct these tests constrains access. The situation is further complicated by the physical distance between patients and clinics, and by the time required to obtain diagnostic results from a central laboratory.[65] It is estimated that 84% of the population in lower-middle-income countries and 96% of the population in low-income countries live in areas where initial testing is not accessible (5). The HCV diagnosis rate in most high-income countries remains below 50% and is estimated to be less than 10% in most low- and lower-middle-income countries.(14) (15) (16)

8.5 Future diagnostics

This section describes the anticipated affordability and appropriateness of the future diagnostic paradigm, considering simplification due to future oral treatments and innovation in POC diagnostics.

In the future, the number of tests required to confirm and treat HCV could be reduced, but would still be expensive for low- and lower-middle-income countries. As described in Section 6, the future HCV testing paradigm after the introduction of DAAs could look like that presented in Table 7. In this future paradigm, the total cost of diagnosing HCV could drop to a range of 220 to $1100.

Table 7. Short-term future HCV diagnostic requirements (potential)

Stage of diagnosis	Type of diagnostic	Number required	Price per test (USD)	Total price (USD)
Confirmation of HCV	Immunoassay	1	~5-10	~5-10
	Qualitative assay	1	~40-50	~40-50
Treatment decision	Genotype test	1	~20-500	~20-500
	Quantitative assay (viral load)	1	~20-80	~20-80
	Liver function test	1	~100-300	~100-300
Treatment monitoring and post-treatment	Viral load assay	2	~20-80	~40-160
			TOTAL PRICE	**~220-1,100**

For source of cost estimates, see Figure 11. Figures were rounded off.

The price of POC diagnostics under development is not yet known. Appropriate diagnostic tools for POC usage are lacking; however there are some such tools in the pipeline (see Section 6). Furthermore, increased demand for future oral drugs would also increase the market size for diagnostics and would create further incentive for manufacturers to develop and market innovative POC solutions.[66]

65 ALT, creatine and haemoglobin tests are often relatively available in developing countries, as part of HIV programmes. Viral load testing may be performed on dried plasma or blood spots (which makes it easy to transport to a central lab at room temperature). Furthermore, the instruments used to measure HCV viral load are usually the same as those available for HIV viral load tests. Therefore, where HIV viral load testing is available, HCV testing could relatively easily be offered too.

66 Conversely, historically, the unaffordability of HCV medication and the subsequent dearth of HCV treatment services in low-income countries have limited the global demand for diagnostics. This weak demand created a disincentive for manufacturers to invest in POC diagnostic solutions for resource-limited settings.

Table 8. Long-term future HCV diagnostic requirements (potential)

Stage of diagnosis	Type of diagnostic	Number required	Price (USD)
Confirmation of HCV	POC qualitative RNA assay	1	~10-40
Treatment monitoring	POC qualitative RNA assay	1	~10-40
Post treatment	POC qualitative RNA assay	1	~10-40
		TOTAL PRICE	**~30 - 120**

If the DAAs live up to their promise, and liver fibrosis staging tests and genotype assays will no longer be needed, then their combination with future POC tests might reduce the cost of diagnosis to $30 to $120. Based on the HIV example, the cost of POC RNA assays may be in the $10 to $40 range. The price of each HCV diagnostic test is driven by its cost of production and by profit margin. HCV viral load tests have been relatively more expensive due to small volumes (i.e., lack of economies of scale). Volumes will likely increase substantially as screening and treatment programs are scaled up. Presumably, price competition will increase as new players enter the market. Overall, prices are expected to be lower than the prices of the current HCV diagnostics that they are replacing, but still likely above comparable HIV tests.

8.6 Interaction between availability of diagnosis and affordability of treatment

There is a vicious cycle between a lack of demand and a lack of affordability. Governments and multilateral institutions have not dedicated large amounts of funding to HCV. Limited screening services result in most HCV-infected people not knowing their status, which limits governments' ability to understand the spread of HCV, and reduces the scale-up of screening and treatment programs. However, the lack of demand also limits economies of scale and cost reductions for medicines. High prices for treatment, in turn, discourage governments from screening and from initiating and funding treatment programs in the first place.

9 Potential opportunities for interventions

This section identifies a number of potential opportunities to intervene in HCV product markets, with the objective of increasing access to HCV treatment among HIV/HCV co-infected people in low- and lower-middle-income countries.

The HCV market is likely to change as new, more effective, and more acceptable drugs and diagnostics come to the market. Figure 12 shows a preliminary overview of the expected launch timings.

Figure 12. Estimated earliest availability of treatment interventions and diagnostics

TREATMENT	2014	2015	2016	2017	2018	2019	2020
Upper-middle- and high-income countries	PI + Peg-IFN + RBV	2-3 DAAs + RBV	2-3 DAAs				
Low- and lower-middle-income countries	PI + Peg-IFN + RBV			2-3 DAAs + RBV	2-3 DAAs		

DIAGNOSIS & MONITORING	2014	2015	2016	2017	2018	2019	2020
Upper-middle- and high-income countries	POC immunoassay to detect HCV antibodies. Does not confirm active disease		POC RNA assay. Confirms active disease and viral load.				
Low- and lower-middle-income countries							

The all-oral treatments that are expected to be available in the future will exclude Peg-IFN and, in the long term, may also exclude RBV. Treatment side effects are thus expected to be reduced. It is expected that the new DAAs will be launched in upper-middle- and high-income country markets first. Opportunities for short- to mid-term interventions would therefore relate to the all-oral regimens (i.e. DAAs plus RBV or a combination of multiple DAAs without RBV). Interventions could, for instance, aim at accelerating the launch of these drugs in low- and lower-middle income countries, as well as at ensuring affordability in these markets.

Meanwhile, some of the DAAs that could reach the market relatively soon may be used in combination with Peg-IFN + RBV, and could significantly reduce the duration of treatment and improve cure rates.(79) This could reduce the magnitude of affordability and adaptability/acceptability concerns related to regimens containing Peg-IFN. Thus, short-term treatment interventions may focus on or include the scale-up of IFN-based treatment in combination with the new DAAs and RBV.

Finally, interventions aimed at accelerating the development, introduction and roll-out of new diagnostics in resource-limited settings could allow for a dramatic expansion and simplification of screening and testing at the POC level.

Examples of interventions that could resolve the market shortcomings discussed above include:[67]

- Increase the affordability of medicines, notably the new DAAs, and/or diagnostics in resource-limited settings, through approaches such as aggregating demand, price negotiations, voluntary licensing or tiered pricing;
- Facilitate the uptake of new medicines and/or diagnostics, through approaches such as demand forecasting or support for the development of country roll-out plans, including updating national guidelines and programmatic integration;

67 This list is not comprehensive, nor are interventions listed in any order of priority.

- Accelerate/streamline the approval process for new medicines and/or diagnostics in low- and middle-income countries;
- Develop new diagnostic and/or treatment approaches tailored for resource-limited settings and demonstrate their feasibility.

New DAAs are potential game changers for the treatment of HCV, including in patients co-infected with HIV and HCV. Their anticipated superior safety and efficacy profiles may reduce the need for extensive monitoring. This, in combination with the anticipated availability of POC diagnostics, could significantly simplify the diagnostic paradigm.

While there still are outstanding concerns, including the identification of optimal treatment regimens for individuals with HIV/HCV co-infection, developments in this field are rapidly unfolding. UNITAID will continue to monitor these developments in order to identify opportunities to increase access to HCV treatment among HIV/HCV co-infected people in low- and lower-middle-income countries.

10 Annexes

Annex 1: Methodology to estimate HIV/HCV co-infected population

To develop the global estimate of HIV/HCV co-infected population, an extensive literature search was conducted. PubMed as well as governmental and non-governmental reports were searched for any reports on HIV and HCV co-infection rates. In PubMed, the following search terms were used = *((hepatitis c) OR hcv) AND ((Human immunodeficiency virus) OR hiv) AND [country name]*. Over 3,000 data sources were identified and reviewed, and a database of co-infection rate by country was developed. For each study, the following information was recorded: year of data collection, sample size, and population studies. If the year was not reported, it was assumed that the data was collected three years prior to the publication date. Studies in sub-populations were ignored for the purposes of this analysis, since the objective was to quantify the HIV/HCV co-infection at the country level. Although studies in sub-populations were informative, they often overestimated (e.g, studies in injecting drug users and prisoners) or underestimated (e.g., studies in pregnant women) the co-infection rate, and were not considered representative of the HIV/HCV co-infection rate at the national level.

HIV/HCV co-infection rates were not available for all countries. Forty-five studies were identified that provided data for 36 countries that accounted for the 67% of the world's total population and 50% of the world's HIV population. For those 36 countries, the total number of HIV/HCV cases in each country was calculated by multiplying the reported co-infection rate by the reported number of HIV prevalent population in the country. The HIV prevalent population, by country, was collected from UNAIDS.(114) (115) When HIV infection rate was not reported, alternative data sources were used: e.g., India (116), Puerto Rico (117).

The co-infection rate was extrapolated, for all countries, using the following methodology.

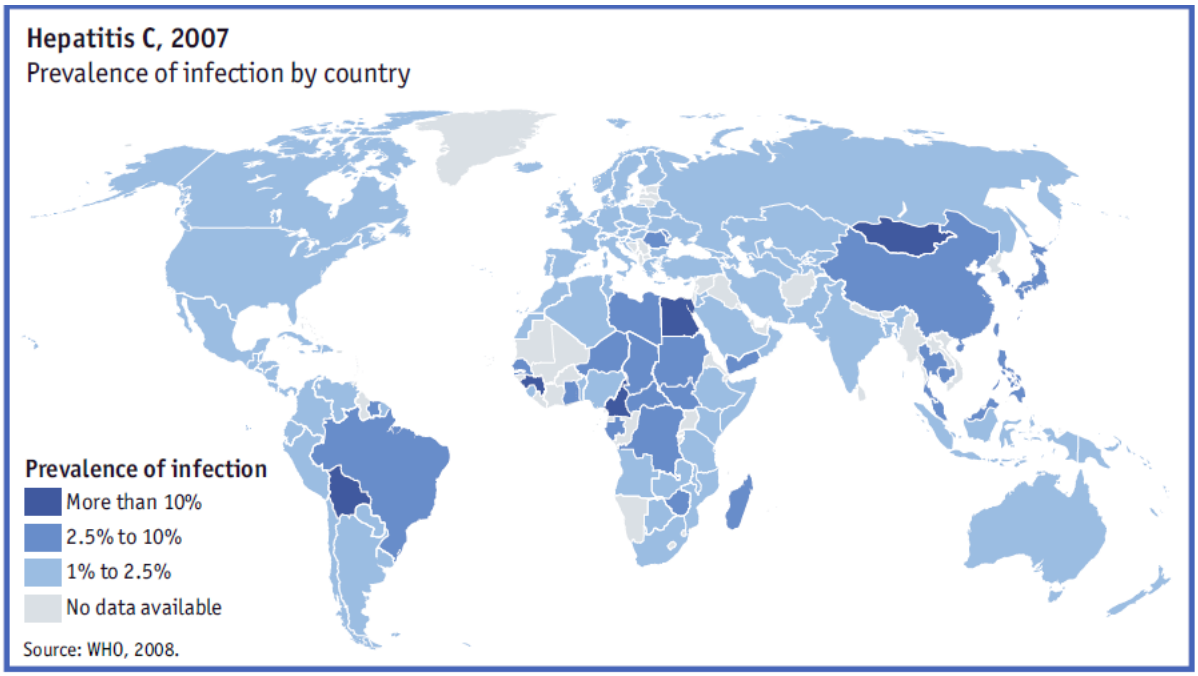
The countries were grouped according to the World Bank income classification (low income, lower-middle income, upper-middle income, and high income). For each group, an average HCV/HIV co-infection rate was then calculated using the co-infection cases in countries where a co-infection rate was reported and the corresponding HIV infected population (total HIV/HCV co-infected cases for all countries with reported data/total HIV cases for the corresponding countries). This average co-infection rate was then applied to all countries within that group.

Thus, HIV/HCV co-infected cases by country were estimated by multiplying the relevant average co-infection rate by the number of HIV prevalent population in the country. Attempts to group countries by more refined regions (e.g., WHO regions or Global Burden of Disease regions) were not successful since some regions did not have a single country with a known co-infection rate to use for extrapolation.

Finally, the total number of HIV/HCV co-infected individuals was calculated by adding up the numbers for all countries.

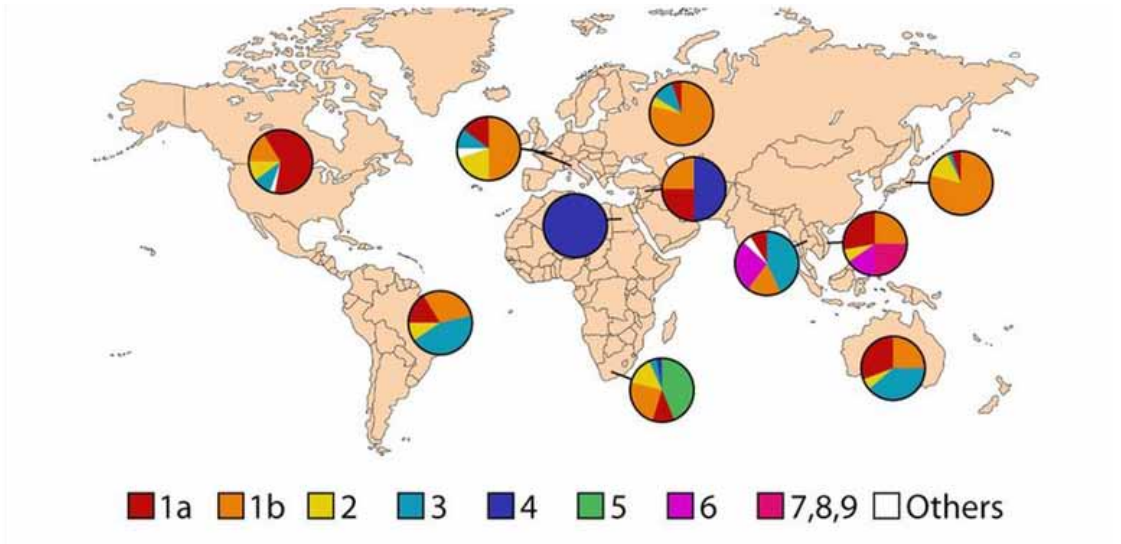
The CDA intends to publish a more detailed description of the methodology and findings of this analysis later this year in a peer reviewed journal.

Annex 2: Distribution of hepatitis C prevalence (11)



Annex 3: Global distribution of hepatitis C genotypes[68]

HCV Genotype 1 is predominantly found in North America, Europe, and Central and East Asia. Genotype 4 is mostly found in Northern Africa, the Middle East and Central Asia, and Genotype 3 is predominant in South America, South Asia and Australia. Genotype 5 is predominant in Southern Africa. The remaining HCV genotypes are relatively rare, found mostly in Southeast Asia.



68 Johns Hopkins School of Public Health, Open Courseware, Epidemiology of Infectious Diseases, Lecture 20: Hepatitis C and E

Annex 4: Findings from systematic review on HIV/HCV comorbidity studies (24)

HIV comorbidity addressed	Focus of Systematic Review	Key Findings	Populations studied	Year of last search	Regions in which studies were conducted	Citation
Co-infections • Hepatitis C	To assess the benefits and harms of antiviral treatment for chronic hepatitis C in patients with HIV	• The present review suggests that among patients with stable HIV, the treatment of concomitant chronic hepatitis C with peginterferon plus ribavirin is more effective than interferon plus ribavirin or peginterferon alone in achieving a virological or histological response. • The overall sustained virological response of previously untreated patients was 37% after treatment with peginterferon plus ribavirin. • Although the included trials had nearly identical patient inclusion criteria, there was considerable intertribal heterogeneity. The sustained response in the individual trials ranged from 27% to 55%. • There were also no noticeable differences between treatments regarding mortality. The number of losses to follow-up and the risk of adverse events were considerable in all treatment groups.	General adult population	2009	North America Europe	Iorio A, Marchesini E, Awad T, Gluud LL. Antiviral treatment for chronic hepatitis C in patients with human immunodeficiency virus. Cochrane Database of Systematic Reviews 2010;(1):CD004888.
Co-infections • Hepatitis C	To estimate the effect of HCV infection on HIV disease progression and overall mortality in the pre-HAART and HAART eras.	• HCV co-infection did not increase mortality among patients with HIV infection before the introduction of HAART. In contrast, in the HAART era, HCV co-infection, compared with HIV infection alone, increases the risk of mortality, but not the risk of AIDS-defining events.	Youth Childhood People who are homeless or marginally housed Injecting drug users General adult population	2008	North America Europe Asia Australasia Latin America & Caribbean	Chen TY, Ding EL, Seage IGR, Kim AY. Meta-analysis: Increased mortality associated with hepatitis C in HIV-infected persons is unrelated to HIV disease progression. New Biotechnology 2009;49(10):1605-15.

HIV comorbidity addressed	Focus of Systematic Review	Key Findings	Populations studied	Year of last search	Regions in which studies were conducted	Citation
Co-infections • Hepatitis C	To analyze the influence of human immunodeficiency virus (HIV) infection on the course of hepatitis C virus (HCV) infection	• A review of 29 trials showed that without HAART, HIV accelerates HCV disease progression, including death, histological fibrosis/cirrhosis and decompensated liver disease • The rate of hepatocellular carcinoma is similar in persons who had HCV infection and were positive for HIV or negative for HIV	Injecting drug users General adult population	2008	North America Europe Africa Asia	Deng LP, Gui XE, Zhang YX, Gao SC, Yang RR. Impact of human immunodeficiency virus infection on the course of hepatitis C virus infection: A meta- analysis. World Journal of Gastroenterology. 2009;15(8):996-1003.
Co-infection • Hepatitis C	To review the use of peginterferon-alpha-2a (40 kD) plus ribavirin in the management of chronic hepatitis C mono-infection.	• The combination of subcutaneous peginterferon-α-2a (40 kD) once weekly plus oral ribavirin twice daily is widely approved for use in adult patients with chronic hepatitis C and is recommended as a first- line treatment option for patients with chronic hepatitis C and compensated liver disease. • In randomized, phase III trials, the combination has consistently demonstrated good therapeutic efficacy and has been generally well tolerated in both treatment- naive and treatment experienced patients with chronic hepatitis C, including those with compensated advanced liver disease.	Men, Women	2008	Not reported	Keam SJ, Cvetkovic RS. Peginterferon-alpha-2a (40 kD) plus ribavirin: a review of its use in the management of chronic hepatitis C mono-infection. Drugs 2008;68(9):1273-1317.

HIV comorbidity addressed	Focus of Systematic Review	Key Findings	Populations studied	Year of last search	Regions in which studies were conducted	Citation
Co-infections • Hepatitis C	To review the evidence for long-term effectiveness and cost-effectiveness of antiviral treatment in patients with chronic hepatitis C.	• Antiviral therapy with peginterferon plus ribavirin in treatment-naive patients with chronic hepatitis C was the most effective (3.6–4.7 life years gained [LYG]) treatment and was reasonably cost-effective (cost- saving to 84 700€/quality adjusted life years [QALY]) when compared to interferon plus ribavirin. • Some results also suggest cost-effectiveness (below 8400€/ (QALY) of re-treatment in non-responders/relapsers. • Review concluded that antiviral therapy may prolong life, improve long-term health-related quality-of-life and be reasonably cost-effective in treatment- naive patients with chronic hepatitis C as well as in former relapsers/non-responders.	General adult population	2007	North America - United States - Canada Europe Australasia	Sroczynski G, Esteban E, Conrads-Frank A, Schwarzer R, Muhlberger N, Wright D et al. Long-term effectiveness and cost- effectiveness of antiviral treatment in hepatitis C. Journal of Viral Hepatitis 2010;17(1):34-50.
Co-infections • Hepatitis C	This paper reviews HCV infection with emphasis on the medical care of HCV- infected, or HCV and human immunodefi-ciency virus co-infected, patients on methadone or buprenorphine maintenance	• Antiviral therapy for HCV can be provided to methadone maintenance patients with accept able rates of adherence and sustained virological response (SVR) • Effective treatment of psychiatric disorders, a multi-disciplinary team and a treatment site that is acceptable to methadone maintenance patients (often but not necessarily the site of methadone treatment) will improve results • Effective treatment of psychiatric disorders, a multi-disciplinary team and a treatment site that is acceptable to methadone maintenance patients (often but not necessarily the site of methadone treatment) will improve results	Injecting drug users	2007	North America Europe	Novick DM, Kreek MJ. Critical issues in the treatment of hepatitis C virus infection in methadone maintenance patients. Addiction 2008;103(6):905-18.

HIV comorbidity addressed	Focus of Systematic Review	Key Findings	Populations studied	Year of last search	Regions in which studies were conducted	Citation
Co-infections • Hepatitis C	The objective of our study was to further elucidate incremental improvement and safety concerns with combinations of pegylated interferon (peginterferon), interferon and ribavirin based on data obtained from prospective randomized controlled trials.	• In six randomized controlled trials, 1756 patients were randomized. Sustained virological response was greater for patients treated with peginterferon plus ribavirin compared with patients treated with interferon plus ribavirin [odds ratio (OR) 3.00; 95% confidence interval (CI) 2.27–3.96]. • This increased sustained virological response with peginterferon and ribavirin was found for patients with HCV genotype 1 or 4 (OR 4.40; 95% CI 2.75–7.03) and genotype 2 or 3 (OR 2.56; 95% CI 1.71–3.85). • Sustained virological responses were also higher with peginterferon and ribavirin as compared with peginterferon monotherapy (OR 2.60; 95% CI 1.84–3.67). Severe adverse effects (OR 1.09; 95% CI 0.74–1.4) and withdrawal rates (OR 0.97; 95% CI 0.75–1.25) were similar between patients treated with peginterferon plus ribavirin and patients treated with interferon plus ribavirin.	General adult population	2005	North America - USA - Europe	Kim AI, Dorn A, Bouajram R, Saab S. The treatment of chronic hepatitis C in HIV-infected patients: a meta-analysis. HIV Medicine 2007;8(5):312-321.
Co-infections • Hepatitis C	The objective of the meta-analysis was to determine whether there is a blunted increase in the CD4 cell count after initiation of HAART in HIV-HCV– coinfected patients relative to patients with HIV infection alone.	• This review of 8 cohort studies showed that the CD4 cell count response for patients with HIV-HCV coinfection when they started receiving HAART was less than that for patients with HIV infection alone by an average 33.4 cells/mm3 (range, 23.5–43.3 cells/mm3). • This result was statistically significant and suggests that HIV-infected patients are likely to have a better immunological response to antiretroviral therapy if they are not coinfected with HCV.	General adult population	2004	North America Europe Australasia	Miller MF, Haley C, Koziel MJ, Rowley CF. Impact of hepatitis C virus on immune restoration in HIV-infected patients who start highly active antiretroviral therapy: A meta-analysis. Clinical Infectious Diseases 2005;41(5):713-20.

HIV comorbidity addressed	Focus of Systematic Review	Key Findings	Populations studied	Year of last search	Regions in which studies were conducted	Citation
Co-infections • Hepatitis C	To summarize evidence on the following questions in the management of chronic hepatitis C: • How well do results of liver biopsy predict outcomes of treatment for chronic hepatitis C? • How well do biochemical blood tests and serologic measures of fibrosis predict the findings of liver biopsy in chronic hepatitis C? • What is the efficacy and safety of current treatment options for chronic hepatitis C in treatment-naive patients and in selected subgroups? • What are the long-term outcomes of current treatment options for chronic hepatitis C? • What is the efficacy of using screening tests for HCC to improve outcomes in chronic hepatitis C? • What are the sensitivity and specificity of tests used to screen for HCC in chronic hepatitis C?	• Studies were relatively consistent in suggesting that advanced fibrosis or cirrhosis on initial liver biopsy may be an independent predictor of a slightly decreased likelihood of having a sustained virological response to treatment; • Studies were relatively consistent in showing that serum liver enzymes have modest value in predicting fibrosis on biopsy; the extracellular matrix tests, hyaluronic acid and laminin, may have value in predicting fibrosis, and panels of tests may have the greatest value in predicting fibrosis or cirrhosis; • Studies of treatment-naive patients with chronic hepatitis C showed greater efficacy of pegylated (peg) interferon plus ribavirin when compared to standard interferon plus ribavirin or peginterferon alone, greater efficacy of peginterferon when compared to standard interferon, and no significant increase in efficacy with standard interferon plus amantadine when compared to interferon monotherapy; for nonresponders and relapsers, standard interferon plus ribavarin was more efficacious than interferon alone; little evidence existed on treatment efficacy in HIV-infected patients, renal patients, hemophiliacs, or intravenous drug users; • Studies were mildly consistent in suggesting that interferon-based therapies decrease the risk of HCC and cirrhosis in complete responders; • One study suggested that HCC was detected earlier and was more often respectable in patients who had quarterly screening with serum alpha-fetoprotein (AFP) and ultrasound than in those who had usual care; • Studies were relatively consistent in suggesting that a serum AFP greater than 10 ng/mL has a sensitivity of 75 to 80 percent and a specificity of about 95 percent in screening for HCC, and a serum AFP greater than 400 ng/mL has a specificity of nearly 100 percent for detection of HCC.	Patients with chronic hepatitis C	2002	North America South America Europe Africa Asia	Gebo K, Jenckes M, Chander G, et al. Management of Chronic Hepatitis C. Evidence Report/ Technology Assessment No. 60 (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No 290-97-0006). AHRQ Publication No. 02- E030. Rockville, MD: Agency for Healthcare Research and Quality. July 2002.

HIV comorbidity addressed	Focus of Systematic Review	Key Findings	Populations studied	Year of last search	Regions in which studies were conducted	Citation
Co-infections • Hepatitis C	Maternal co-infection with human immuno-deficiency virus (HIV) has been implicated as a potentially im-portant co-factor for enhanced vertical transmis-sion of hepatitis C virus (HCV). A system-atic review and subsequent meta-analysis of current published and unpublished reports was performed.	• In total, 2382 infants from 10 studies were included in an analysis of HCV-infected mothers (defined by anti-HCV+ antibody assays) with and without concomitant HIV infection. • The risk estimate (OR) of HCV vertical transmission was 2.82 (95% CI: 1.78–4.45; P= 0.00001) from anti-HCV+/HIV+ co- infected mothers compared with anti-HCV+/HIV– mothers. • In a subanalysis of 1327 infants born to viraemic (HCV RNA+) mothers, the risk estimate of HCV vertical transmission was 1.97 (95% CI: 1.04–3.74; P = 0.04) from HCV viraemic/HIV+ co-infected mothers compared with HCV viraemic/HIV– mothers.	Pregnant Women Infants	2002	North America – USA – Europe	Pappalardo BL. Influence of maternal human immunodeficiency virus (HIV) co-infection on vertical transmission of hepatitis C virus (HCV): a meta-analysis. International Journal of Epidemiology 2003;32(5):727-34.

Annex 5: Summary of literature on the impact of HIV/HCV co-infection on HIV and HCV disease progression

This annex gives an overview of studies that have examined the impact of HIV/HCV co-infection on the progression of both HIV and HCV. Please note that these studies were performed at different points in time. During this period, the treatment paradigm for HIV, the associated life expectancy and the prevalence of specific co-infections may have changed significantly.

Author	Study	Location/Time/Objective	Key Findings	Link (PubMed)
Sherman KE, 2002	Hepatitis C Virus prevalence among patients infected with Human Immunodeficiency Virus: a cross-sectional analysis of the US adult AIDS Clinical Trials Group.	United States Patients enrolled through April 2000 Describe the prevalence and characteristics of HCV in HIV-infected cohort	- Co-infection with HCV is associated with increased measures of HCV RNA as compared to monoinfected patients - Genotype 1 was found in 83.3% of infected patients	http://www.ncbi.nlm.nih.gov/pubmed/?term=11833007
Thein HH, 2008	Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis	Meta-analysis; Risk of cirrhosis between individuals monoinfected with HCV and coinfected with HIV/HCV were compared by HAART status.	- Meta-analysis suggested that HIV coinfected patients progress to cirrhosis at twice the rate of monoinfected patients, with 21% of coinfected experiencing cirrhosis after 20 years, and 49% after 30 years	http://www.ncbi.nlm.nih.gov/pubmed/?term=18784461
Kirk GD, 2013	HIV, Age, and the Severity of Hepatitis C Virus-Related Liver Disease: A Cohort Study	Baltimore, Maryland 2006-2011 Comparison of the severity of liver fibrosis by age among persons who have HCV with and without HIV	- The prevalence of clinically significant fibrosis without cirrhosis (12.9% vs. 9.5%) and of cirrhosis (19.5% vs. 11.0%) was greater in persons coinfected with HIV and HCV than in those with only HCV - Coinfected exhibited accelerated liver fibrosis, with fibrosis measures equivalent to monoinfected individuals who were 9.2 years older, after controlling for other factors linked to fibrosis	http://www.ncbi.nlm.nih.gov/pubmed/?term=23440167
Sulkowski MS, 2002	Hepatitis C and progression of HIV disease	University clinic, urban; United States 1995-2001 Assess the effect of HCV infection on clinical and immunologic progression of HIV disease and immunologic response to HAART	- Coinfected patients did not experience increased mortality or risk for progressing to AIDS, as compared to patients infected with HIV alone	http://www.ncbi.nlm.nih.gov.proxy-remote.galib.uga.edu/pubmed/12095384

Rockstroh JK, 2005	Influence of Hepatitis C Virus Infection on HIV-1 Disease Progression and Response to Highly Active Antiretroviral Therapy	Patients from 89 centers across Europe 1994-2004 Examined clinical outcome and the virologic and immunologic responses to HAART in a large group of HIV- 1–infected patients in the EuroSIDA cohort, comparing patients with and without HCV co-infection	- In the EuroSIDA cohort, HCV did not affect the risk of HIV disease progression. - Among 2,260 coinfected patients initiating HAART, the overall virologic and immunologic responses to HAART were not affected by HCV serostatus.	http://jid.oxfordjournals.org/content/192/6/992.short
Sabin C, 1997	The Association between Hepatitis C Virus Genotype and Human Immunodeficiency Virus Disease Progression in a Cohort of Hemophilic Men	London Infected between 1979-1985; Assessed the possible effects of HCV co-infection on HIV disease progression in a group of hemophilic patients	- Hemophiliac men infected with HCV genotype 1 experienced a more rapid progression to both AIDS and death than those infected with other HCV genotypes. - Results suggest an association between HCV genotype and progression of HIV disease.	http://jid.oxfordjournals.org/content/175/1/164.short
Carlos Marin J, 2004	Impact of chronic hepatitis C on HIV-1 disease progression.	Spain 1998 Analyze the impact of HCV on CD4 counts and plasma HIV RNA in a large group of HIV-positive individuals	- Mean plasma HIV RNA was higher in individuals coinfected with HCV as compared to HIV alone. - CD4 counts were significantly lower in those coinfected with HCV, as compared to HIV alone.	http://www.ncbi.nlm.nih.gov/pubmed/15248136
Greub G, 2000	Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus co-infection: the Swiss HIV Cohort Study.	Swiss HIV Cohort Study 1996-1999 Analyze clinical progression of HIV-1, and the virological and immunological response to potent antiretroviral therapy in HIV-1-infected patients with or without concurrent HCV infection.	- In the Swiss HIV cohort, co-infection with HCV and active injection drug use were associated with progression to AIDS and death	http://www.ncbi.nlm.nih.gov/pubmed/11117912

Annex 6: Treatments for chronic HCV infection[69]

Phase	Class	Name	Company
Launched	Interferon	peginterferon alfa-2b	Merck
Launched	Interferon	peginterferon alfa-2a	Roche
Launched	NS3/4A inhibitor	boceprevir	Merck
Launched	NS3/4A inhibitor	telaprevir	Vertex
Launched	Nucleoside analogue	ribavirin	
Reg Approval	NS3/4A inhibitor	simeprevir (TMC-435)	Janssen
Reg Approval	Nucleoside NS5B inhibitor	sofosbuvir (GS-7977)	Gilead
III	Cyclophilin inhibitor	alisporivir (DEB-025)	Novartis
III	Interferon	peginterferon lambda-1a	BMS
III	Non-nucleoside NS5B inhibitor	ABT-333	AbbVie
III	Non-nucleoside NS5B inhibitor	deleobuvir (BI-207127)	BI
III	NS3/4A inhibitor	asunaprevir (BMS-650032)	BMS
III	NS3/4A inhibitor	faldaprevir (BI-201335)	BI
III	NS3/4A inhibitor	vaniprevir (MK-7009)	Merck
III	NS3/4A inhibitor	ABT-450/r	AbbVie
III	NS5A inhibitor	ABT-267	AbbVie
III	NS5A inhibitor	daclatasvir (BMS-790052)	BMS
III	NS5A inhibitor	ledipasvir (GS-5885)	Gilead
II	Cyclophilin inhibitor	SCY-635	Scynexis
II	miR-122 inhibitor	miravirsen	Santaris Pharma
II	Non-nucleoside NS5B inhibitor	ABT-072	AbbVie
II	Non-nucleoside NS5B inhibitor	BMS-791325	BMS
II	Non-nucleoside NS5B inhibitor	GS-9669	Gilead
II	Non-nucleoside NS5B inhibitor	setrobuvir (ANA-598)	Anadays
II	Non-nucleoside NS5B inhibitor	tegobuvir (GS-9190)	Gilead
II	Non-nucleoside NS5B inhibitor	TMC-647055	Janssen
II	Non-nucleoside NS5B inhibitor	lomibuvir (VX-222)	Vertex
II	NS3/4A inhibitor	GS-9256	Gilead
II	NS3/4A inhibitor	vedroprevir (GS-9451)	Gilead
II	NS3/4A inhibitor	MK-5172	Merck
II	NS3/4A inhibitor	sovaprevir (ACH-1625)	Achillion
II	NS3/4A inhibitor	danoprevir (RG-7227/r)	Roche
II	NS5A inhibitor	ACH-3102	Achillion
II	NS5A inhibitor	GS-5816	Gilead
II	NS5A inhibitor	GSK-2336805	GSK
II	NS5A inhibitor	IDX-719	Idenix
II	NS5A inhibitor	MK-8742	Merck
II	NS5A inhibitor	PPI-668	Presidio Pharma
II	Nucleoside NS5B inhibitor	GS-0938 (PSI-352938)	Gilead
II	Nucleoside NS5B inhibitor	mericitabine (RG-7128)	Roche

69 HCV treatments, CDA

Annex 7: Pipeline of HCV vaccines (118)

Currently there are no HCV vaccines in late-stage development; the only vaccine candidates are still in Phase I or II.

Additional information on the history and challenges of developing HCV vaccines can be found in "Vaccination for hepatitis C virus: closing in on an evasive target" by Halliday et al.(119)

Vaccine	Subject	Stage	Outcome	Testing Companies
Peptides (core, NS3, NS4)/poly-L-arginine (IC41)	60 HLA-A2+ chronic HCV nonresponders	II	67% responding to peptide plus adjuvant treatment versus 17% to peptide alone; 3 patients with transient decline of serum HCV RNA (>1 log)	Genway Biotech/ GeneTex, Inc.
Peptide (core)/ emulsified with ISA51	26 chronic HCV patients	I	Well tolerated with no severe toxicity; 15/25 responder; 2/25 with 1 log decline on HCV RNA	
Peptides (NS3)/Virosome	30 healthy volunteers	I	No result released	Pevion Biotech Ltd.
MVA-HCV NS3/NS4/NS5B (TG4040)	15 chronic HCV patients	I	Well tolerated; 6/15 with decline on HCV RNA (0.5–1.4 log)	Transgene
HCV gpE1/E2 glycoproteins/MF59	60 healthy volunteers	I	No result released	
Recombinant yeast transfect with HCV NS3-core fusion protein (GI5005)	Chronic HCV patients	II	Well tolerate and showed better virology response in chronic patients after triple therapy	Globe Immune
HCV core protein/ ISCOMATRIX	30 healthy volunteers	I	Well tolerated with mild local redness; all developed antibody response, 7/8 showed cytokine production & 2/8 showed cytotoxic T cell response in the group with highest antigen dose (50 µg)	US Biological
NS3/4A DNA vaccine (ChronVac-C)	12 chronic HCV patients	I/IIa	Safe, immunogenic with transient effect on serum viral load	ChronTech Pharma AB
Recombinant core protein & core/E1/E2 DNA vaccine (CIGB-230)	15 chronic HCV patients	I	Safe, immunogenic, and stabilized liver function with persistence detection of HCV RNA	

Annex 8: Financing of HCV treatment in eastern European region (100)

Lithuania	Basic health insurance (excluding drug users)
Latvia	Basic health insurance covers 50% of treatment costs; patients cover 50%
Russia	Government for HIV/HCV co-infected cases. Patients in most regions if only HCV infected
Ukraine	Patients
Georgia	Patients
Kazakhstan	Patients HCV monitored in the national health program
Kyrgyzstan	Patients

Annex 9: Selected treatment guidelines for HCV management

The goal of therapy is to eradicate HCV infection in order to prevent the complications of HCV-related liver disease and death. The endpoint of therapy is evaluated by SVR. Clinical practice guidelines define the use of HCV therapies and are intended to assist physicians and healthcare providers in the clinical decision making process. In the absence of WHO guidelines for HCV infection, guidelines developed by other organizations, notably the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL), are being used widely. With the constant development of new therapies, these guidelines are updated regularly as new therapies are approved. In general, guidelines have focused on the administration and duration of Peg-IFN + RBV. In 2011, the AASLD updated its clinical practice guidelines for G1 patients based on the advent of first-generation DAAs.(41) (120) EASL is currently in the process of developing a revised set of clinical guidelines.(121)

The AASLD and EASL guidelines (see below for more details) are evidence-based, based on the GRADE methodology. The current standard of care is to treat with interferon alpha plus ribavirin. Although standard of care for Genotype 1 disease includes a DAA (telaprevir or boceprevir), because of cost and toxicity requiring monitoring, use of these agents is not feasible in resource-limited settings. Diagnosis involves a serologic test, confirmation with a viral load and subsequent staging to identify candidates for treatment who have evidence of significant liver fibrosis. For HIV/HCV coinfected people, earlier treatment is recommended due to rapid disease progression.

A recent survey shows that only 32 out of 93 developing countries surveyed (34%) provided some guidance.

EASL Clinical Practice Guidelines: management of hepatitis C virus infection (121)

At the time of publication, protease inhibitors had not been approved for triple therapy. Current EASL guidelines focus on treatment with Peg-IFN + RBV. As mentioned, EASL is currently updating its clinical guidelines.

Treatment-Naïve patients:

It is recommended that all treatment-naïve patients with compensated disease due to HCV infection be considered for therapy. Treatment should be initiated in all patients with advanced fibrosis and strongly considered in those with moderate fibrosis.

For treatment-naïve patients, the recommend therapy is a combination of weekly Peg-IFN injections with daily oral RBV. The recommended dosage of RBV, and duration of treatment, varies according to patient's genotype. G1 and G4-6 patients are recommended a therapy of Peg-IFN and weight-based RBV (15mg/kg/day) for 48 weeks. G2/3 patients are recommended a therapy of Peg-IFN and a flat dosage RBV (800mg/day) for 24 weeks. (G2/3 patients with baseline factors that are suggestive of low responsiveness are recommended to receive the same treatment dosage as G1 and G4-6 patients.)

Patients are recommended to be seen at weeks 4 and 12, and every subsequent 12 weeks, to assess efficacy and side effects. In addition, patients should been seen 24 weeks after the end of therapy to assess cure.

Treatment duration may be tailored according to on-treatment virological response for all genotypes. It is recommended that treatment be stopped if there is less than a $2\log_{10}$IU/ml at week 12 of therapy and if HCV RNA is still detectable at week 24. Patients with a rapid response may be considered for shortened therapy. G1 patients with a delayed virological response may be treated for 72 weeks.

Treatment should be reduced or stopped in the case of severe side effects and/or clinically significant changes in neutrophil or platelet count, among others.

For patients who achieve SVR are not cirrhotic, it is recommended to retest ALT and HCV RNA at 48 weeks and 1 year following the completion of treatment. For patients who achieve SVR and are cirrhotic, it is recommended that they be monitored every 1-2 years for esophageal varices and every 6 months for the development of HCC.

Treatment-Experienced:

Retreatment with PegIFN + RBV is not recommended for G1 patients who fail to achieve cure. Patients with all other genotypes who fail to achieve cure may be retreated with PegIFN + RBV. For patients with a non-sustained virological response, retreatment with PegIFN + RBV may be recommended if there is an urgent indication.

Special groups:

HIV co-infection

Indication for and treatment of HIV/HCV co-infection is the same as HCV monoinfection. PegIFN + RBV (weight-based) should be used in co-infected patients; however, treatment duration may increase to 72 weeks and 24 weeks for G1 and G2/3 patients, respectively.

HBV co-infection

Indication for and treatment of HBV/HCV co-infection is the same as HCV monoinfection.

Acute hepatitis:

Most acute patients are asymptomatic; however, if infection is detected, the recommended treatment is 24 weeks with Peg-IFN monotherapy.

Please see EASL guidelines for additional details on the presented information, as well as the following:

- Contraindications to treatment
- Measures to improve treatment success
- Treatment of patients with severe liver disease
- Treatment of patients with comorbidities (i.e. hemodialysis, drug abuse, etc.)

AASLD Practice Guidelines (41) [70]

Treatment-Naïve:

The recommend therapy for chronic HCV infection is the combination of PegIFN + RBV. For G1 and G4 patients, it is recommended to treat with PegIFN + RBV (weight-based) for 48 weeks. Treatment may be extended to 72 weeks for G1 patients with a delayed virological response. Treatment may be discontinued in patients who do not achieve an early virological response ($\geq$2log reduction in HCV RNA after 12 weeks of treatment), or in patients who do not achieve a complete EVR and are positive for HCV RNA at 24 weeks.

For G2 and G3 patients, the recommended therapy is Peg-IFN and a flat dosage RBV (800mg/day) for 24 weeks.

70 See subsequent section "Update: AASLD Clinical Guidelines for G1 patients" for revised recommendations for G1 patients.

Patients who complete treatment, regardless of genotype, should be retested for HCV RNA at 24 weeks to confirm cure. Patients with HCV-related cirrhosis who complete treatment, regardless of genotype, should also be monitored at 6 and 12 month intervals to assess development of HCC.

Treatment-Experienced:

It is not recommended to retreat null responders who completed treatment with PegIFN + RBV. For patients who have been treated with Peg-IFN monotherapy or non-pegylated interferon with or without RBV, retreatment may be considered.

Special groups:

HIV co-infection

Patients co-infected with HIV are indicated to receive treatment if they are at an increased likelihood of serious liver disease and treatment response outweighs the risk of morbidity from adverse events. The recommend course of therapy is PegIFN + RBV for 48 weeks at the same dosages recommended for monoinfected patients. HIV co-infected patients with decompensated liver disease should not be treated with PegIFN + RBV. These patients may be considered for liver transplantation.

Acute Hepatitis:

The recommended treatment for patients with acute HCV infection is interferon-based monotherapy. There are no recommendations for optimal duration; however, the standard course is between 12-24 weeks. The addition of RBV can be made on a case-by-case basis.

Please see AASLD guidelines for additional details on the presented information, as well as the following:

- Selection of patients and contraindications to treatment
- Treatment in children
- Treatment of patients with severe liver disease, kidney disease, or patients after solid organ transplant
- Treatment of patients with comorbidities (i.e. drug abuse, psychiatric illness, etc.)

Update: AASLD Clinical Guidelines for G1 patients (120)

For G1 patients, the recommended treatment is the use of one protease inhibitor, boceprevir or telaprevir, in combination with PegIFN + RBV. The use of a protease inhibitor together with Peg-IFN and RBV is known as triple therapy.

Treatment Naïve:

Boceprevir

The recommended treatment using boceprevir begins with a 4 week lead-in treatment of PegIFN + RBV followed by 24-44 weeks of boceprevir together with PegIFN + RBV. The recommended dose of boceprevir is 800 mg and is administered with food three times per day (every 7- 9 hours). Patients without cirrhosis and undetectable HCV RNA at 8 and 24 weeks may be considered for shortened therapy (4 week lead-in followed by 24 weeks of triple therapy).Triple therapy should be stopped if the HCV RNA level is > 100IU/ml at 12 weeks of treatment or detectable at 24 weeks.

Telaprevir

The recommended therapy using telaprevir is 12 weeks of telaprevir with PegIFN + RBV (weight-based) followed by 12-36 weeks of PegIFN + RBV. The recommended dose of telaprevir is 750 mg administered with food (non fat-free) three times per day (every 7- 9 hours). Patients without cirrhosis and with undetectable HCV RNA at 4 and 12 weeks should be considered for a shortened therapy (24 weeks). Triple therapy should be stopped if the HCV RNA level is > 1,000IU/ml at 4 or 12 weeks of treatment and/or detectable 24 weeks.

Boceprevir or Telaprevir

Patients with cirrhosis should receive triple therapy with either protease inhibitor for 48 weeks.

Treatment Experienced:

Boceprevir or Telaprevir
For partial responders or relapsers following a complete treatment with standard interferon or PegIFN + RBV, retreatment with boceprevir or telaprevir in combination with PegIFN + RBV (weight-based) can be recommended. For prior null responders, the efficacy is not as well established; however, retreatment with boceprevir or telaprevir in combination with PegIFN + RBV (weight-based) may be recommended. Further, response-guided therapy can be considered for relapsers and may be considered for partial responders, but cannot be recommended for null responders. Patients retreated with boceprevir or telaprevir who continue to have detectable HCV RNA (> 100IU at week 12 for boceprevir and > 1,000IU at weeks 4 or 12 for telaprevir) are recommended to stop therapy because of an increased likelihood for drug resistance.

Special Populations:

There are currently no clinical guidelines for special populations (i.e. patients co-infected with HIV, those with decompensated cirrhosis, and those after liver transplantation) due to limited data from clinical trials in these populations.

Please see the AASLD Practice Guidelines for additional details on the presented information, as well as the following:

- Adverse events
- Drug-drug interactions
- Viral resistance and monitoring
- Role of IL28B Testing in Decision to Treat and Selection of Therapeutic Regimen

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