

Simplification of Care for Chronic Hepatitis C Virus Infection

Jean-Michel Pawlotsky, MD, PhD¹ Christian B. Ramers, MD, MPH² John F. Dillon, MD, PhD³
Jordan J. Feld, MD, MPH⁴ Jeffrey V. Lazarus, PhD, MIH, MA⁵

¹Department of Virology, National Reference Center for Viral Hepatitis B, C and D, Henri Mondor Hospital, University of Paris-Est—INSERM U955, Créteil, France

²Division of Infectious Diseases, Department of Medicine, UC San Diego School of Medicine, La Jolla, California

³Division of Molecular and Clinical Medicine, School of Medicine, University of Dundee, Dundee, United Kingdom

⁴Toronto Centre for Liver Disease, University Health Network, Sandra Rotman Centre for Global Health, Toronto, ON, Canada

⁵Barcelona Institute for Global Health (ISGlobal), Hospital Clínic, University of Barcelona, Barcelona, Spain

Address for correspondence Jean-Michel Pawlotsky, MD, PhD, Department of Virology, National Reference Center for Viral Hepatitis B, C and D, Henri Mondor Hospital, 51 Avenue du Maréchal de Lattre de Tassigny, 94010 Créteil, France (e-mail: jean-michel.pawlotsky@aphp.fr).

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Abstract

In 2016, the World Health Organization (WHO) set a target for eliminating viral hepatitis as a major public health threat by 2030. However, while today's highly effective and well-tolerated pangenotypic direct-acting antiviral regimens have maximized simplification of hepatitis C virus (HCV) treatment, there remain a plethora of barriers to HCV screening, diagnosis, and linkage to care. As of 2017, only 19% of the estimated 71 million individuals living with chronic HCV worldwide were diagnosed and in 2015 to 2016, only 21% of diagnosed individuals had accessed treatment. Simplification and decentralization of the HCV care cascade would bolster patient engagement and support the considerable scale-up needed to achieve WHO targets. Recent developments in HCV screening and diagnosis, together with reduced pretreatment assessment and on-treatment monitoring requirements, can further streamline the care continuum, ensuring patients are linked to care quickly and earlier in the disease course, and minimize clinic visits.

Keywords

- ▶ hepatitis C virus
- ▶ care cascade
- ▶ screening
- ▶ diagnosis
- ▶ treatment

The availability of highly effective, well-tolerated, all-oral, direct-acting antiviral (DAA) combinations for the treatment of chronic hepatitis C virus (HCV) infection has made the elimination of HCV a theoretically achievable goal within the next decade.¹ In May 2016, the World Health Organization (WHO) adopted their “Global Health Sector Strategy on Viral Hepatitis, 2016–2021,” which aims to eliminate viral hepatitis as a major public health threat by 2030 by reducing new chronic infections by 90% and mortality by 65%. To achieve this goal, 90% of individuals with chronic HCV infection need to be diagnosed, and 80% of those need to be treated.² Worldwide, however, the majority of people infected with HCV are not diagnosed and, therefore, remain untreated. In 2017, an estimated 71 million individuals were living with chronic HCV worldwide.³ Of these, it is thought that only 13.1

million (19%) knew of their infection and only 5 million of those (38%) had accessed treatment by the end of 2017.³ Simplification of the HCV care cascade, ideally at all steps in the continuum of care, would help to ensure that more patients remain engaged in the care pathway and ultimately support the considerable scale-up needed to achieve WHO targets.⁴ In this article, we review the existing care pathway and discuss potential opportunities in which the patient journey from HCV screening to cure could be streamlined.

Overview of the Current HCV Care Pathway

Depending on the setting, and despite a current concerted effort toward simplification, the current HCV care pathway can be visualized as a sequence of anywhere up to 10 steps (▶ Fig. 1A),

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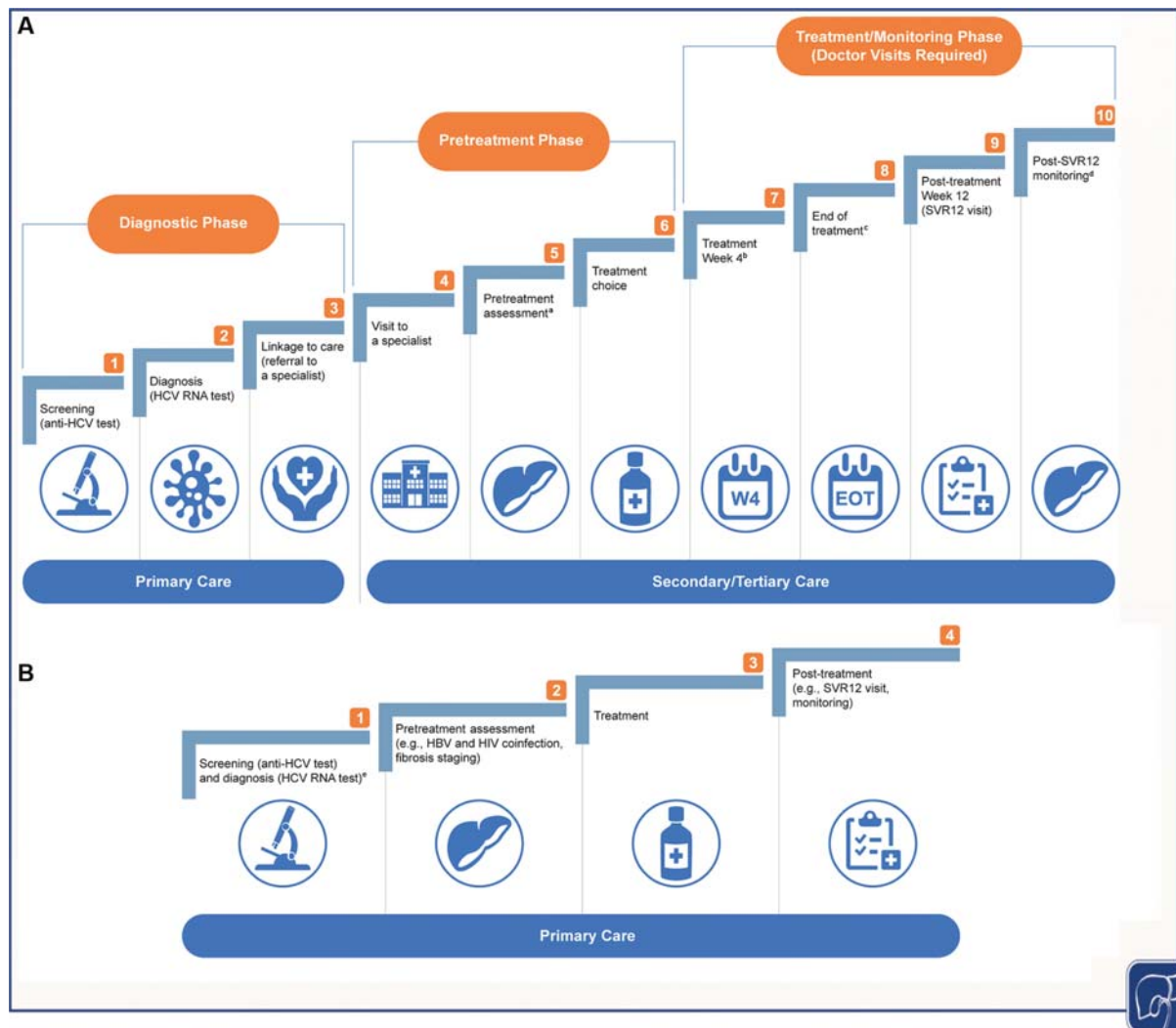


Fig. 1 Overview of the HCV care cascade: (A) the traditional care cascade and (B) a potentially simplified HCV care cascade for treatment-naïve patients without cirrhosis managed in a primary care setting. ^aPretreatment assessments previously recommended by AASLD/IDSA and EASL: HCV genotype and subtype; HCV viral load; fibrosis staging; HBV coinfection; HIV coinfection; complete blood count; international normalized ratio; hepatic function panel; estimated glomerular filtration rate; potential drug–drug interactions. ^bOn-treatment monitoring previously recommended by AASLD/IDSA: HCV viral load; creatinine level; estimated glomerular filtration rate; hepatic function panel. ^cOn-treatment monitoring previously recommended by WHO: routine laboratory monitoring for treatment toxicity. ^dPost-SVR12 monitoring recommended by AASLD/IDSA and EASL: surveillance for hepatocellular carcinoma by twice-yearly ultrasound examination in patients with advanced fibrosis (i.e., METAVIR stage F3 or F4). ^eWith reflex testing, screening and diagnosis can be combined to enable confirmatory HCV diagnosis with fewer patient visits. AASLD/IDSA, American Association for the Study of Liver Diseases/Infectious Diseases Society of America; EASL, European Association for the Study of the Liver; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; RNA, ribonucleic acid; SVR12, sustained virologic response 12 weeks after completion of treatment; WHO, World Health Organization.

from screening to cure, as advocated by international guidelines for HCV management, such as those from the American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA),⁵ the European Association for the Study of the Liver (EASL),⁶ and WHO.⁷ The steps can be grouped into three distinct phases: screening and diagnosis, pretreatment, and treatment and monitoring (including posttreatment follow-up).

Screening and Diagnosis

The screening and diagnosis phase includes screening for the presence of anti-HCV antibodies and confirming active HCV replication. Traditionally, screening of individuals at risk of HCV infection using an anti-HCV antibody test has been

widely recommended, with periodic retesting for those at ongoing risk of (re)infection, such as people who inject drugs (PWID).^{5–7} However, recent guideline updates have seen the broadening of this recommendation to one-time, routine, opt-out HCV testing for all individuals aged 18 years and older, with some also recommending testing in the prenatal setting during each pregnancy.^{3,5,8,9} Other screening strategies include birth cohort testing or screening the general population in areas where HCV seroprevalence is intermediate ($\geq 2\%$) or high ($\geq 5\%$).^{6,7} In individuals who are anti-HCV antibody positive, HCV replication is confirmed using a qualitative/quantitative HCV RNA test.^{5–7} HCV core antigen detection and quantification may also be used to diagnose acute or chronic HCV infection.^{6,7} With both assays, only the

presence, not the amount, of marker is used for medical decisions. For payer reimbursement in some regions, namely the United States and Canada, two separate HCV RNA tests at least 6 months apart are required to confirm a diagnosis of chronic HCV infection. Guidelines now recommend that individuals with acute HCV infection are linked to appropriate care with a health care provider who will administer comprehensive management, rather than waiting for progression to chronic disease.^{5,10}

Pretreatment Phase

For many patients, the pretreatment phase includes an initial visit to a specialist (hepatologist, gastroenterologist, or infectious disease specialist) for pretreatment assessments and selection of an appropriate HCV treatment. Prior to treatment initiation, a series of recommended tests are performed to identify viral and host factors that may impact the choice of treatment, prognosis, and/or required follow-up. In the DAA era, and with pangenotypic options available, the number of pretreatment tests has been reduced; in particular, viral factors (e.g., HCV genotype/subtype, presence of HCV drug resistance-associated substitutions) that may have previously impacted viral response and, therefore, treatment choice are not always required. However, it is still generally important to assess other active infections, such as hepatitis B virus (HBV) or human immunodeficiency virus (HIV), and confirm HCV genotype where appropriate.⁵⁻⁷ Furthermore, it is considered good clinical practice to assess the degree of liver fibrosis to inform treatment decisions.⁵⁻⁷

Treatment and Monitoring Phase

In most cases, the choice of DAA and treatment duration have been based on HCV genotype, liver disease severity, and prior HCV treatment status. AASLD/IDSA guidance and 2018 EASL recommendations advocate ribavirin-free DAA regimens, preferably pangenotypic if available (i.e., those effective against the main HCV genotypes 1–6), for HCV treatment-naïve or -experienced adults without cirrhosis or with compensated cirrhosis.³ Ribavirin is required in patients with decompensated cirrhosis.^{5,6} In addition, EASL guidelines recommend combination regimens comprising two rather than three DAAs to minimize the risk of adverse effects or drug–drug interactions.⁶ Finally, WHO guidelines only recommend pangenotypic DAA regimens for all adults with or without cirrhosis.⁷

Although DAAs are generally well tolerated, patients should be assessed for adverse events or potential drug–drug interactions at each visit or, according to WHO guidelines, at the end of treatment.⁵⁻⁷ HBV reactivation during or after DAA treatment has been reported in patients who are hepatitis B surface antigen–positive and not receiving HBV antiviral therapy.⁵ Therefore, patients meeting criteria for active HBV infection should be started on HBV antiviral therapy. Patients with low or undetectable HBV DNA levels can either receive prophylactic HBV therapy or be monitored for HBV reactivation during and immediately after HCV DAA therapy; HBV therapy should be initiated in patients with evidence of HBV reactivation.⁵⁻⁷

The final monitoring step is assessment of HCV cure, defined as a sustained virologic response (SVR; i.e., undetectable HCV RNA) 12 weeks after completion of treatment (SVR12).⁵⁻⁷ Some guidelines suggest SVR at 24 weeks after completion of treatment (SVR24) can also be used to define cure^{6,7}; however, because of the high rate of concordance between SVR12 and SVR24 (sensitivity and specificity of 99 and 98%, respectively), the U.S. Food and Drug Administration and AASLD/IDSA guidelines have defined HCV cure as SVR12.^{5,11} Some patients may require additional monitoring, for instance to minimize drug–drug interactions between HCV DAAs and anti-HIV medications or immunosuppressants that could jeopardize graft success in liver transplant recipients.^{5,6} Patients with advanced cirrhosis should also be monitored closely during treatment, and for hepatocellular carcinoma (HCC) after treatment.⁵⁻⁷

Simplifying the HCV Care Pathway

The current HCV care pathway is complex and often difficult to navigate for many patients, with multiple office visits, blood draws, assessments, and interactions with different health care providers and payers. This level of continuous care can be a particularly challenging barrier in some populations that require specific public health approaches because of a high incidence of HCV, high prevalence of HCV, stigma, discrimination, criminalization or vulnerability, and/or difficulty accessing health care services, such that they would benefit from a streamlined care pathway.⁷ Examples of such populations include PWID, prisoners, homeless individuals, migrants, those in rural communities with poor access to care, those struggling with mental health or substance use disorders, some groups of men who have sex with men, sex workers, and indigenous populations who are historically less engaged in health care. In addition, the current pathway requires high-level laboratory and clinical capabilities to diagnose infection, identify the HCV genotype, assess fibrosis, and monitor treatment. These requirements potentially create barriers for HCV care management.

Based on recent advances in diagnostic techniques and HCV treatments, the current HCV care pathway can be streamlined (→ **Fig. 1B**), and simplification of care is an increasing focus within the field of HCV treatment.⁴ Simplification will potentially have multiple benefits, including better allocation of resources to diagnose and treat more patients (expanding access and coverage), acceleration of treatment initiation (linkage to care), reduction in HCV transmission among high-risk populations (treatment as prevention), improvement in patient adherence, facilitation of task-sharing/patient management by nonspecialists, and lowering the long-term medical costs of untreated HCV infection, such as those associated with advanced liver disease, extrahepatic complications of HCV infection, or liver transplant.

For many patients, the ideal HCV care pathway would involve diagnosis, pretreatment work-up, and treatment initiation in a single day. A U.S. study modeled the impact of a hypothetical “consolidated” HCV care pathway that required at least two visits for patients to receive treatment.¹² In this

scenario, a positive anti-HCV test led immediately to an HCV RNA test, HCV genotyping, and fibrosis staging, which took place during a single visit. Referral to a specialist was required only for patients with moderate to advanced fibrosis (METAVIR stage \geq F2); therefore, an estimated 40% of patients could be managed by their primary care provider. Compared with the current HCV care pathway that requires at least four visits before receiving treatment, the consolidated pathway reduced the percentage of patients lost to follow-up from screening to treatment from 71 to 76% (depending upon the insurance provider) to 4 to 5%. Therefore, reducing the steps in the care pathway increased the number of patients who learned of their HCV status, were linked to care, and received HCV treatment. The cost to identify and link to care one additional patient with HCV was \$1,586 to \$2,546 with the current HCV care pathway and \$212 to \$548 with the consolidated pathway.¹² However, these findings may not be generalizable to all geographical settings or certain high-risk populations.

Simplifying the Screening and Diagnosis Phase

Screening and diagnostic services need to reach much larger numbers of individuals with HCV infection to achieve the WHO elimination target of 90% diagnosed by 2030. Strategies to increase anti-HCV screening and diagnosis rates include risk factor–based screening, universal screening in specific populations, simplification of sampling using capillary whole blood, dried blood spot (DBS) testing, and point-of-care (PoC) testing using rapid diagnostic tests (RDTs).

Screening Programs

Risk factor–based anti-HCV screening has previously been a prominent feature of international guidelines. However, screening for specific risk factors for HCV infection (i.e., risk behaviors or exposures) has largely been unsuccessful because of patients' reluctance to disclose these risks and provider limitations in collecting risk information.⁵ Population-based screening methods may be more successful (i.e., identifying and screening populations that have a relatively high prevalence of HCV infection). For example, in the United States, 50% of all HCV infections occur in individuals born between 1945 and 1965; therefore, one-time HCV testing has been recommended in this birth cohort.¹³ Nevertheless, screening rates are still low in this population because of, among other reasons, the stigma associated with HCV infection, the asymptomatic course of the disease, the lack of awareness of testing recommendations, and low health care engagement of the most at-risk populations.¹⁴

However, recent guideline updates have seen recommendations for screening to broaden to include routine one-time HCV testing for all individuals aged 18 years and older.^{3,5,8,9} Practical implementation measures, such as electronic medical record prompts, that have been shown to significantly increase screening rates in individuals born between 1945 and 1965 may help to facilitate universal screening and alleviate any stigma related to the disease. For example, in one study of this demographic group, screening rates in-

creased from 7.6% during the 6 months before their introduction to 72% over the year after their introduction.¹⁵

PWID have been identified as a priority population for HCV elimination. Worldwide, approximately 40% of people with recent injection drug use are infected with HCV and 9% of all people living with HCV infection are those who recently injected drugs, with wide variation among countries.¹⁶ It has been estimated that 43% of all new HCV infections could be prevented over 12 years (2018–2030) if the HCV transmission risk associated with PWID was removed over that period.¹⁷ Uptake of HCV treatment in this group is historically low,¹⁸ despite guideline recommendations to regularly screen PWID for HCV.^{5–7} The challenge for screening this population is the lack of engagement with traditional sources of health care; therefore, alternative options must be explored. One successful strategy is to integrate HCV screening programs into harm reduction and community outreach facilities, thereby offering a comprehensive “one-stop strategy” at the PoC for HCV screening and diagnosis, treatment initiation, and follow-up. Such approaches have been successfully implemented in several countries including France,¹⁹ Switzerland,²⁰ and the United States.²¹ In Scotland, the launch of the Hepatitis C Action Plan introduced DBS sampling into community drug services to increase access to testing.²² Between the pre-Action Plan (1999–2006) and Action Plan (2007–2011) periods, the average number of annual tests increased from 67 to 973; the percentage of individuals testing positive for HCV also increased across these periods (from 19 to 38%).

Unfortunately, screening birth cohorts and high-risk populations such as PWID will not find all of the remaining individuals infected with HCV. Achieving WHO elimination targets will require the adoption of broader, simpler screening policies. Different regional strategies will be needed because of the variable global epidemiology of HCV infection.¹⁶ One strategy under consideration is universal anti-HCV screening of all adults. Egypt, which has the highest prevalence of HCV worldwide and access to low-cost generic DAA treatments, has embarked on one such program: following a campaign of targeted screening, all adults aged 18 years and older are now being screened.²³ This approach may be too costly in regions with low HCV prevalence because of the large number of patients needed to be screened. However, modeling studies in France and the United States have shown that universal screening can be cost-effective in low prevalence regions.^{24,25} Indeed, the U.S. Preventative Services Task Force has recently updated their recommendations to include HCV screening for all adults 18 to 79 years of age.⁸ Likewise, the U.S. Centers for Disease Control and Prevention (CDC) recently updated their recommendations to include screening of all adults aged 18 years and older in addition to all pregnant women; except in settings where the prevalence of HCV is less than 0.1%.⁹

HCV screening in pregnancy represents an important opportunity for health care provider interaction with women of childbearing age, in whom rates of HCV have been increasing in recent years.²⁶ The prevalence of HCV antibodies in pregnant women is thought to be 0.1 to 3.6% worldwide, and some studies suggest that chronic HCV infection is associated with

an increased risk for adverse neonatal outcomes.²⁷ Furthermore, vertical transmission of HCV from mother to child will occur in up to 5% of cases of HCV mono-infection and is a common source of HCV infection in children.²⁸

Around 3.5 million children are estimated to be infected globally,²⁸ representing an important pool of unidentified HCV cases, with as many as 95% of HCV-infected children in the United States of America remaining undiagnosed.²⁹ In one study including 119 perinatally infected patients, 38% of those aged >33 years had developed cirrhosis, despite the low prevalence of traditional risk factors.³⁰

Alternatively, pragmatic approaches to screening strategies, such as random selection or using a hub-and-spoke model as trialed in Italy, can provide a practical compromise between universal and targeted screening.³¹

Regardless of the model employed and populations targeted, screening to identify undiagnosed cases is vital in achieving elimination targets.

Virologic Tools to Simplify HCV Screening

PoC testing provided outside traditional centralized laboratories can be used with the goal of delivering test results to patients during the same visit.³² PoC testing relies extensively on the use of one of the many RDTs available for anti-HCV antibody detection, several of which are prequalified by WHO.³³ RDTs can be performed in 20 minutes for anti-HCV antibodies using whole blood obtained by venipuncture or finger prick, or oral fluid. Anti-HCV antibody RDTs have excellent sensitivity and specificity compared with ELISA-based laboratory methods (98 and 100%, respectively).³⁴ RDTs are valuable in high-throughput settings where results are needed quickly, such as prisons and harm reduction programs. An example of the value of RDTs within a harm reduction setting is provided by Bregenzer et al, where the introduction of an anti-HCV antibody RDT led to 23.9% of PWID undergoing HCV screening, compared with only 2% prior to its introduction.³⁵ Confirmation of infection after detection of anti-HCV antibodies requires HCV RNA or core antigen testing. A few PoC HCV RNA assays, which generate results from plasma or whole blood within 60 to 90 minutes, are available.³² The increasing availability of such assays in high-income settings has the potential to transform HCV testing. In low-income countries, providers need to take advantage of the availability of such technologies, which to date have typically been used for HIV or tuberculosis testing.

To meet the WHO goal of identifying 90% of all HCV-infected individuals, PoC testing needs to be implemented into nontraditional settings to capture individuals not actively engaged in health care, including emergency departments, obstetric centers, surgical and psychiatric wards, dental clinics, and pharmacies.³⁶⁻⁴¹ Potential benefits of increased PoC testing include reducing the number of clinic visits, which may increase screening and treatment rates, and reducing late presentation, which is common in patients with HCV.⁴²

Using DBS samples is an alternative method to PoC testing. A few drops of fingerstick whole blood are placed onto a special absorbent filter paper. After desiccation, DBS can be

shipped as nonhazardous materials using regular mail or courier services to reference laboratories for anti-HCV antibody and HCV RNA assessments.³² DBS diagnostic accuracy is high for anti-HCV antibodies (sensitivity, 96.1%; specificity, 99.2%) and HCV RNA (sensitivity, 97.8%; specificity, 99.2%), with no relevant differences in diagnostic accuracy according to the type of test used.⁴³ DBS has distinct advantages over blood and oral fluid in terms of ease of transport and storage and may be particularly useful in low- and middle-income countries with high HCV prevalence and limited health care infrastructure. In high-income countries, DBS could be used where facilities and treatment for PWID or migrant populations are community located and staffed by workers with limited clinical training.

Methods to Improve Linkage to Care

In addition to increasing screening rates, loss to follow-up between screening and diagnosis must be reduced. Studies in Europe and the United States show that 69 and 47% of screened patients, respectively, did not receive a confirmatory diagnosis of HCV infection.^{44,45} Some countries have higher diagnosis rates, particularly those with national screening plans, such as France (74%) and Australia (75%).^{46,47} Reinforcing the link between screening and diagnosis will ensure better identification of infected individuals and improve rates of retention in the HCV care pathway. The screening and diagnosis phase will continue to be a two-step process until it becomes more cost-effective to perform a single HCV RNA test to confirm active HCV infection (e.g., in areas with very high HCV prevalence). Alternatively, advances such as reflex testing combine these steps into a single clinic visit.

Reflex HCV RNA testing, in which a positive anti-HCV test triggers an immediate HCV RNA test on the same sample, eliminates an extra visit for a new sample and enables more rapid linkage to care.¹² Reflex HCV RNA testing, as used by the U.S. Veterans Affairs (VA) system,⁴⁸ is important in large health systems, with centralized testing where most patients are actively engaged in care and undergoing phlebotomy rather than PoC testing.⁴⁸ However, this approach may be suitable for some field-based PoC approaches outlined above. AASLD/IDSA guidelines recommend that harm reduction programs offer anti-HCV testing with reflex or immediate confirmatory HCV RNA testing,⁵ 2018 EASL recommendations state that reflex HCV RNA testing should be applied whenever possible,⁶ and WHO guidelines include reflex HCV RNA testing as an approach to promote linkage to care in all patients with HCV.⁷

Increases in screening and diagnosis rates will have a limited impact on WHO elimination targets without concomitant improvements in linkage to care. Although specialist referral may be required for some complex cases, most patients could be treated by their primary care provider if the providers were given adequate training.⁷ Therefore, the role of the primary care provider is considered critical for expanding access to HCV care, especially in areas of high HCV prevalence.⁴⁹ Recently released "Simplified HCV Treatment Algorithms" from AASLD/IDSA reinforce the concept that less complex cases can be successfully managed by

primary care providers with less intensive monitoring.^{50,51} Indeed, decentralizing HCV treatment to utilize primary care physicians significantly increased treatment uptake in PWID in Australia and New Zealand compared with hospital-based specialist care (75 vs. 34%), with significantly higher cure rates (49 vs. 30%).⁵² Telementoring programs can be used to educate and support nonspecialist providers. These programs take advantage of approaches such as videoconferencing and knowledge networks to establish close collaborations between HCV specialists and primary care providers or other health care professionals. One such program, the VA-Extension for Community Healthcare Outcomes (ECHO) program, demonstrated an increase in the rate of primary care provider-initiated HCV treatment from 2.5 to 21.4% ($p < 0.01$) with program participation.⁵³ The ECHO model also demonstrated that HCV treatment administered by nonspecialist providers was as safe and effective as that provided by specialists in underserved populations.⁵⁴ An alternative telementoring approach investigated in the ASCEND study indicates that under specialist oversight, nurse practitioners or primary care physicians only required a short 3-hour training session to treat patients as effectively as specialists.⁵⁵ Decentralizing HCV care from specialists to primary care providers, as well as other health care professionals such as addiction specialists, prison doctors, and advanced practice providers, would simplify the continuum of care and expand access to HCV treatments without compromising outcomes.⁵⁶ Furthermore, integrating HCV care pathways with those for common copathologies such as HIV, malaria, or sexually transmitted diseases represents another important method for expanding access to HCV diagnosis and treatment⁵⁷⁻⁵⁹ and can increase HCV diagnosis and treatment uptake.^{59,60}

Simplifying the Pretreatment Phase

Assessing Liver Fibrosis

Once chronic HCV infection has been confirmed, patients undergo several pretreatment assessments.⁵⁻⁷ Staging of liver fibrosis by at least one method is required for all patients prior to treatment to determine the need for posttreatment monitoring (i.e., bi-annual HCC ultrasound screening) in patients with advanced fibrosis (METAVIR score F3) or cirrhosis (METAVIR score F4).⁵⁻⁷ If advanced fibrosis or cirrhosis is present, these patients should be referred to a specialist provider for their continued care requirements. However, the remaining population with HCV infection is evolving to generally be younger and have milder liver disease,^{61,62} which may help to support more nonspecialist provider involvement.

Although biopsy was previously used for assessing liver fibrosis, the procedure is invasive and minor complications are common. Alternative, validated, and noninvasive methods including serologic, physical, and imaging protocols have replaced biopsy and are preferred to stage liver fibrosis.⁶³ Simplifying the initial liver fibrosis assessment using noninvasive methods would enable decision-making by nonspecialist providers, which would reduce referrals to specialists and improve access to care for patients. This could be particularly

impactful for high-risk groups, such as PWID, who may already be managed in several health care settings.^{64,65}

The calculation of an aspartate aminotransferase (AST)-to-platelet ratio index (APRI) score using AST concentrations and platelet count has excellent negative predictive value and can identify patients not at risk for advanced liver fibrosis who could be easily managed by nonspecialist providers.⁶³ In a prospective study in treatment-naïve patients chronically infected with HCV genotype 1 to 6 and no history of cirrhosis, $APRI \leq 1$ was used to select patients for 8 weeks' treatment with the pangenotypic DAA combination glecaprevir/pibrentasvir.⁶⁶ The results showed that $APRI \leq 1$ (mean, 0.41; range, 0.13-1.00) identified patients without cirrhosis who could then be appropriately treated by nonspecialist providers. Fibrosis-4 (FIB-4) is another tool that uses a formula based on age, AST, platelets, and alanine aminotransferase to score fibrosis.⁶³ FibroTest is a laboratory-ordered test using a proprietary formula based on age, gender, and five additional biomarkers.⁶³ Transient elastography (e.g., FibroScan) measures liver stiffness to assess fibrosis; in addition, other physical technologies have been developed to assess liver fibrosis.⁶³ FibroScan and FibroTest use may be restricted by cost and availability in resource-limited settings. AASLD/IDSA guidelines recommend liver biopsy and/or noninvasive markers to evaluate liver fibrosis in patients with chronic HCV infection.⁵ The new simplified algorithms from AASLD/IDSA emphasize the utility of noninvasive tests for fibrosis assessment.^{50,51} EASL and WHO guidelines recommend noninvasive methods, especially APRI and FIB-4, outside specialty clinics in resource-limited settings.^{6,7}

HCV Genotype Determination

With the introduction of pangenotypic DAAs, some guidelines consider that the need for HCV genotyping is reduced, particularly where tests are not available or not affordable, or to improve access by simplifying the care pathway.⁵⁻⁷ However, identifying patients infected with genotype 3, particularly those who have cirrhosis, remains important because SVR rates can be impacted by prior HCV treatment experience or the presence of NS5A inhibitor resistance-associated substitutions at baseline.⁵⁻⁷ Longer treatment durations, baseline resistance testing, or the addition of a third drug (e.g., a DAA with another target or ribavirin) may be required in patients with HCV genotype 3 infection and cirrhosis. The decision to identify the HCV genotype may ultimately be one of cost-effectiveness (i.e., relative cost of regimens without genotype 3 restrictions) and the epidemiologic profile of endemic HCV genotypes within specific regions. WHO guidelines stipulate that where HCV genotype 3 prevalence is $< 5\%$, genotyping could be excluded and a uniform pangenotypic treatment duration could be used.⁷

However, the prevalence of other potentially difficult-to-treat genotypes such as non-1a/b subtypes of GT1 or non-4a/d subtypes of GT4 is increasing worldwide, largely driven by migration from areas of high endemicity for these subtypes, such as sub-Saharan Africa (SSA).⁶⁷ These subtypes are associated with higher failure rates to earlier NS5A inhibitors than other subtypes, with sofosbuvir/velpatasvir/voxilaprevir

being the only currently approved re-treatment option for those failing initial NS5A-based regimens.⁶⁷ This potentially poses a barrier to re-treatment success, as there is limited routine access to this therapy in SSA. Furthermore, settings that cannot access this treatment rely on viral sequencing to inform decision making regarding the most suitable alternative treatment options, but this is also not routinely available in SSA. It will therefore be crucial for settings such as these to increase access to newer pangenotypic regimens, as well as testing and documenting patient genotypes and resistance profiles, to monitor the success of first- and second-line HCV treatments.⁶⁷

Simplifying the Treatment and Monitoring Phase

Treatment

Despite the availability of curative HCV treatments, most persons infected with HCV remain untreated.⁶⁸ International guidelines recommend that all persons diagnosed with chronic HCV infection should be considered for treatment.⁵⁻⁷ Adopting a “treat all” approach helps to simplify clinical decision-making; streamline patient management; reduce transmission, morbidity, and mortality; and, ultimately, furthers progress toward WHO elimination targets.

Access restrictions to HCV treatment remain a significant barrier to care in many countries.^{69,70} Depending upon the country or health care system, access can be restricted by one or more of the following: high cost, the degree of liver disease (e.g., only patients with progressive liver disease [METAVIR stage \geq F2] can receive DAAs), the prescribing physician (e.g., only specialists can prescribe DAAs), or recent illicit drug or alcohol abuse (e.g., only patients enrolled in an addiction management program or with demonstrated sobriety can receive DAAs).^{69,70} Most restrictions are not evidence-based or supported by guidelines. For example, guidelines state that recent or active injection drug use is not a contraindication to HCV therapy.⁵⁻⁷ Numerous studies have demonstrated a lack of impact on treatment adherence and high cure rates with DAAs among recent or active drug users.^{71,72} Although these restrictions are slowly being lifted in the United States, over 30 state Medicaid plans still have prescriber and sobriety restrictions in place, and approximately 15 states have fibrosis score restrictions; removing these will improve access to HCV treatment for all patients and is a key recommendation in the U.S. National Strategy to eliminate viral hepatitis.^{69,70,73}

The latest DAA combinations have transformed the treatment landscape for chronic HCV infection, offering high cure rates with favorable safety profiles.⁷ The fixed-dose DAA combinations glecaprevir/pibrentasvir and sofosbuvir/velpatasvir are pangenotypic, well tolerated, have virologic cure rates $> 95\%$, and have treatment courses of 8 to 12 weeks for most patients.^{6,7,74,75}

Improving access to HCV treatment worldwide is vital, and in low-to-middle income countries, generic formulations of approved HCV treatments represent an important step toward making HCV elimination an achievable goal.⁶⁸ Globally, over 60% of people with HCV infection live in

countries with access to affordable generic DAAs,⁶⁸ such as generic formulations of sofosbuvir and daclatasvir, also considered pangenotypic, at costs as low as approximately US \$60 per 12-week supply.⁷⁶ Many of these countries have negotiated discounts from manufacturers to help provide universal access to HCV treatment with minimal financial contributions required by patients.⁷⁷

These generic formulations provide a viable option for HCV treatment, as a recent systematic review and meta-analysis of the effectiveness of generic formulations demonstrated equivalent outcomes between generic and licensed DAA formulations in the treatment of HCV.⁷⁸

The treatment profiles of the pangenotypic DAAs support the practicality of a “treat all” approach and have already helped to streamline the HCV care pathway by simplifying treatment choice.^{6,7} However there is further room for expansion to include indications for children under the age of 12 years, who represent an important population to target to achieve elimination efforts. Indeed, AASLD/IDSA guidelines state that the approval of additional DAA regimens for children aged 3 to 11 years is anticipated in the near future,⁵ and sofosbuvir/velpatasvir has recently been approved for use in children from 6 years of age.⁷⁵

On-Treatment Monitoring

There appears to be no requirement for on-treatment monitoring for virologic efficacy, given the very high cure rates with current DAA combinations, and steps toward simplification with regards to this aspect of HCV treatment have already been made. AASLD/IDSA guidelines previously recommended that HCV RNA viral load was assessed 4 weeks after treatment initiation, 12 weeks after therapy completion (SVR12), and as a consideration at the end of treatment.⁵ However, evidence suggests HCV RNA measurements at 4 weeks and at the end of treatment are unnecessary because they are not predictive of SVR12. In a retrospective review of 208 patients infected with HCV receiving DAAs, no difference was reported in SVR12 rates between patients with detectable and undetectable HCV RNA at week 4 (96.5 vs. 97.5%; $p = 0.69$).⁷⁹ These results have been replicated irrespective of treatment regimen or duration.^{80,81} AASLD/IDSA guidelines have recently been updated to dispense with 4-week HCV RNA viral load assessment, now recommending testing only at 12 or more weeks posttreatment completion.⁵ Furthermore, 2018 EASL recommendations advocate HCV RNA viral load testing at 12 or 24 weeks posttreatment only but state SVR assessment is dispensable, given the high cure rates expected with pangenotypic regimens.⁶ WHO recommends viral load testing at 12 or 24 weeks posttreatment.⁷ Patients at risk for reinfection should be tested for SVR12 and yearly thereafter whenever possible.⁶

Another strategy aimed at reducing the reliance on clinic visits and simplifying on-treatment patient monitoring is telemedicine (or telecare). Telemonitoring or teleconsulting programs, which use telephone contact instead of clinic visits, can be used to ensure medication adherence and monitor for adverse events and potential drug-drug interactions. These programs have been successful in underserved

populations, such as prisoners.⁸² Simplified HCV treatment monitoring via telephone calls versus standard clinic visits was assessed in the SMART-C study, and no differences were seen in virologic or safety outcomes in “easy-to-manage” patients.⁸³ Taken together with the simplicity, safety, and effectiveness of the latest DAA regimens, measures aimed at reducing clinic visits, especially in high prevalence settings, will relieve the burden on health care systems.⁸⁴ These strategies will facilitate the retention of patients in care, supporting patients’ preferences for treatment attributes that offer more convenience, and require less disruption to daily life (e.g., shorter treatment duration and fewer office visits).⁸⁵

In the past, concerns regarding low treatment adherence to interferon-based therapies in PWID meant that additional on-treatment monitoring was warranted.^{64,86} However, in the DAA era, evidence suggests that treatment adherence and SVR rates are high in PWID. In the SIMPLIFY study, median adherence to sofosbuvir/velpatasvir for 12 weeks was 94% in PWID with recent injection drug use (≤ 6 months), with 32% of patients considered nonadherent ($< 90\%$ adherence).⁷¹ Although adherence decreased during therapy, similarly high SVR12 rates were seen in PWID who were adherent ($\geq 90\%$ of doses received) and nonadherent (94 vs. 94%; $p = 0.944$).⁷¹ In the ongoing ANCHOR study, in which 97 PWID with recent injection drug use (≤ 3 months) received sofosbuvir/velpatasvir for 12 weeks, SVR12 was achieved by 90% of PWID who attended the week 24 visit.⁷² SVR12 rates were unaffected by treatment interruptions that delayed the anticipated date for end of treatment, providing the treatment course was completed.⁷² Additional monitoring for treatment adherence in PWID is no longer warranted; instead, pretherapeutic education and on-treatment support delivered via a decentralized multidisciplinary care approach are important for successful treatment in PWID.

Status: Simplifying the HCV Care Pathway

Simplifying the diagnosis, treatment, and monitoring of patients with chronic HCV infection has improved the prospects for scaling up the management of patients by primary care providers and other nonspecialist health care professionals to further progress toward achieving the WHO goal of HCV elimination.⁸⁷ AASLD/IDSA acknowledge that treatment simplification could expand the number of health care providers who can prescribe HCV therapy and increase the number of individuals who are treated.⁵ EASL recommendations are also comprehensive but propose that simplified HCV care pathways are now possible using a pangenotypic DAA regimen for 12 weeks.⁶ Recent label updates mean that treatment-naïve patients without cirrhosis or with compensated cirrhosis can now both receive glecaprevir/pibrentasvir for 8 weeks. The only assessments required are to confirm chronic HCV infection and advanced fibrosis or cirrhosis (using noninvasive markers) and establish possible drug–drug interactions. Genotyping can be dispensed with, and SVR12 assessment is not required in patients who are adherent and not at

high risk for reinfection.⁶ WHO also has specific recommendations to support their “treat all and use pangenotypic DAAs” recommendation, including simplified treatment pathways and decentralization of testing and treatment services at the primary care level.⁷ Simpler HCV care pathways to encourage HCV testing and treatment at the primary care level have been successful in expanding treatment in France⁸⁸ and Australia,⁸⁹ for example.

Conclusion

Today’s highly effective, safe, and well-tolerated pangenotypic DAA regimens have maximized the opportunity to simplify treatment strategies in the HCV care pathway. Recent developments in HCV screening and diagnostic procedures, together with lower requirements for pretreatment assessments and on-treatment monitoring, can further streamline the continuum of care, ensuring more patients are linked to care quickly and earlier in the disease course, and with minimal clinic visits. These advances also allow HCV treatment to be prescribed by nonspecialist providers, which can reduce overall health care costs and further support efforts toward meeting the WHO viral hepatitis elimination goal. Patients and health care providers should both be motivated to embark on a simplified HCV care pathway by knowing that, if diagnosed with chronic HCV, the journey from screening to cure can be achieved in as few as five steps and in as little as 20 to 24 weeks.

Main Concepts and Learning Points

- Today’s highly effective, well-tolerated, all-oral, direct-acting antiviral combinations for the treatment of chronic hepatitis C virus infection have made elimination of the virus theoretically achievable by the World Health Organization’s target of 2030.
- Despite the availability of curative hepatitis C virus treatments, most persons infected with hepatitis C virus remain untreated.
- Recent developments in hepatitis C virus screening and diagnostic procedures, as well as reduced pretreatment assessments and on-treatment monitoring requirements, can simplify the hepatitis C virus continuum of care.
- Simplification of the hepatitis C virus care cascade would facilitate patient engagement and support the current concerted effort toward hepatitis C virus elimination.
- The journey from hepatitis C virus screening to cure can be achieved in as few as five steps and in as little as 20 to 24 weeks.

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Conflict of Interest

Jean-Michel Pawlotsky: research grants from Abbott and Vela Diagnostics; advisor for AbbVie, Gilead, Glaxo-SmithKline, Merck, Regulus, and Siemens Healthcare; speaker for AbbVie and Gilead. Christian B. Ramers:

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