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Simplification of antiviral hepatitis C virus therapy to support expanded access in resource-limited settings

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Summary

Currently, access to treatment for HCV is limited, with treatment rates lowest in the more resource-limited countries, including those countries with the highest prevalence. The use of oral DAAs has the potential to provide treatment at scale by offering opportunities to simplify drug regimens, laboratory requirements, and service delivery models. Key desirable characteristics of future HCV treatment regimens include high efficacy, tolerability, pan-genotype activity, short treatment duration, oral therapy, affordability, and availability as fixed-dose combination. Using such a regimen, HCV treatment delivery could be greatly simplified. Treatment could be initiated following confirmation of the presence of viraemia, with an initial assessment of the stage of liver disease. A combination DAA therapy that is safe and effective across genotypes could remove the need for genotyping and intermediary viral load assessments for response-guided therapy and reduce the need for adverse event monitoring. Simpler, safer, shorter therapy will also facilitate simplified service delivery, including task shifting, decentralization, and integration of treatment and care. The opportunity to scale up HCV treatment using such delivery approaches will depend on efforts needed to guarantee that the new DAAs are affordable in low-income settings. This will require the engagement of all stakeholders, ranging from the companies developing these new treatments, WHO and other international organizations, including procurement and funding mechanisms, governments and civil society.

Keywords: Access; Direct-acting antivirals; Simplification; Scale-up.
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Abbreviations: ARV, antiretroviral; ART, antiretroviral therapy; DAA, direct-acting antiviral agent; FDC, fixed-dose combination; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; PCR, polymerase chain reaction; RBV, ribavirin; WHO, World Health Organization.

Introduction

In April 2014, the World Health Organization (WHO) released its first set of global guidelines for hepatitis C virus (HCV) treatment [1]. These guidelines include recommendations for the use of recently approved oral direct-acting antivirals (DAAs) that have shown high treatment success rates with limited side effects and shorter treatment duration compared to interferon-based therapy.

Currently, access to treatment for HCV is limited, with only a minority of the estimated 130–150 million people infected world-wide receiving a diagnosis, and even fewer assessed for eligibility and initiated on treatment. Treatment rates are lowest in resource-limited countries [2], including those countries with the highest prevalence [3]. Until now, key reasons for limited treatment access have been the cost, complexity, limited effectiveness of treatment, and lack of access to reliable and affordable diagnostics. The standard treatment of pegylated-interferon and ribavirin requires injections and thus is difficult to administer, is associated with common and sometimes severe adverse drug reactions, and has limited treatment success that varies according to genotype. These challenges, together with the long treatment duration and high prices, have restricted treatment to specialist centres, with patients selected according to their chances of achieving treatment success, as determined by genotyping and early virological response.

The use of oral DAAs has the potential to substantially increase success rates for treatment-naïve patients, from around 50% with pegylated-interferon and ribavirin (with significantly lower rates for certain genotypes and among HIV co-infected individuals) [4,5] to over 90% with sofosbuvir-based regimen [6,7]. This, together with the improved safety and tolerability, shorter treatment duration, and simpler administration compared to the interferon-based therapy, opens up the prospect of providing treatment at scale, including in resource-limited settings.

The situation for HCV treatment today has been compared with the situation for HIV treatment in the late 1990s, when combination antiretroviral therapy was found to dramatically reduce mortality among people living with HIV, but access to diagnostics and treatment was extremely limited in resource-limited settings where the vast majority of the 34 million people infected

reside [8]. HIV and HCV share common routes of infection; both diseases have a long period of asymptomatic infection before the appearance of symptoms, and both lack an effective vaccine. There are also important differences, notably the more important contribution of sexual transmission in the case of HIV, and the possibility of cure following antiviral therapy in the case of HCV. Nevertheless, HCV and HIV have a number of important overlapping challenges, and efforts to control HCV infection can be informed by the experience of the global HIV response.

This article discusses the recent advances in HCV treatment and reflects on the evolution of the public health response to HIV/AIDS over the last decade to outline opportunities for expanding access to HCV treatment provided by advances in treatment (Table 1).

Key Points

- Direct acting antivirals with improved efficacy and tolerability, shorter treatment duration and simpler administration open up the potential to provide HCV treatment at scale, including in resource-limited settings
- Key desirable characteristics of HCV therapy include high efficacy, tolerability, pan-genotypic activity, short treatment duration, oral therapy, affordability and availability as fixed-dose combination
- Strategies to support access to treatment at scale include simplification of screening for treatment, treatment regimens, laboratory monitoring, and service delivery
- Efforts are needed to guarantee that the new DAAs are affordable in low- and middle-income settings

Approaches to the simplification of HCV treatment delivery

The first set of WHO guidelines for antiretroviral therapy (ART) for HIV/AIDS in resource-limited settings, released in 2002, were presented as guidelines for a public health approach [9]. At the time these guidelines were launched, there were over 20 drugs available to treat HIV, and the established model of care was developed in the USA and Europe where HIV was managed by a team of medical specialists, using a range of diagnostic tests and treatments tailored to individual needs and preferences. Central to the public health approach for ART delivery was the simplification of treatment initiation, therapeutic options and laboratory monitoring requirements, which in turn led to a simplification of service delivery. This approach allowed for a greater role of patients in the self-management and care of HIV [10]. At each step, parallels can be drawn with the potential offered by DAAs to simplify HCV treatment delivery.

The availability of safe, simple, efficacious and affordable treatment for HIV has allowed delivery of treatment to over 10 million people within a decade. In a similar way, the new DAAs offer the opportunities to simplify drug regimens, laboratory requirements, and service delivery models to scale up treatment.

Simplification of screening for treatment

The last decade of antiretroviral therapy provision to people living with HIV/AIDS in resource-limited settings has seen a gradual shift towards expanded treatment eligibility as the risk-benefit profile has evolved towards favouring earlier treatment [11]. The latest WHO guidelines for antiretroviral therapy provide recommendations for initiating treatment in certain populations without any baseline laboratory testing beyond confirmation of HIV positive status (a so-called "test-and-treat" approach). Where this is not recommended, treatment initiation is based on a simple clinical or immunological assessment, without the need for baseline genotyping or viral load.

In well-resourced settings, a range of laboratory tests are required prior to initiation of HCV treatment, including confirmation of antibody screening, followed by RNA PCR to confirm the presence of viraemia, assessment of liver disease severity (using non-invasive tests or liver biopsy), viral load, HCV genotype and subtype determination, and host genetics [12]. All of these tests depend on a level of laboratory infrastructure that is poorly accessible in resource-limited settings. HCV treatment scale-up will need the expansion of screening, with easy access to confirmatory testing, or the development of a combined test (e.g. antibody and antigen) [13] for a one-step diagnosis. The improved safety profile of the new DAAs and improved efficacy across genotypes allows for the possibility to greatly simplify the approach to pre-treatment screening, possibly to the point that, in the future, HCV treatment could be initiated following confirmation of infection and the presence of viraemia, with an initial assessment of the stage of liver disease, without requiring further baseline tests.

Simplification of treatment regimens

For HIV there are currently 27 U.S. Food and Drug Administration (FDA)-approved antiretrovirals (ARVs) that collectively target five different points in the HIV life cycle. In order to scale up treatment, efforts have been made to standardize the number of treatment options recommended for use in resource-limited settings. The WHO-recommended first-line formulary for HIV therapy has been reduced from five recommended options in 2002 to a single preferred option in 2013 [9]; fixed-dose combination therapy is preferred as this facilitates drug supply management and has been shown to be associated with improved adherence and clinical outcomes compared to separate tablets [14].

As of September 2014, six drugs were approved by the FDA for the treatment of HCV – standard interferon (IFN) or pegylated interferon alpha (PegIFN), ribavirin (RBV), three protease inhibitors (boceprevir, simeprevir, and telaprevir), and the nucleotide analogue and polymerase inhibitor sofosbuvir. There is a robust pipeline of new drugs for HCV treatment, with over 25 new drugs and combinations in clinical development, including two nucleotide polymerase inhibitors, six non-nucleoside polymerase inhibitors, eight non-structural protein inhibitors, seven protease inhibitors, one microRNA targeting compound, and several fixed-dose combinations (Table 2) [15]. While there has been a pressing need for improved treatments, the availability of such an extensive number of drugs also comes with challenges, including the need to simplify prescribing, and ensuring availability at an affordable price.