Clinical Infectious Diseases Advance Access published March 19, 2012

VIEWPOINTS ARTICLE

Expanding Access to Treatment for Hepatitis C in Resource-Limited Settings: Lessons From HIV/AIDS

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The need to improve access to care and treatment for chronic hepatitis C virus (HCV) infection in resource-limited settings is receiving increasing attention. Key priorities for scaling up HCV treatment and care include reducing the cost of current and future treatment; simplifying the package of care; identifying opportunities to shift specific tasks to nonspecialists to overcome human resource constraints; service integration with human immunodeficiency virus (HIV) clinics, prison health services, and needle syringe and oral substitution therapy programs; improving surveillance, monitoring, and research; encouraging patient and community engagement; focusing specifically on the needs of vulnerable groups; and increasing financial and political commitment. Many of these obstacles have been addressed in rolling out treatment for human immunodeficiency virus during the last decade, and a number of lessons can be drawn to help improve access to HCV care.

Hepatitis C virus (HCV) infection is a growing public health concern, with an estimated 170 million persons infected globally and 350 000 deaths each year due to hepatitis C–related liver disease [1]. In 2010 the World Health Assembly adopted a resolution promoting integrated and cost-effective approaches to the prevention, control, and management of viral hepatitis and noted in particular the need to address hepatitis in the context of the human immunodeficiency virus (HIV) epidemic [2]. A number of countries in resource-limited settings are providing treatment of HCV infection through dedicated services with reasonable success [3]. Generally, however, access to care remains limited, particularly in poorer regions such as India and sub-Saharan Africa [4].

Challenges to increasing access to treatment of HCV infection in resource-limited settings include the high cost and perceived complexity of treatment, side effects that hamper adherence, long treatment duration, and insufficient political commitment. Early efforts to increase access to antiretroviral therapy (ART) for HIV/AIDS in resource-limited settings were impeded by similar challenges. We reflect on the experience of scaling up access to ART during the last decade and draw lessons for improving access to treatment and care for persons with HCV.

A decade ago, treatment for persons living with HIV/AIDS was unavailable in most developing countries, and there was debate about whether treatment should be considered given the considerable challenges faced [5]. Yet despite these early concerns, >6.6 million persons are now receiving ART in the developing world [6]. Several critical issues had to be confronted before large-scale HIV treatment programs could be

Received 23 November 2011; accepted 30 January 2012.

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Clinical Infectious Diseases

DOI: 10.1093/cid/cis227

Table 1. Overcoming Barriers to Increasing Access to Treatment for Hepatitis C Virus Infection

Challenge	Lessons From HIV/AIDS	Action Points for HCV
Decrease cost of care		
Ensure affordable, quality drugs	WHO prequalification project provided quality assurance mechanism for generic antiretrovirals	Internationally recognized quality assurance of generic/biosimilar sources of drugs for HCV treatment
	Several legal mechanisms have proved successful for overcoming patent barriers to stimulating market competition	Prioritize policies that are proved to work to reduce prices
	Lower prices of originator drugs	Lower prices of originator drugs
	Reporting of treatment trends has supported market forecasting	Develop international disease and treatment surveillance for HCV
	Dose optimization research is encouraged to reduce cost of drugs and reduce toxicity	Encourage dose optimization research in HCV drug development
Simplification		
Treatment guidelines	WHO guidelines for management of HIV/AIDS in resource-limited settings published every 2–3 years	Develop international guidelines for management of HCV in resource-limited settings
Drug regimens	Trials undertaken to determine optimal first-line regimens and sequencing of future regimens; fixed-dose combinations supported treatment adherence and simplified drug supply	Use in resource-limited settings should be introduced as an important consideration in HCV drug development and clinical research, including development of oral and fixed-dose combinations
Investigations	Simple laboratory tests prioritized; lack of laboratory tests should not be a barrier to accessing treatment	Validate noninvasive techniques for assessment of fibrosis in different populations and their use in resource-limited settings; explore use of facilities that have been developed for HIV viral load testing for HCV virology
	Research into simplified technologies to support access to viral load and genotyping (eg, dried blood spot and point-of-care testing)	Evaluate potential for advances in HIV testing to be applied to HCV, such as dried blood spot and point-of-care tests
Cohort reporting	Simplified monitoring integrated into other national programs	Develop and evaluate indicators to enable simplified monitoring tools
Task shifting		
Task shifting guidelines	WHO guidelines for task shifting in HCV care	WHO guidelines for task shifting in HCV care
Validation of different approaches	Operational research, supported by dedicated donor funding, has provided a substantial evidence base to inform future programming	Establish a prioritized operational research agenda
Integration	HIV diagnosis and treatment integrated into other health services, such as tuberculosis programs, STI care, and antenatal care services	Evaluate the opportunities and challenges of integrated vs vertical care models for HCV diagnosis and treatment into other services (HIV clinics, prison health services, needle syringe and oral substitution therapy programs)
	Decentralization of services to primary care level supports access and retention in care	Develop models for integrating HCV care into primary care
Research and surveillance	High-quality epidemiological data available from a wide variety of locations and settings	Develop strategies to improve epidemiological information, including genotype
	Treatment monitoring and evaluation built into some national programs	Consider monitoring and evaluation from outset of program development
	Low-technology solutions to investigations, such as rapid testing and dried blood spot testing	Consider applicability of advances made in HIV research to HCV testing

Table 1 continued.

Challenge	Lessons From HIV/AIDS	Action Points for HCV
Patient and community engagement		
Define roles	Treatment literacy recognized early on as a key part of patient engagement	Treatment literacy materials should be developed to support patient involvement in HCV care
Define incentives for community engagement	Community health workers are an important resource in treatment delivery, provided they are adequately supported.	Engage patients and community workers to promote adherence to treatment and retention in care
Human rights		
Monitor treatment access	Reporting of numbers receiving treatment disaggregated for specific vulnerable groups	Ensure reporting of numbers receiving treatment for specific vulnerable groups
Dedicated funding targeted to vulnerable groups	Dedicated donor funding provided to support treatment and care of vulnerable groups	Encourage dedicated donor funding for treatment and care of vulnerable groups; increase HCV funding from AIDS donors, such as GFATM or UNITAID
Financing		
	New funding mechanisms were created to provide dedicated funding for HIV/AIDS care in resource-limited settings	The provision of specific, additional funding to kick-start HCV treatment programs
	Donor support needs to be matched by political and financial support at the national level	Political commitment from governments with high burden of disease

Abbreviations: GFATM, Global Fund to Fight AIDS, Tuberculosis, and Malaria HCV; hepatitis C virus; HIV, human immunodeficiency virus; STI, sexually transmitted infections; WHO, World Health Organization.

established. These are summarized in Table 1 and discussed below.

REDUCING THE COST OF TREATMENT

Until mid-2000, ART cost about US $10 000 per patient per year, and cost-effectiveness studies concluded that treatment should not be prioritized [7]. This equation shifted as generic competition drove down the cost of treatment. This was largely achieved thanks to significant political support by a global alliance of civil society groups, and in particular persons living with HIV/AIDS and health providers, nongovernmental organizations, and academics who worked together as a global coalition for the rights of those with HIV/AIDS to access treatment [5]. In 2001 a generics manufacturer announced that triple therapy could be manufactured for less than a dollar a day. This created a dynamic of global market competition that drove down the price of standard triple therapy from US $10 000 per patient per year to almost US $60. Today, >80% of ART used in low-income and middle-income countries is manufactured by Indian generics firms [8].

Treatment of HCV infection is currently expensive in developing countries. Generic forms of ribavirin are available, but pegylated interferon is patented in a number of low- and middle-income countries, and overall costs of treatment are high: a recent survey of 5 Asian countries reported that public sector prices for a 48-week course of combination therapy range from US $12 000 (Vietnam) to US $18 500 (Indonesia) [9]. Several alternative sources of pegylated interferon have recently been developed that have helped drive down the cost of treatment. In Egypt, for example, a locally manufactured biosimilar of pegylated interferon is produced [10], and market competition has supported a 6-fold reduction in the price of both originator and generic products: a 48-week treatment course of pegylated interferon and ribavirin currently costs less than US $2000 in Egypt. Although comparative safety and efficacy data are limited for generic pegylated interferon products, this nevertheless demonstrates that substantial price reductions are possible.

The World Health Organization (WHO) prequalification scheme has played a critical role in the availability of affordable antiretrovirals. This scheme is used by donors, implementing organizations and many national programs to assure the quality of generically produced antiretroviral drugs [11]. Similarly, quality assurance of antivirals for HCV would give confidence to donors, patients, and implementing organizations and would allow developing countries to fast-track registration of generic and biosimilar sources of antivirals for HCV. Existing biosimilars of pegylated interferon are registered in only a few

countries and have not been quality assessed by WHO, although guidance for the evaluation of biosimilars has been published elsewhere [12].

Access to the newest generation of HCV medicines will be critical, because these drugs have the potential to significantly simplify treatment regimens and improve outcomes, offering particular advantages for use in settings with limited facilities [13, 14]. This will likely require concerted public and political mobilization to pressure originator companies to reduce prices and stimulate generic competition.

SIMPLIFYING THE MODEL OF CARE

HIV/AIDS care in developed countries is highly specialized. Treatment initiation decisions are informed by CD4 count and viral load, and treatment regimens are individualized according to genotypic resistance pattern, clinical response, side effects, and patient preference. More than 30 different antiretroviral drugs are currently approved, allowing for frequent medication adjustments.

In resource-limited settings, access to laboratory tests and choice of medication are limited. Guidelines for the management of HIV/AIDS in resource-limited settings developed by the WHO have helped to simplify management by specifying only a limited selection of once- or twice-daily regimens for first- and second-line therapy and recommending a limited set of laboratory tests that are desirable but not essential [15]. The development of antiretroviral agents as fixed-dose combination tablets has greatly helped to standardize and simplify patient care. In addition, low-technology innovative solutions to provision of essential tests have also been pursued, such as dried blood spots for viral load testing [16].

Similar simplification is required to support HCV management in poorly resourced settings. Current guidelines for treatment of HCV infection are from developed country tertiary care settings; include a variety of tests to initiate and guide care, such as regular viral load monitoring; and involve a range of antiviral and supplementary medications. Research to determine the need for each test will be important to make HCV treatment feasible and cost-effective in resource-limited settings.

Recent innovations enabling noninvasive assessment of liver fibrosis have important possible applications in HCV management decisions in resource-limited settings. These range from those employing the use of widely available blood tests, such as aspartate transaminase (AST) to platelet ratio (APRI) and potentially portable new technologies, such as transient elastography (eg, FibroScan) [17]. These tests generally perform well in distinguishing mild liver fibrosis from advanced fibrosis and cirrhosis, but clinical decisions for treatment often require the diagnosis of intermediate stages of fibrosis and this limits the usefulness of such tests [18]. Findings of a large European study suggest that the FibroScan technique might be more useful than blood markers [19]. Small, portable FibroScan units make the approach more feasible in resource-poor settings, but problems with unreliable readings in inexperienced hands and maintenance of equipment create significant challenges.

The necessity of other investigations in the treatment of HCV infection, in particular HCV viral load monitoring and genotype tests, is an important consideration in planning implementation of HCV treatment programs in resource-limited and isolated settings. Increasing access to viral load technology is becoming a priority within HIV/AIDS programs, and this could serve to benefit HCV programs [20]. Given the paucity of clinical findings in HCV infection before end-stage disease with hepatic decompensation, the availability of investigations may prove to be a larger hurdle for HCV programs than it has been in the case of HIV. Finally, the relative benefit of interleukin 28B testing, which is increasingly used to help predict treatment response in Western settings, needs careful consideration [21].

HCV program development can also learn from simplification approaches to scaling up treatment for multidrug-resistant tuberculosis. Multidrug-resistant tuberculosis care requires frequent injections, multiple medications, and long durations of treatment. Through models of care that provide psychosocial support and early recognition and management of adverse effects and through the decentralized provision of care, good programmatic outcomes have been achieved [22].

In the treatment of HIV infection, the introduction of less toxic drugs and simplified, fixed-dose combinations has been associated with improved adherence [23]. The arsenal of HCV drugs is rapidly changing, and with recent data on newer oral antiviral agents [24], interferon-free treatment for HCV now seems achievable, offering the possibility of injection-free treatment [25]. Mechanisms for accelerated access to simplified treatment of HCV infection should be prioritized.

The simplification agenda for HCV management will need to take into account the different capacities of different settings. Just as guidelines for ART specify a number of diagnostic tests that, although not essential, are nevertheless highly desirable [15], so recommendations for HCV management will need to strike a balance between what can be done today and what should be the standard for tomorrow.

TASK SHIFTING TO OVERCOME HUMAN RESOURCE SHORTAGES

In developed countries, HIV/AIDS has conventionally been managed by specialist physicians. However, health systems in

resource-poor settings where the burden of HIV/AIDS is greatest face a critical shortage of the most basic essential health staff, with some high-burden countries having a 100-fold fewer doctors per population compared with the United Kingdom or United States [26]. To address this challenge, the WHO published guidelines for task shifting, outlining a range of tasks that could, with adequate training and supervision, be delegated to nonphysician clinicians [27]. Randomized trials and cohort studies have subsequently validated the safety and effectiveness of task shifting for the provision of ART [28].

The decentralization of HCV management to lower levels of the health system has been assessed in the United States as a way to improve access to care. Outcomes of HCV treatment provided at community settings with specialist supervision via videoconference were found to be comparable to care provided at a dedicated HCV clinic in a tertiary center [29]. This strategy will help to ensure that care is not limited by a lack of specialists and the need to travel to tertiary level centers. Operational research should be conducted to assess the potential for different models of patient support and define the appropriate skills mix for resource-limited settings.

SERVICE INTEGRATION

The provision of ART as a vertical (disease-specific) program was an important early starting point in the AIDS response, allowing for rapid establishment of services. As programs expanded, integration of HIV/AIDS services into the broader health system has become a priority [30]. Primary care services in general, and clinics for antenatal care, tuberculosis, and sexually transmitted infections in particular, have proved to be important entry points for the diagnosis and treatment of HIV, and integration of services has had an important influence on patient outcomes [31].

Similarly, for HCV services to reach larger numbers of persons in a sustainable way, efforts will need to be made to link HCV prevention and treatment services and integrate treatment and care with other health services in which persons at risk are likely to be identified and where provision of quality of care is possible: needle syringe and oral substitution therapy programs, HIV clinics, and prison health services. The first step would be to increase access to HCV diagnostics in such services.

Integration of HIV management into general health services has had mixed results, providing both positive and negative lessons for HCV care [32]. The resulting literature provides an important resource for HCV management programs. For example, a recent review of integration of HIV and tuberculosis highlights some of the ways in which vertical approaches have led to inefficient and ineffective programming for both diseases [33].

SURVEILLANCE, EVALUATION, AND RESEARCH

During the past decade, significant improvements in HIV disease surveillance have informed service provision and directed research. In contrast, there is a dearth of epidemiological information regarding HCV infection rates in most parts of the world [4]. Improved epidemiological information will be critical in expanding HCV services, and many of the approaches developed to collect information about HIV incidence and transmission could be adapted for use in HCV. Increased information regarding the global scale and burden of the epidemic in different settings will increase awareness of the epidemic. Increased testing for HCV infection will be an important component of accurate disease surveillance and is also critical to treatment and prevention efforts [34]. This is particularly important because the development of appropriate treatment strategies will require accurate information regarding genotype prevalence in different countries.

The use of simplified reporting systems with standardized indicators in ART programs has allowed regular monitoring and the strategic direction of resources to improve service provision through operational research [35]. In the development of treatment programs for HCV infection, building in methods of data collection and recording to allow regular and routine program review will help facilitate ongoing service feedback and improvement and will also help generate evidence around the relative benefits and cost-effectiveness of different program strategies.

The research and development agenda for HCV needs to take better account of the specificities of resource-limited countries. For HIV, factors such as heat stability of medications, minimal monitoring of drug regimens, and simplified drug dosing are important for simplifying care [36]. The consideration of such factors in the process of drug development for HCV could greatly facilitate the adoption of treatments in resource-constrained settings.

PATIENT AND COMMUNITY ENGAGEMENT

In the scale-up of treatment for HIV infection, lack of patient knowledge and stigma are understood to influence uptake of testing and adherence to treatment. Efforts to tackle HIV thus need to address both access to diagnosis and care, as well as community education and stigma reduction components [37]. Similarly, persons with HCV infection are often not aware of their diagnosis or lack access to information about the benefits of treatment [38–41]. Efforts to scale up HCV treatment must tackle community education and stigma issues, especially among intravenous drug users.

Initially, there was considerable concern about the challenge of achieving adequate adherence to ART in resource-limited settings, but reported rates of early adherence in sub-Saharan Africa were found to be better than in North America [42]. Adherence counseling by patient experts or community health workers has been demonstrated to be one of the most effective ways of supporting patient adherence [43], while at the same time relieving the burden on health workers. More recent reviews have documented substantial attrition between diagnosis and initiation of ART, highlighting the need to develop supportive models of care that start at the point of diagnosis [44].

The treatment of HCV infection, like ART for HIV infection, is associated with a range of adverse effects, many of which are nonsevere but can lead to poor treatment adherence. A recent meta-analysis of HCV program outcomes in low- and middle-income settings found relatively low rates of defaulting from care (4%) and low frequency of adverse events leading to treatment discontinuation (4%) [3]. Nevertheless, adherence support interventions for HCV treatment need to be better defined, particularly as a proportion of patients who will be eligible for treatment may be asymptomatic. Treatment literacy programs to increase patients' understanding of HCV disease and treatment, together with dedicated peer support to assist with adherence and social issues, will likely be an effective way to ensure that patients are supported during the course of their treatment. Community engagement in other areas of the care pathway such as testing and screening have proved effective in scaling up access to HIV care [45] and should also be explored for HCV.

The engagement of persons living with HIV has been acknowledged as one of the most important achievements in the AIDS response [46]. Persons living with HIV/AIDS have also played a critical political role through activism to pressure price reductions for antiretroviral drugs, increased funding, and acceleration of research and development [47]. Similar activism is beginning to take shape for HCV and will be critical to making treatment more widely available [48].

ADDRESSING THE NEEDS OF VULNERABLE GROUPS

From the outset, efforts to scale up ART in developing countries have included a specific focus on such populations who, because of oppression and vulnerability [49], have been systematically excluded from access to treatment and care. International reports mapping progress toward universal access to prevention and treatment dedicate specific sections to population groups, such as sex workers, injection drug users, men who have sex with men, and prisoners [50], and international funding mechanisms provide specific funding for programs addressing the needs of vulnerable groups.

Given the high burden of HCV infection among injection drug users [51], increased transmission risk in prisoners, and the substantial overlap between the HIV and HCV epidemics, national and international efforts to support improved access to HCV prevention, treatment, and care should benefit from the positive experiences of expanding ART to vulnerable groups.

FINANCIAL AND POLITICAL COMMITMENT

The dramatic reduction in the cost of treatment was essential to shifting the cost-effectiveness equation in favor of the widespread provision of ART. In addition to increased bilateral funding from a number of Western governments, several international funding streams were established to support ART scale-up, notably the Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM), and the US President's Emergency Plan for AIDS Relief [52].

To support an international effort to increase access to treatment and care for HCV infection, dedicated funding will be required to support the expansion of access to diagnostics and treatment and the promotion of operational research to develop adapted models of care. The GFATM is already providing some, albeit limited, funding for HCV treatment for individuals coinfected with HCV and HIV, and other donors, such as UNITAID, should explore how they can support HCV care [53]. However, recent reductions in donor contributions to GFATM threaten to limit the number of programs that can be supported [54]. Political commitment from the national governments of countries most affected by HIV/AIDS has also been an essential driver of the global response to HIV and will be critical in enabling the provision of HCV treatment and care in institutions under the management of correctional services.

CONCLUSIONS

Expanding access to hepatitis treatment in resource-limited settings will require a dedicated effort to overcome practical and political challenges. This also applies to care and treatment for persons with hepatitis B virus infection [55], for which many of the lessons outlined in this article apply. Perhaps the most important lessons from the scaling up of ART during the last decade is that this will not happen without clear political commitment, and the engagement of civil society to hold policy makers and drug manufacturers to account. Recent demonstrations by activists in India to call for reduced drug prices for hepatitis treatment could be the first step toward reducing the present inequality where hepatitis treatment and care are, for the most part, available

only to patients who are fortunate enough to live in the developed world.

Notes

Acknowledgments. We thank Paul Cawthorne, Arnaud Fontanet, and Els Torrele for kindly providing information on treatment costs.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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