AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 09: Infectious Disease Including HIV/AIDS

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290-2010-00006-C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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Financial Disclosure Statement

None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the National Academy of Medicine (formerly the Institute of Medicine) and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 24,500 leads about potential topics has resulted in identification and tracking of about 2,400 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 700 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 195 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the five to eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts' rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ's Effective Health Care Web site.

Results

The table below lists the eleven topics for which (1) preliminary phase III data for drugs were available; (2) information was compiled and sent for expert comment before November 6, 2015, in this priority area; and (3) we received six to eight sets of comments from experts between January 1, 2015, and November 16, 2015. (Sixty topics in this priority area were being tracked in the system as of November 6, 2015.) Eight topics (indicated by an asterisk) were deemed through expert comment processes to have potential for high impact; four of these topics were in the June 2015 Potential High-Impact Interventions report.

We present two summaries on eight topics (indicated by an asterisk) that emerged as having higher-impact potential on the basis of expert comments and assessment of potential impact. One of the summaries covers seven hepatitis C virus (HCV)-infection antiviral drugs and the other discusses a vaccine for preventing Ebola virus disease (EVD). The material on interventions in this Executive Summary and report is organized alphabetically by disease state. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Priority Area 09: Infectious Disease Including HIV/AIDS

Topic	High-Impact Potential
1. * Daclatasvir (Daklinza)/sofosbuvir (Sovaldi) for treatment of chronic hepatitis C virus infection	High
2. Eravacycline for treatment of complicated bacterial infections	No high-impact potential at this time
3. * Grazoprevir/elbasvir for treatment of chronic hepatitis C virus infection	High
4. * Ledipasvir/sofosbuvir (Harvoni) for treatment of chronic hepatitis C virus infection	High
5. Nitazoxanide for treatment of influenza	No high-impact potential; archived
6. * Ombitasvir/paritaprevir/ritonavir (Technivie) for treatment of chronic hepatitis C virus infection	High
7. * Ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak) for treatment of chronic hepatitis C virus infection	High
8. * rVSV-ZEBOV for preventing Ebola virus disease	High
9. * Sofosbuvir (Sovaldi) for treatment of chronic hepatitis C virus infection	High

Topic	High-Impact Potential
10. * Sofosbuvir/velpatasvir for treatment of chronic hepatitis C virus infection	High
11. Tetravalent vaccine (ChimeriVax) for prevention of dengue virus infection	No high-impact potential; archived

Discussion

Infectious diseases including HIV/AIDS are a priority area for which we have identified a large number of interventions as meeting criteria for tracking in the AHRQ Healthcare Horizon Scanning System. Experts considered a vaccine (rVSV-ZEBOV) for preventing Ebola virus disease to have high-impact potential. Experts also deemed seven drugs for treating chronic HCV infection as having high-impact potential: daclatasvir (Daklinza®) and sofosbuvir (Sovaldi®), grazoprevir/elbasvir, ledipasvir/sofosbuvir (Harvoni®), ombitasvir/paritaprevir/ritonavir (Technivie™), ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak™), sofosbuvir (Sovaldi), and sofosbuvir/velpatasvir.

Prior Potential High-Impact Topic Archived

The following topic that was deemed to have high-impact potential in previous Potential High-Impact Interventions reports has been archived since the June 2015 report: Xpert MTB/RIF Test for simultaneous detection and drug-sensitivity testing of *Mycobacterium tuberculosis.* This topic was tracked for two years before U.S. Food and Drug Administration (FDA) approval and 2 years after FDA approval, and no longer meets criteria for tracking. This intervention was cleared through FDA's 510(k) de novo pathway in June 2013.

Eligible Topics Not Deemed High Impact

In this section, we briefly discuss three topics that were deemed to have no high-impact potential based on experts' comments, poor outcomes in clinical trials, or no longer meeting Healthcare Horizon Scanning System criteria for tracking. We archived two of these topics.

- **Eravacycline for treatment of complicated bacterial infections:** Eravacycline is in phase III clinical trials for treating complicated intra-abdominal infection and complicated urinary tract infection. In September 2015, the manufacturer announced that the primary endpoint was not met in a clinical trial testing the drug's safety and efficacy in treating complicated urinary tract infection. However, the company is discussing development plans with FDA and may continue developing eravacycline for a complicated intra-abdominal infection indication (the primary endpoint was met in a clinical trial for this indication). We continue to track this intervention in our system.
- **Nitazoxanide for treatment of influenza:** Experts thought that nitazoxanide offered no additional benefit in treating patients with influenza versus available therapies; this topic has been archived.
- **Tetravalent vaccine (ChimeriVax) for prevention of dengue virus infection:** Experts thought that the vaccine had limited efficacy because it doesn't sufficiently prevent cases. That limited efficacy coupled with low incidence of dengue virus infection in the United States limit its potential for high impact. This topic has been archived.

Eligible Topics Deemed High Impact

Ebola Virus Disease

rVSV-ZEBOV vaccine for preventing Ebola virus disease

- **Key Facts:** Although Ebola virus disease (EVD) is extremely rare in the U.S., the communicability of the disease and consequences of even one infection make it a very concerning disease with high interest in a vaccine for health care workers and any others who may come into contact with an infected person. *Zaire ebolavirus* (ZEBOV) is the most virulent species of Ebola virus. No approved vaccines are available for preventing Ebola infection and EVD. Treatment consists of supportive care.

  rVSV-ZEBOV is an investigational Ebola vaccine based on a recombinant vesicular stomatitis virus (rVSV) vector that has been genetically engineered to express ZEBOV glycoprotein (GP). It is intended for preventing Ebola infection and subsequent development of EVD. rVSV vectors are replication-competent, but attenuated (weakened) for safety. The VSV glycoprotein (VSV-G) is usually removed or truncated to attenuate viral replication. rVSV vectors can be engineered to express foreign genes and are being used to develop vaccines against several pathogens, including HIV, influenza virus, and Marburg virus. GP is expressed on the surface of the Ebola virus and is responsible for attaching to and infecting cells; it is thought to be the key immunogenic viral protein of the Ebola virus. The rVSV-ZEBOV vaccine confers protection to ZEBOV challenge in murine and primate models and purportedly induces strong antibody and cellular immune responses against ZEBOV. However, vaccination with rVSV-ZEBOV did not cross-protect these animals from infection with Ebola Sudan virus. rVSV-ZEBOV purportedly elicits Ebola-specific protective immune responses in patients receiving the vaccine, which could prevent Ebola infection and EVD and could curb viral outbreaks in endemic areas. Investigators have reported preliminary data from the ongoing phase III "Ebola ça suffit" trial that suggest that the vaccine had 100% efficacy when a ring vaccination method was used (in which persons who had indirect or direct contact with patients with confirmed EVD were vaccinated). One serious adverse event, a febrile episode, was judged to be causally related to vaccination, but resolved without sequelae.

  Four clinical trials on rVSV-ZEBOV for preventing EVD in adults 18 years or older are ongoing. Our searches found no data regarding the rVSV-ZEBOV vaccine's regulatory status or anticipated cost.
- **Key Expert Comments:** Experts commenting on this intervention stated that a large unmet need exists for preventing Ebola infection and EVD, because no vaccines are available for the disease. Based on available data from a single trial, experts thought that the rVSV-ZEBOV vaccine could partially meet this need, but that more long-term safety and efficacy data are needed. A large vaccination effort may initially strain the limited health care infrastructure in areas where Ebola outbreaks have historically occurred, the experts thought; this strain may be offset by a reduced number of patients contracting EVD and requiring treatment, should the vaccine prove effective in preventing infection. However, adoption of rVSV-ZEBOV could be limited if patients in Ebola-endemic areas do not accept the vaccine for cultural or political reasons or do not have access to it, thought experts.

  High-Impact Potential: High

Hepatitis C Virus Infection

HCV is the primary cause of death from liver disease and the leading cause for liver transplantation in the United States. HCV has six genotypes, with genotype 1 accounting for about 70% of HCV infections in the United States. According to a U.S. Centers for Disease Control and Prevention (CDC) report issued in June 2014, titled "Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945–1965," an estimated 3.2 million Americans have chronic HCV infection, and 75% of those infected are baby boomers. From 45% to 85% of infected people are unaware that they are infected and can potentially transmit the disease. Additionally, HIV/HCV coinfection is common, complicating treatment options for these medically vulnerable patients. Of the 1 million people with HIV infection in the United States, about 50,000 also have chronic HCV infection. Some calculations suggested that HCV-related mortality would continue to increase over the next two decades without effective new treatments. Also, total U.S. annual medical costs for HCV-infected people are expected to almost triple by 2029, from $30 billion in 2009 to about $85 billion.

Chronic HCV infection is considered clinically "curable"—that is, the virus can be suppressed to undetectable levels with antiviral therapy. In general, patients with HCV infection are considered to be cured if they achieve a sustained virological response (SVR), which is defined as undetectable HCV RNA levels 12 or 24 weeks after treatment (SVR12 or SVR24, respectively). Until 2011, the only approved treatment for chronic HCV infection was interferon (IFN) and ribavirin (RBV) for 24–48 weeks; about 40% to 50% of patients with HCV genotype 1 infection who completed treatment achieved SVR with IFN/RBV. These two drugs' low treatment success rate, coupled with their high toxicity, presented a significant unmet need for new antiviral drugs for treating chronic HCV infection.

The HCV drug pipeline is rapidly evolving, and clinicians, patients, and other stakeholders are particularly interested in oral, once-daily, IFN-free direct-acting antiviral (DAA) regimens that can be completed in 12 weeks or less—a shorter time frame than previous treatments. To date, FDA has approved DAAs for treating patients who are infected with HCV genotypes 1 through 6. However, a significant unmet need persists for hard-to-treat patient populations (e.g., those who have experienced prior treatment failures, who have advanced cirrhosis, who have renal disease, who require a liver transplant, or who are also infected with HIV). Because the generic names of these HCV drugs and drug combinations are long and complex, for the reader's ease, we will refer to their recognized brand names, when available.

Direct-Acting Antiviral Regimens for Treating Chronic Hepatitis C Infection

- **Key Facts:** Several oral DAAs have become available in the past 2 years to address the significant unmet need for HCV therapies that provide safe, effective, and rapid treatment of chronic HCV infection of any genotype, including hard-to-treat infections.

  We discuss seven DAA options: grazoprevir/elbasvir, Sovaldi (sofosbuvir) and three DAAs containing Sovaldi (Harvoni [ledipasvir/Sovaldi], Daklinza/Sovaldi, Sovaldi/velpatasvir), Viekira Pak, and Technivie. A number of other manufacturers also have all-oral HCV DAA regimens in phase II or phase III development, with treatment regimens as short as 4 weeks. Manufacturers with the most advanced candidates include the Janssen Pharmaceuticals unit of Johnson & Johnson and Merck & Co., Inc. In the June 2015 Potential High-Impact Interventions report, we briefly discussed Bristol-Myers Squibb's investigational DAA triplet therapy (DCV-TRIO®); however, the manufacturer has since halted development of this therapy.

Grazoprevir/elbasvir (MK-5172A). This is an investigational, fixed-dose combination of two DAA agents that target two distinct HCV proteins required for viral replication, the NS3/4A protease and the nonstructural protein NS5A. Grazoprevir (MK-5172) inhibits the HCV NS3 protease and its essential cofactor, NS4A, which cleave viral polyproteins, allowing assembly of functional virus particles. Elbasvir (MK-8742) inhibits the activity of the HCV NS5A protein, which is thought to play a key role in the packaging, assembly, and release of viral particles. Grazoprevir/elbasvir is being evaluated in several phase II and III trials for treating chronic HCV genotype 1, 4, or 6 infection; the drug is also being evaluated in patients who have HIV-HCV coinfection. In clinical trials, grazoprevir/elbasvir is being administered once daily with or without RBV for 12 weeks. Additionally, the drug is being evaluated for oral administration once daily with Sovaldi for 4, 6, 8, or 12 weeks. The manufacturer has released data from four trials: C-SURFER for patients with HCV genotype 1 infection and chronic kidney disease; C-EDGE TE and C-EDGE TN for patients with HCV genotype 1, 4, or 6 infection who were treatment-experienced or naïve to treatment, respectively; and C-EDGE COINFXN for patients with HCV genotype 1, 4, or 6 infection who were coinfected with HIV. Overall, patients in these trials had SVR12 rates ranging from 92% to 99%, depending on several variables including treatment duration, prior HCV treatment, HCV genotype, existing liver disease, and other comorbidities.

Four additional phase III trials on grazoprevir/elbasvir are ongoing. In April 2015, FDA granted the drug breakthrough therapy status for treating patients with chronic HCV genotype 4 infection and for treating patients with chronic HCV genotype 1 infection with end-stage renal disease on hemodialysis. In May 2015, the manufacturer submitted a new drug application for treating chronic HCV genotype 1, 4, or 6 infection; in July 2015, FDA granted the application priority review and set a decision date of Jan 28, 2016.

Because grazoprevir/elbasvir is not yet approved for treating HCV infection, no cost or coverage information is available. However, if approved, this therapy would likely be priced competitively and be covered by third-party payers with prior authorization requirements, which may require documentation of HCV genotype, liver disease status (e.g., whether cirrhosis and/or fibrosis are present), or other comorbidities (e.g., chronic kidney disease or HIV infection).

Sovaldi and Sovaldi combination therapies. Sovaldi is a uridine nucleotide analogue that targets the active site of the HCV NS5B RNA polymerase to inhibit elongation of the growing HCV RNA genomic transcript. Phase III trials have shown it to have broad and high efficacy (>85% SVR) against several HCV genotypes. In December 2013, FDA approved Sovaldi in combination with IFN/RBV for treating chronic HCV genotype 1 or 4; Sovaldi was also approved for treating HIV/HCV coinfection or hepatocellular carcinoma in patients who are awaiting a liver transplant. It was approved in combination with RBV for treating chronic HCV genotype 2 or 3 infection. Sovaldi is administered orally, once daily for 12 or 24 weeks in combination with RBV for treating HCV genotype 2 or 3, and with RBV and IFN for treating genotypes 1 or 4 in patients who have had no prior treatment.

Besides its use with IFN/RBV, Sovaldi also can be used in combination with other DAAs. In November 2014, FDA approved the NS3/4A protease inhibitor simeprevir (Olysio®) for use with Sovaldi for treating chronic HCV genotype 1 infection in adults who have had no prior treatment or who have had treatment but do not have cirrhosis. In a phase III study, patients with HCV genotype 1 infection achieved an average SVR12 rate of 92%.

Harvoni, a second Sovaldi-containing therapy, is a fixed-dose of Sovaldi and ledipasvir, a DAA that inhibits the HCV NS5A protein. Harvoni was approved in October 2014 as the first all-oral, IFN-free treatment for chronic HCV genotype 1 infection. Harvoni may be

administered for 8, 12, or 24 weeks depending on HCV RNA level, treatment history, and cirrhosis status. In the phase III ION studies, patients achieved SVR12 rates of 94% to 99%. In November 2015, Harvoni received expanded approval for use in patients with HCV genotype 4, 5, or 6 infection; the drug was also approved for use in patients who are coinfected with HCV and HIV. Additionally, Harvoni may now be used with RBV in a 12-week treatment regimen in patients with HCV genotype 1 with cirrhosis; the drug was previously prescribed as a 24-week regimen for treating this patient population.

Sovaldi is also used in combination with Daklinza, an HCV NS5A inhibitor. In July 2015, Daklinza/Sovaldi was approved for use in patients with chronic HCV genotype 3 infection. In the phase III ALLY 1 trial, patients with cirrhosis or those who received a liver transplant achieved SVR12 rates of 83% and 94%, respectively, after 12 weeks of once-daily Daklinza/Sovaldi and RBV. In another phase III trial, patients with chronic HCV genotype 1, 2, 3, or 4 and HIV-1 coinfection were treated with Daklinza/Sovaldi, once daily, without RBV for 8 to 12 weeks; these patients had SVR12 rates ranging from 76% to 100%, depending on variables including treatment duration, prior HCV treatment, and HCV genotype. In October 2015, Daklinza's manufacturer submitted supplemental new drug applications to FDA for Daklinza/Sovaldi use in three hard-to-treat patient populations: those who have cirrhosis, who require a liver transplant, or who are coinfected with HIV; these applications were granted priority review.

Finally, Sovaldi is being developed for use in combination with velpatasvir, an investigational pan-genotypic HCV NS5A inhibitor, for treating patients infected with any HCV genotype. Sovaldi/velpatasvir is also intended for use in two hard-to-treat patient populations: those with cirrhosis or those who are coinfected with HIV. Preliminary data from the phase III ASTRAL-1 study suggest that patients with HCV genotype 1, 2, 4, 5, or 6 infection, with or without cirrhosis, achieve SVR12 rates of 97% to 100% after 12 weeks of once-daily Sovaldi/velpatasvir treatment. Interim data from the phase III ASTRAL-3 study, which is evaluating Sovaldi/velpatasvir in patients with HCV genotype 3 infection with or without cirrhosis, suggest that 95% of patients achieve SVR12 after 12 weeks of Sovaldi/velpatasvir treatment, compared with 80% of patients achieving SVR12 after 24 weeks of treatment with Sovaldi and RBV.

The retail cost of Sovaldi is about $81,000 for a 12-week treatment course, depending on the pharmacy and geographic location. The cost of the fixed-dose combination Harvoni is about $64,000 for 8 weeks and about $91,000 for 12 weeks. The cost of a 4-week supply of generic RBV (1,000 mg) is about $500. The cost of a 4-week supply of IFN is about $3,500. Daklinza/Sovaldi costs about $147,000 for a 12-week course. No cost information is available for the investigational DAA velpatasvir. Significant discounts of 20% up to 45% have been reportedly negotiated by the Veteran's Administration and several pharmacy benefit management companies, such as ExpressScripts and CVS.

Our searches of 11 representative, private, third-party payers that publish their coverage policies online found that all have policies providing coverage of Sovaldi and Harvoni, typically as a specialty tier drug requiring prior authorization and quantity limits; 10 payers have policies regarding Daklinza. Five third-party payers consider Sovaldi a preferred drug; nine consider Harvoni a preferred drug. Additionally, some third-party payers have indicated that patients must have documented advanced liver disease to be considered for coverage for one or more DAAs.

Viekira Pak and Technivie. Viekira Pak consists of co-formulated NS5A inhibitor ombitasvir (ABT-267), boosted protease inhibitor paritaprevir (ABT-450), and ritonavir and the nonnucleoside polymerase inhibitor dasabuvir (ABT-333), which is administered

separately. The regimen was designed to induce high SVR12 rates in patients with chronic HCV genotype 1 infection by targeting three distinct processes that are essential for HCV replication. In December 2014, FDA approved Viekira Pak for treating patients with chronic HCV genotype 1 infection, including those with compensated (mild) cirrhosis. Patients with HCV genotype 1a infection with cirrhosis require 24 weeks of therapy; patients with HCV genotype 1b infection without cirrhosis do not require RBV. Viekira Pak, with or without RBV, has been studied in a number of clinical trials evaluating treatment of HCV genotype 1 infection. In the PEARL-III and PEARL-IV trials, treatment-naïve patients with HCV genotype 1a and 1b infections and no evidence of cirrhosis achieved SVR12 rates greater than 90% when given Viekira Pak in combination with RBV or Viekira Pak with placebo. Patients with HCV genotype 1 infection and Child-Pugh class A cirrhosis achieved SVR rates of more than 90% after 12 or 24 weeks of Viekira Pak and RBV.

Technivie (ombitasvir/paritaprevir/ritonavir) is a 12-week regimen used with RBV for treating chronic HCV genotype 4 infection in patients who do not have cirrhosis; it was approved by FDA in July 2015. In the phase II PEARL-I trial, patients infected with HCV genotype 1b or genotype 4 with or without cirrhosis and with or without treatment experience received Technivie plus RBV for 12 weeks, or Technivie alone for 24 weeks. All treatment-experienced patients achieved SVR12; patients naïve to treatment who received Technivie with or without RBV had SVR12 rates of 100% and 90.9%, respectively.

At the time of their approval, the prescribing information for both products stated that the drugs were contraindicated only in patients with severe hepatic impairment (i.e., decompensated cirrhosis). However, in October 2015, FDA issued a warning letter advising that Viekira Pak and Technivie are not to be used in patients with moderate-to-severe hepatic impairment, because of concerns that these drugs caused worsening of cirrhosis, liver failure, and, in some cases, death. The manufacturer has updated Viekira Pak's and Technivie's prescribing information to reflect these contraindications and potential adverse events.

The retail cost of Viekira Pak is about $89,000 for a 12-week treatment course, depending on the pharmacy and geographic location. Technivie reportedly costs about $82,000.

Our searches of 11 representative, private, third-party payers that publish their coverage policies online found 11 payers that cover Viekira Pak, typically as a specialty tier drug requiring prior authorization and quantity limits. One third-party payer considers Viekira Pak a preferred drug. Additionally, one pharmacy benefits manager, Express Scripts, has made Viekira Pak the required treatment regimen for its members with chronic HCV genotype 1 infection, in exchange for a steep discount from the manufacturer. Express Scripts' national preferred formulary is used by many employers and covers about 25 million people. Seven third-party payers have published coverage policies regarding Technivie, typically as a specialty tier drug requiring prior authorization and quantity limits.

The cost of all HCV DAAs remains controversial, despite the significant discounts negotiated. Global sales of Sovaldi and Harvoni, which together account for more than 85% of the HCV drug market, reached $14.2 billion in the first three quarters of 2015. Viekira Pak's manufacturer reported that the regimen's global sales for the first nine months of 2015 were about $1.1 billion.

- **Key Expert Comments:** Overall, experts commenting on these DAAs regarded the interventions as having high potential for addressing the significant unmet need for new therapies to treat HCV infection. These all-oral drug regimens for treating chronic HCV infection have relatively short treatment regimens; they have been reported to have high efficacy and are well-tolerated by patients, noted the experts. Multiple DAAs are now on the

market for treating the genotype with the highest incidence in the United States, they opined. Some experts noted that DAAs intended for treating genotypes 2 through 6 may have the largest potential for diffusion outside the United States. The high cost of these DAAs, combined with the large population of patients requiring treatment, could be unaffordable to the health care system, the experts thought; however, the availability of multiple DAA options could potentially reduce costs due to price competition between manufacturers. Additionally, some experts thought that if DAAs are effective at delaying or preventing the development of liver disease, avoiding long-term treatment costs could potentially offset the high initial cost of DAA treatment. Finally, some experts were concerned that some payers are implementing controversial coverage policies and limiting coverage to patients who already have advanced liver disease. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

- **High-Impact Potential:** High

Ebola Virus Disease Intervention

rVSV-ZEBOV Vaccine for Preventing Ebola Virus Disease

Unmet need: Although Ebola virus disease (EVD) is extremely rare in the U.S., the communicability of the disease and consequences of even one infection make it a very concerning disease with high interest in a vaccine for health care workers and any others who may come into contact with an infected person. *Zaire ebolavirus* (ZEBOV) is the most virulent species of Ebola virus. It was responsible for an EVD outbreak in West African nations that began in March 2014 and was the largest and most complex outbreak reported.[1,2] In this outbreak, 28,295 suspected, probable, and confirmed cases were reported in Guinea, Liberia, and Sierra Leone alone; of those, 11,295 died.[3] Case fatality has ranged from 25% to 90% in past outbreaks, with an average fatality rate of 50%.[1] No approved vaccines exist for preventing Ebola infection and EVD; treatment consists of supportive care.

Intervention: rVSV-ZEBOV is an investigational Ebola vaccine based on a recombinant vesicular stomatitis virus (rVSV) vector that has been genetically engineered to express ZEBOV glycoprotein (GP); it is intended for preventing Ebola infection and subsequent development of EVD.[4] rVSV vectors are replication-competent, but attenuated (weakened) for safety; the VSV glycoprotein (VSV-G) is usually removed or truncated to attenuate viral replication. rVSV vectors can be engineered to express foreign genes and are being used to develop vaccines against several pathogens, including HIV, influenza virus, and Marburg virus.[5]

GP is expressed on the surface of the Ebola virus and is responsible for attaching to and infecting cells; it is thought to be the key immunogenic viral protein of the Ebola virus.[6] The rVSV-ZEBOV vaccine has been shown to confer protection to ZEBOV challenge in murine and primate models and purportedly induces strong antibody and cellular immune responses against ZEBOV. However, vaccination with rVSV-ZEBOV did not cross-protect these animals from infection with Ebola Sudan virus.[5] rVSV-ZEBOV purportedly elicits Ebola-specific protective immune responses in patients receiving the vaccine, which could prevent Ebola infection and EVD and could curb viral outbreaks in endemic areas. In clinical trials, rVSV-ZEBOV is being tested in patients who are 18 years or older. It is administered intramuscularly, as a single dose of 2×10^7 plaque-forming units.[7]

Clinical trials: Preliminary data are available for the ongoing phase III "Ebola ça suffit" trial evaluating the safety and efficacy of the rVSV-ZEBOV vaccine. Patients (n=7,651) who had direct or indirect contact with a patient who had confirmed EVD (an epidemiologically defined ring) were vaccinated with rVSV-ZEBOV. Patients received the vaccine either immediately after identification, or vaccine administration was delayed until 21 days after identification. In the immediate vaccination group, there were no cases of EVD with symptom onset at least 10 days after random assignment; there were 16 cases of Ebola virus disease from seven clusters in the delayed vaccination group, showing a vaccine efficacy of 100% (95% confidence interval [CI], 74.7 to 100.0; p=0.0036). Forty-three serious adverse events were reported; one serious adverse event, a febrile episode in a vaccinated participant resolved without sequelae and was causally related to vaccination.[4,8]

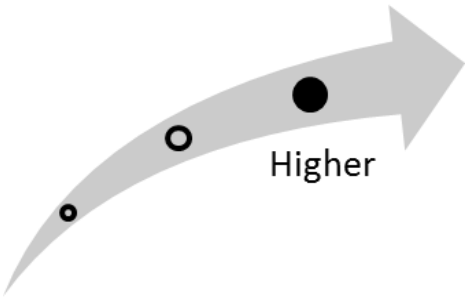
Manufacturer and regulatory status: The rVSV-ZEBOV vaccine was developed by the Public Health Agency of Canada's National Microbiology Laboratory (Winnipeg, Manitoba, Canada) and licensed to New Link Genetics Corp. (Ames, IA) and Merck & Co, Inc. (Whitehouse Station, NJ).[4] Phase II and III clinical trials are ongoing.[7,9-11]

Diffusion and cost: Our searches found no information regarding cost or third-party coverage of the rVSV-ZEBOV vaccine at this time.

Clinical Pathway at Point of This Intervention

No FDA-approved vaccines or antiviral agents exist for EVD, although several therapeutic agents have been administered through FDA's compassionate use program, depending on availability.[12] Providing supportive care, maintaining hydration through oral or intravenous fluids, and treating disease-specific symptoms have been shown to improve survival.[1,13]

Figure 1. Overall high-impact potential: rVSV-ZEBOV vaccine for preventing Ebola virus disease



Overall, experts commenting on this intervention stated that a large unmet need exists for preventing Ebola infection and EVD, because no vaccines exist. They thought that the rVSV-ZEBOV vaccine demonstrates potential in protecting against Ebola infection and EVD, but that more long-term efficacy data are needed. A large vaccination effort may initially strain the limited health care infrastructure in areas where Ebola outbreaks usually occur, the experts thought; however, this may be offset by a reduced number of patients with EVD requiring treatment, should the vaccine prove effective in preventing infection. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on this intervention.[14-19] We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: The experts stated that a large unmet need exists for a vaccine to prevent Ebola infection and EVD. Based on preliminary, short-term efficacy data from a single clinical trial, the experts generally thought that the data suggested that the rVSV-ZEBOV vaccine could address this need. However, two experts with research perspectives questioned whether the vaccine could provide long-term protection from infection.[16,18] Two experts, one with a health systems and one with a research background wanted more data to demonstrate the safety of the rVSV vector.[15,19]

Acceptance and adoption: All experts agreed that clinicians are likely to accept rVSV-ZEBOV as a vaccine for preventing EVD; however, they offered mixed perspectives on patient adoption of the vaccine. Most thought that patients would accept the vaccine because no treatments exist,[14,16,18,19] but two experts had concerns that some patients in Ebola-endemic areas might refuse to accept the vaccine for cultural or political reasons.[15,17]

Health care delivery infrastructure and patient management: Although two experts with clinical and research backgrounds noted that the process of implementing a vaccination program significantly disrupts health care infrastructure,[14,15] all thought that reducing EVD incidence would, in turn, reduce the care burden on health care facilities and staff. Some experts questioned whether manufacturers or government entities would cover vaccination costs for patients who may not be able to afford it.[16,19]

Health disparities: Overall, experts thought that establishing an Ebola vaccination program using the rVSV-ZEBOV vaccine would reduce existing health disparities in countries where Ebola outbreaks usually occur, by reducing incidence of the disease. However, some experts noted that this reduction in disparities may depend on the ability of health care infrastructure to successfully implement a vaccination program or on patients in these areas being willing to use such a program.[15-17]

Hepatitis C Virus Infection Interventions

Direct-Acting Antiviral Regimens for Treating Chronic Hepatitis C Virus Infection

Unmet need: Until a few years ago, treatment for patients with chronic hepatitis C virus (HCV) infection involved 24–48 weeks of therapy with interferon (IFN) and ribavirin (RBV), a lengthy regimen with significant toxicity and a high rate of treatment failure. In December 2013, FDA approved the direct-acting antiviral (DAA) sofosbuvir (Sovaldi®) in combination with RBV as a 12-week regimen for treating patients infected with HCV genotypes 1, 2, 3, or 4. However, IFN injections were still required for patients infected with HCV genotype 1 or 4, and patients infected with HCV genotype 3 still required 24 weeks of treatment.[20,21] Combination sofosbuvir/ledipasvir (Harvoni®), a DAA that does not require IFN injections, was approved in 2014 for treating HCV genotype 1. The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) recommend IFN-free, all-oral options for treating all HCV genotypes; 12-week treatment or less is optimal but may be extended to 24 weeks in some patient populations.[22]

Despite these advances, a need exists for additional HCV IFN-free therapies with the potential to improve upon available DAAs, particularly for hard-to-treat patient populations (e.g., patients who have experienced prior treatment failures, who require a liver transplant, who are coinfected with HCV and HIV, or patients with advanced cirrhosis).

Intervention: Seven novel DAA options are discussed in this section:

- Grazoprevir/elbasvir for treating HCV genotype 1, 4, or 6 infection
- Sofosbuvir (Sovaldi) and three other DAA regimens containing Sovaldi:
    - Ledipasvir/sofosbuvir (Harvoni) for treating HCV genotype 1, 4, 5, or 6 infection
    - Daclatasvir/sofosbuvir (Daklinza®/Sovaldi) for treating HCV genotype 3 infection
    - Sofosbuvir (Sovaldi)/velpatasvir for treating chronic HCV infection with any genotype
- Ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak™) for treating chronic HCV genotype 1 infection
- Ombitasvir/paritaprevir/ritonavir (Technivie™) for treating chronic HCV genotype 4 infection

Because the generic names of these HCV drugs and drug combinations are long and complex, for the reader's ease, we will refer to their recognized brand names throughout the remainder of this report.

Grazoprevir/elbasvir (MK-5172A). This is an investigational, fixed-dose combination of two DAA agents that target two distinct HCV proteins required for viral replication, the NS3/4A protease and the nonstructural protein NS5A.[23] Grazoprevir (MK-5172) inhibits the HCV NS3 protease and its essential cofactor, NS4A, which cleave viral polyproteins, allowing assembly of functional virus particles.[24,25] Elbasvir (MK-8742) inhibits the activity of the HCV NS5A protein, which is thought to play a key role in the packaging, assembly, and release of viral particles.[26-28] Grazoprevir/elbasvir is being evaluated in several phase II and III clinical trials for treating patients who have chronic HCV genotype 1, 4, or 6 infection;[23,29] the drug is also being evaluated in patients who have HIV-HCV coinfection.[23] In clinical trials, fixed-dose grazoprevir 100 mg/elbasvir 50 mg was administered orally, once daily for 12 weeks, with or without RBV.[23,29]

Sovaldi and Sovaldi-containing regimens. Sovaldi is a uridine nucleotide analogue polymerase inhibitor approved for treating chronic HCV genotype 1, 2, 3, or 4 infection.[30] The HCV NS5B polymerase plays an essential role in HCV genome replication. As a nucleotide analogue, Sovaldi is said to target the active site of the enzyme and inhibit elongation of the growing HCV RNA genomic transcript.[31] Nucleot(s)ide analogues such as Sovaldi are thought to have broader efficacy against

different HCV genotypes and a higher barrier to viral resistance than nonnucleot(s)ide polymerase inhibitors, which function via allosteric inhibition.[31] Sovaldi is administered orally, 400 mg once daily, for 12 weeks in combination with RBV for patients infected with HCV genotype 2, for 24 weeks for patients infected with genotype 3, and for 12 weeks with IFN and RBV for patients chronically infected with HCV genotypes 1 or 4.[20]

Sovaldi has been investigated in combination with a number of other DAAs and investigational agents. It was first approved as part of a fixed-dose combination with ledipasvir, a drug that inhibits activity of the HCV NS5A protein, providing the first all-oral DAA treatment that eliminated the need for IFN or RBV in patients with chronic HCV genotype 1 infection.[32] The indications for fixed-dose combination Harvoni (ledipasvir 90 mg/Sovaldi 400 mg) were expanded in November 2015,[33] and Harvoni is now administered for 12 weeks in patients who have chronic HCV genotype 1, 4, 5, or 6 infection with or without cirrhosis who are naïve to treatment, or in patients without cirrhosis who are treatment experienced. Treatment-experienced patients with cirrhosis are given Harvoni for 24 weeks or in combination with RBV for 12 weeks.[34] Additionally, the drug's prescribing information states that patients who are naïve to treatment, without cirrhosis, and who have pretreatment HCV RNA less than 6 million IU/mL could be considered for 8 weeks of therapy.[35] According to the manufacturer, these patients could comprise between 35% and 40% of individuals infected with HCV genotype 1.[36]

Sovaldi is also approved for use with Daklinza, an HCV NS5A inhibitor, for treating patients who have chronic HCV genotype 3 infection.[37] Additionally, this combination regimen is being investigated in difficult-to-treat patients, including those with cirrhosis, who experience HCV recurrence after receiving a liver transplant, and who are coinfected with HCV and HIV. Daklinza purportedly has a low drug-drug interaction profile, which could support its use in patients with comorbidities.[38] In clinical trials, daclatasvir 60 mg/sofosbuvir 400 mg has been administered with RBV orally, once daily, for 12 weeks.[39]

Finally, Sovaldi is being developed as a fixed-dose combination therapy with velpatasvir, an investigational pan-genotypic HCV NS5A inhibitor, for treating patients infected with *any* HCV genotype. Sovaldi/velpatasvir is also intended for use in two hard-to-treat patient populations: those with cirrhosis or those who are coinfected with HIV. In clinical trials, patients are receiving fixed-dose sofosbuvir 400 mg/velpatasvir 100 mg for 12 or 24 weeks, depending on liver cirrhosis status.[40]

Viekira Pak and Technivie. Viekira Pak consists of the NS5A inhibitor ombitasvir, the boosted NS3 protease inhibitor paritaprevir, and ritonavir—those three drugs are coformulated in one tablet—and the nonnucleoside polymerase inhibitor dasabuvir. Viekira Pak was designed to optimize SVR12 rates across different patient populations by targeting three processes that are essential for HCV replication.[24,41] Two ombitasvir 12.5 mg/paritaprevir 75 mg/ritonavir 50 mg tablets are taken once daily and one 250 mg dasabuvir tablet is taken twice daily for 12 weeks with RBV.[42] Patients with HCV genotype 1a infection with cirrhosis require 24 weeks of therapy. Patients with HCV genotype 1b infection without cirrhosis do not require RBV.[42]

Technivie consists of the same formulation of fixed-dose ombitasvir/paritaprevir/ritonavir as Viekira Pak, but does not contain dasabuvir. In patients with HCV genotype 4 infection without cirrhosis, two ombitasvir 12.5 mg/paritaprevir 75 mg/ritonavir 50 mg tablets are taken once daily for 12 weeks with RBV.[43]

Clinical trials: *Grazoprevir/elbasvir.* As a once-daily, oral, fixed dose-combination DAA, this drug has been studied in several clinical trials of patients infected with HCV genotype 1, 4, or 6. We provide selected recent data from trials that demonstrated the emerging potential of the drug in HCV care.

The phase III C-EDGE TE and TN trials evaluated grazoprevir/elbasvir in patients with chronic HCV genotype 1, 4, or 6 infection who were treatment-experienced or naïve to treatment,

respectively. In the C-EDGE TE trial, patients (n=420) received grazoprevir 100 mg/elbasvir 50 mg with or without RBV for 12 or 16 weeks. Overall, after 12 weeks of treatment with or without RBV, 94% and 92% of patients achieved SVR12, respectively. After 16 weeks of treatment with or without RBV, 97% and 92% of patients, respectively, achieved SVR12.[44] In the C-EDGE TN trial, patients (n=421) received grazoprevir 100 mg/elbasvir 50 mg or placebo for 12 weeks. Overall, 95% of patients achieved SVR12 (95% CI, 92% to 97%).[45]

In the phase II/III C-SURFER trial, patients (n=235) with chronic HCV genotype 1 infection and chronic kidney disease received grazoprevir 100 mg/elbasvir 50 mg for 12 weeks; 99% of patients achieved SVR12.[46] In the phase III C-EDGE COINFXN trial, patients (n=218) with HCV genotype 1, 4, or 6 infection and HIV coinfection received grazoprevir 100 mg/elbasvir 50 mg for 12 weeks. Overall, 95% of patients achieved SVR12.[44]

In these studies, the most common treatment-emergent adverse events were headache, fatigue, and nausea.[45,46]

Sovaldi and Sovaldi-containing regimens. Sovaldi has been studied in numerous clinical trials of patients infected with various HCV genotypes. Many treatment regimens have been tested, some with and others without IFN and RBV. We present selected recent data from Sovaldi trials.

Sovaldi. In the phase III VALENCE trial, patients (n=419) with chronic HCV genotype 2 or 3 infection were given Sovaldi 400 mg and RBV or placebo once daily for 12 weeks. Among enrolled patients, 58% had received previous IFN-based treatment and 21% had cirrhosis. Data from phase III trials prompted the investigators to extend treatment in patients with HCV genotype 3 to 24 weeks, unblind the study, and terminate the placebo group. Patients infected with HCV genotype 2 or 3 achieved SVR12 of 93% and 85%, respectively. Patients with HCV genotype 2 and 3 infection and cirrhosis achieved SVR12 rates of 82% and 68%, respectively.[47]

In the phase III PHOTON-2 trial, patients (n=275) with chronic HCV genotype 1, 2, 3, or 4 and HIV-1 coinfection, were given Sovaldi 400 mg once daily and RBV twice daily, for 24 weeks, except patients with HCV genotype 2 infection who were naïve to treatment, who received a 12- week regimen. Patients with HCV genotype 1 or 4 infection had SVR12 rates of 85% and 84%, respectively. Patients with HCV genotype 2 and 3 infection had SVR12 rates of 88% and 92%, respectively.[48]

In these studies, the most common side effects reported were dizziness, fatigue, headache, insomnia, and nausea.[49]

Harvoni. In the phase III ION-3 trial, patients (n=647) with chronic HCV genotype 1 infection who were naïve to treatment were given either Harvoni (ledipasvir 90 mg/Sovaldi 400 mg) once daily with or without RBV for 8 weeks, or Harvoni once daily without RBV for 12 weeks. Patients treated with Harvoni with or without RBV for 8 weeks had SVR12 rates of 94% and 93%, respectively. Patients treated for 12 weeks had an SVR12 of 95%. Eight weeks of Harvoni therapy was noninferior to 12 weeks of therapy.[50]

In the phase III ION-2 trial, patients (n=440) with chronic HCV genotype 1 infection who were previously treated with IFN-based therapy were given Harvoni once daily with or without RBV for 12 weeks, or Harvoni once daily with or without RBV for 24 weeks. Twenty percent of patients in the study had liver cirrhosis. The SVR12 rate for patients treated with Harvoni with or without RBV for 12 weeks was 94% and 96%, respectively. In patients treated with or without RBV for 24 weeks, 99% in both groups achieved SVR12.[51]

In the phase III ION-4 trial, patients (n=335) with chronic HCV genotype 1 or 4 and HIV-1 coinfection were given Harvoni once daily with RBV for 12 weeks. SVR12 rates were similar among patients with and without cirrhosis (94% and 96%, respectively) and among patients who were treatment-naïve or treatment-experienced (94% and 97%, respectively).[52]

The most common adverse reactions reported in 5% or more of patients taking Harvoni for 8, 12, or 24 weeks were diarrhea, fatigue, headache, insomnia, and nausea.[35] Fewer than 1% of patients in the ION trials discontinued treatment because of treatment-emergent adverse events.[35]

Daklinza/Sovaldi. In the phase III ALLY 1 trial, patients (n=110) with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection with cirrhosis or who had received a liver transplant and were naïve to treatment or treatment-experienced were given Daklinza 60 mg/Sovaldi 400 mg once daily with RBV for 12 weeks. Among patients with cirrhosis, 75% were infected with HCV genotype 1; in patients who received a liver transplant, 77% had HCV genotype 1 infection. The overall SVR12 rate was 83% in patients with cirrhosis. In patients who received a liver transplant, SVR12 was 94%. SVR12 rates were comparable regardless of prior treatment experience.[53]

In the phase III ALLY 2 trial, patients (n=203) coinfected with HCV genotype 1, 2, 3, 4, 5, or 6 and HIV-1 who were naïve to treatment or treatment-experienced were given Daklinza (30, 60, or 90 mg)/Sovaldi 400 mg once daily for 8 or 12 weeks. Patients naïve to treatment or who were treatment-experienced with HCV genotype 1 infection had SVR12 rates of 96% and 98%, respectively, after 12 weeks of Daklinza/Sovaldi treatment. SVR12 was 76% in patients naïve to treatment after 8 weeks of therapy. SVR12 rates were 100% in patients infected with HCV genotypes 2 or 3, and 78% in patients infected with HCV genotype 4. SVR12 rates were similar in patients with or without cirrhosis. No HCV virologic breakthroughs were observed, and HIV control was not compromised throughout the study. Post-treatment HCV relapse occurred in 1% to 2% of patients in the 12-week treatment groups and 20% in the 8-week group.[54]

The most common adverse events observed in patients given Daklinza and Sovaldi were anemia, arthralgia, diarrhea, fatigue, headache, and nausea.[53,55]

Sovaldi/velpatasvir. The manufacturer has released topline data from the four phase III ASTRAL trials in patients infected with HCV genotypes 1, 2, 3, 4, 5, or 6.

In the ASTRAL-1 trial, patients (n=624) with chronic HCV genotype 1, 2, 4, 5, or 6 infection with or without cirrhosis were given fixed-dose Sovaldi 400 mg/velpatasvir 100 mg or placebo orally, once daily for 12 weeks. Overall, 99% of patients achieved SVR12; patients infected with HCV genotype 5 had the lowest SVR12 rates (97%).[40]

In the ASTRAL-2 and ASTRAL-3 trials, patients with chronic HCV genotype 2 infection (n=624) or genotype 3 infection (n=552), with or without cirrhosis, were given fixed-dose combination Sovaldi 400 mg/velpatasvir 100 mg orally, once daily for 12 weeks, or Sovaldi 400 mg plus RBV for 12 weeks (genotype 2) or 24 weeks (genotype 3). After 12 weeks of treatment, patients with HCV genotype 2 infection who received Sovaldi/velpatasvir had SVR12 rates of 99%. Patients who received Sovaldi and RBV had SVR12 rates of 94%. Patients with HCV genotype 3 infection who received Sovaldi/velpatasvir had SVR12 rates of 95% after 12 weeks of treatment. Patients who received Sovaldi and RBV had SVR12 rates of 80% after 24 weeks of treatment.[40]

The ASTRAL-4 study evaluated Sovaldi/velpatasvir in patients (n=267) infected with one of six HCV genotypes who had decompensated (severe) cirrhosis. These patients were given fixed-dose Sovaldi/velpatasvir for 12 weeks with or without RBV or for 24 weeks without RBV. SVR12 rates in these three treatment arms were 94%, 83%, and 86%, respectively.[40] In these trials, the most common reported treatment-emergent adverse events after Sovaldi/velpatasvir administration were headache, fatigue, and nausea.[40]

Viekira Pak and Technivie. Viekira Pak, with or without RBV, has been studied in a number of clinical trials in various patient populations infected with HCV genotype 1. Technivie, with or without RBV, has been studied in a number of clinical trials in various patient populations infected with HCV genotype 1 or 4.

Viekira Pak. In two phase III trials (PEARL-III and PEARL-IV), patients with chronic HCV genotype 1a (n=305) and HCV genotype 1b (n=419) infection with no evidence of cirrhosis and who

were not previously treated were given Viekira Pak and RBV or Viekira Pak with placebo twice daily for 12 weeks. Patients infected with genotype 1a treated with Viekira Pak with or without RBV had SVR12 rates of 97.0% and 90.2%, respectively. Patients infected with genotype 1b treated with Viekira Pak with or without RBV had SVR12 rates of 99.5% and 99.0%, respectively.[56]

In the phase III TURQUOISE-II trial, patients (n=380) with HCV genotype 1 infection and Child-Pugh class A cirrhosis were treated with Viekira Pak with RBV for either 12 or 24 weeks. In patients treated for 12 weeks, 92% achieved SVR12; in patients treated for 24 weeks, 96% achieved SVR12. These rates were superior to the estimated historical control rate of 47% achieved using telaprevir-based regimens.[57]

In the phase III SAPPHIRE-II trial, patients (n=394) with chronic HCV genotype 1 infection and no cirrhosis who were previously treated with IFN/RBV and had a relapse, a partial response, or a null response, were treated with Viekira Pak and RBV or matching placebos for 12 weeks. Overall, 96% of patients receiving Viekira Pak achieved SVR12 which was noninferior and superior to the historical control rate of 65% assumed with telaprevir-based treatment. Patients with prior relapse had SVR12 rates of 95%; 100% of patients with prior partial response achieved SVR12; and with prior null response had a 95% SVR12 rate.[58]

The most common adverse events reported in patients taking Viekira Pak included insomnia, nausea, and pruritus. In patients taking Viekira Pak in combination with RBV, the most common adverse events reported were asthenia, fatigue, insomnia, nausea, and pruritus and other skin reactions.[59]

Technivie. In the phase II PEARL-I trial, patients (n=316) who were infected with HCV genotype 1b or genotype 4 with or without cirrhosis and with or without treatment experience received Technivie plus RBV for 12 weeks or Technivie alone for 24 weeks. All treatment-experienced patients achieved SVR12; patients naïve to treatment receiving Technivie with or without RBV had SVR12 rates of 100% and 90.9%, respectively.[60]

The most common treatment-emergent adverse event reported in patients taking Technivie was headache. Four percent of patients receiving Technivie and RBV required dose modification due to anemia.[60]

At the time of each drug's approval, the prescribing information for both Viekira Pak and Technivie stated that the drugs were contraindicated only in patients with severe hepatic impairment (i.e., decompensated cirrhosis). However, in October 2015, FDA issued a warning letter advising that Viekira Pak and Technivie are not to be used in patients with moderate-to-severe hepatic impairment, because of concerns that the use of these drugs in these patients caused worsening of their cirrhosis, liver failure, and, in some cases, death.[61] The manufacturer has since updated Viekira Pak's and Technivie's prescribing information to reflect these contraindications and potential adverse events.[43,62]

Manufacturer and regulatory status: Grazoprevir/elbasvir is being developed by Merck & Co., Inc. (Whitehouse Station, NJ) and received breakthrough therapy status in October 2013 from FDA for treating chronic HCV genotype 1 infection. However, in January 2015, FDA notified Merck of its intention to rescind this status on the basis that grazoprevir/elbasvir would not provide a significant improvement over existing HCV antivirals approved for treating patients with chronic HCV genotype 1 infection (i.e., Harvoni, Viekira Pak).[63] In April 2015, FDA granted two new breakthrough therapy statuses for grazoprevir/elbasvir: one for treating chronic HCV genotype 4 infection and another for treating chronic HCV genotype 1 infection in patients with end-stage renal disease on hemodialysis.[23] Merck submitted a new drug application for treating chronic HCV genotype 1, 4, and 6 infections in May 2015.[64] In July 2015, FDA granted priority review to grazoprevir/elbasvir, with a decision date set for January 28, 2016.[65]

Gilead Sciences, Inc. (Foster City, CA), makes Sovaldi and Harvoni and is developing velpatasvir. In December 2013, FDA approved Sovaldi in combination with RBV for treating patients infected with HCV genotypes 2 or 3 and in combination with IFN/RBV for treating patients infected with HCV genotype 1 or 4. Sovaldi is also approved for treating patients coinfected with HIV or with hepatocellular carcinoma awaiting liver transplantation.[20,21] In October 2014, FDA approved Harvoni for treating patients infected with HCV genotype 1;[32] the drug's approval was expanded in November 2015 to include indications for treating HCV genotype 4, 5, and 6 infections, as well as for treating patients coinfected with HIV.[33,34] In September 2015, Gilead announced plans to submit a new drug application for fixed-dose combination sofosbuvir/velpatasvir to FDA by the end of 2015;[40] if approved, sofosbuvir/velpatasvir would be the first pan-genotypic HCV regimen available for treating chronic HCV infection.

Bristol-Myers Squibb (New York, NY), makes Daklinza. In July 2015, FDA approved Daklinza/Sovaldi for treating chronic HCV genotype 3 infection.[66] In October 2015, the manufacturer submitted three supplemental new drug applications to FDA for Daklinza/Sovaldi's use in patients with chronic HCV infection who also have cirrhosis, who require a liver transplant, or who are coinfected with HIV; these applications were accepted and granted priority review.[67]

AbbVie (North Chicago, IL), makes Viekira Pak and Technivie.[43,62] In December 2014, FDA approved Viekira Pak for treating patients with chronic HCV genotype 1 infection, including those with compensated cirrhosis.[68] In July 2015, FDA approved Technivie for treating patients with chronic HCV genotype 4 infection who do not have cirrhosis.[69]

Diffusion and cost: *Grazoprevir/elbasvir*. Because grazoprevir/elbasvir is not yet approved for treating patients with HCV infection, no cost or coverage information is available. However, if approved, this therapy would likely be priced similarly to its competitors and be covered by third-party payers with prior authorization requirements, which may require documentation of HCV genotype, liver disease status (e.g., whether cirrhosis and/or fibrosis are present), or other comorbidities (e.g., chronic kidney disease or HIV infection).

Sovaldi and Sovaldi-containing regimens. The retail cost of Sovaldi is roughly $81,000 for a standard 12-week course.[70] For patients infected with HCV genotype 2 who are naïve to treatment, daily Sovaldi and weight-based RBV for 12 weeks costs about $81,500.[70,71] The retail cost of an 8- or 12-week regimen of Harvoni is about $64,000 or $91,000, respectively.[72,73] A 12-week regimen of Daklinza/Sovaldi for treating HCV genotype 3 infection is estimated to cost approximately $147,000.[74] For benchmarking purposes, a 24-week regimen of sofosbuvir plus RBV, the only other FDA-approved regimen for treating HCV genotype 3 infection,[20] costs about $172,000.[71,75] No cost information for velpatasvir in combination with Sovaldi is available.

Viekira Pak and Technivie. The retail cost of a 12-week regimen of Viekira Pak is about $89,000;[76] the retail cost of a 12-week regimen of Technivie is about $82,000.[77]

Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found the following for treating HCV infection:

- 11 have policies regarding coverage of Sovaldi[78-88]
- 11 have policies regarding coverage of Harvoni[78,80-86,88-90]
- 10 have policies regarding coverage of Daklinza/Sovaldi[78,82-84,91-96]
- 11 have policies regarding coverage of Viekira Pak[78,80-82,84,85,88,97-100]
- 7 payers have policies regarding coverage of Technivie[78,82-85,91,101]

Because velpatasvir and grazoprevir/elbasvir are not yet FDA approved, our searches found no coverage information regarding these drugs. Third-party payers generally consider DAAs specialty-tier drugs requiring prior authorization and quantity limits for coverage.

The high cost of HCV DAAs remains controversial, and many payers have reportedly negotiated discounts up to 45% off list prices. Even with those discounts, Gilead, which has more than 85% of the HCV drug market currently, reported $14.2 billion in Sovaldi and Harvoni sales for the first three quarters of 2015,[102] far surpassing the launch of the HCV protease inhibitor telaprevir (Incivek), which grossed $1.56 billion in the first year.[103] In 2014, in its first quarter after launch, Viekira Pak generated sales of $231 million, with $138 million in the United States alone.[104] Global sales of Viekira Pak in the first nine months of 2015 were $1.1 billion.[105]

The high cost of these drugs has often led third-party payers to designate either Sovaldi/Harvoni or Viekira Pak as their preferred drug(s), based on negotiated costs from manufacturers. The State of Missouri has reportedly received a 30% to 40% discount on Viekira Pak for its Medicaid patients,[106] and discounts upwards of 40% have been reported for other third-party payers for both Gilead and AbbVie drugs.[107,108] One pharmacy benefit manager, Express Scripts, has made Viekira Pak the required treatment regimen for its members with chronic HCV genotype 1 infection who use the company's national preferred formulary. This formulary is used by many employers and covers about 25 million people. It excluded 72 drugs in 2015, including Harvoni, Sovaldi, and Olysio. However, its 2015 Preferred Drug Exclusions List states that Sovaldi may be covered in patients who are infected with HCV genotypes 2–6, pending a coverage review.[109] In contrast, other third-party payers such as Aetna, Anthem, CIGNA, Humana, Medica, United Healthcare, and Wellmark consider Sovaldi and/or Harvoni preferred drugs over Viekira Pak.[78,82-85,96,99,106] Aetna now covers Sovaldi/RBV and Harvoni for treating all HCV genotypes, and patients must have documented intolerance or contraindication to both of these regimens before coverage of other DAAs is considered.[78] Additionally, some third-party payers' coverage policies indicate that HCV DAAs will be considered for coverage only when patients with chronic HCV infection also have advanced liver disease (i.e., fibrosis, cirrhosis, hepatocellular carcinoma), regardless of whether or not the drugs are considered preferred by the payer.[80,82,88-90,94] These coverage restrictions, coupled with the high cost of the drugs in the United States, have led some patients with chronic HCV infection to file lawsuits against third-party payers[110] or to seek treatment outside of the United States, where prices for generic versions of HCV DAAs are lower.[111]

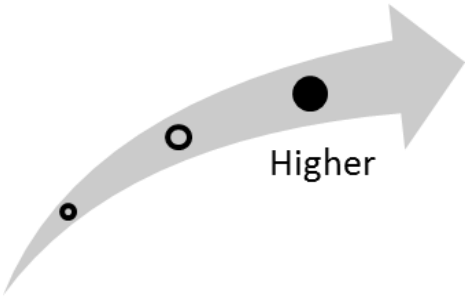
Clinical Pathway at Point of This Intervention

Patients who test positive for HCV and HCV RNA may be considered to have acute or chronic HCV infection, depending on the context. A patient who tests negative for antibodies to HCV and positive for HCV RNA might be chronically infected if immunosuppressed.[112] Subsequent HCV genotype testing is performed to determine the therapy regimen and likelihood of a positive clinical outcome.[112] Rest and hydration are typically prescribed. AASLD and IDSA recommend the following for patients with HCV who are naïve to treatment:[113]

- For patients infected with HCV genotype 1, daily Daklinza/Sovaldi, Harvoni, Viekira Pak, or Sovaldi plus Olysio for 12 weeks. For patients with HCV genotype 1a and cirrhosis, Daklinza/Sovaldi, Viekira Pak, or Sovaldi/Olysio require 24 weeks of treatment and weight-based RBV.
- For patients infected with HCV genotype 2, daily Daklinza/Sovaldi or Sovaldi plus weight-based RBV for 12 weeks. Patients with cirrhosis may require 16 weeks of treatment.

- For patients infected with HCV genotype 3, daily Daklinza/Sovaldi, with or without RBV for 12 weeks (up to 24 weeks in patients with cirrhosis), or Sovaldi plus weight-based RBV and weekly PEG-IFN for 12 weeks.
- For patients infected with HCV genotype 4, daily Harvoni for 12 weeks, Technivie plus weight-based RBV for 12 weeks, or Sovaldi plus weight-based RBV for 24 weeks.
  For patients infected with HCV genotype 5 or 6, daily Harvoni for 12 weeks, or daily Sovaldi and weight-based RBV plus weekly PEG-IFN for 12 weeks.

Figure 2. Overall high-impact potential: interferon-free regimens for treating chronic hepatitis C virus infection



Overall, experts commenting on these DAAs regarded them as having high potential for addressing the significant unmet need for new therapies to treat HCV infection. These all-oral drugs for treating chronic HCV infection have relatively short treatment regimens; reportedly high efficacy, and are well-tolerated by patients, noted the experts. Some experts noted that DAAs intended for treating the less common HCV genotypes (2 – 6) may have the largest potential for diffusion outside the United States. The high cost of these DAAs, combined with the large population of patients requiring treatment, could be unaffordable to the health care system, the experts thought; however, the availability of multiple DAAs could spur price competition among manufacturers. Additionally, some experts thought that if DAAs effectively delay or prevent the development of liver disease, avoiding long-term treatment costs might offset the high initial cost of DAA treatment. Finally, some experts were concerned that some payers are implementing controversial coverage policies and limiting coverage to patients who already have advanced liver disease. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Experts with clinical, research, and health systems backgrounds provided perspectives on these interventions. Six experts commented on grazoprevir/elbasvir,[114-119] six commented on Sovaldi,[120-125] six commented on Harvoni,[126-131] six commented on Sovaldi/velpatasvir,[132-137] six commented on Daklinza/Sovaldi,[138-143] six commented on the Viekira Pak regimen,[144-149] and six commented on Technivie.[150-155] Some of the experts commented on two or more of these interventions. We have organized the following discussion of expert comments by the parameters on which they commented.

Of note, we solicited comments on Harvoni before the drug received an expanded indication for treating patients with HCV genotype 4, 5, and 6 infection; thus, comments received on Harvoni did not consider its impact on these patient populations.

Unmet need and health outcomes: The number of patients chronically infected with HCV is high in the United States, the experts pointed out. Many of these patients have advanced liver disease or other comorbidities. Experts thought the reported data from multiple studies evaluating Sovaldi, Harvoni, and Viekira Pak have consistently demonstrated high efficacy and tolerability in a variety of

HCV patient populations (e.g., treatment-naïve, treatment-experienced, cirrhosis, no cirrhosis). Additionally, three experts with research and health systems backgrounds noted that off-label use of two DAAs for treating HCV genotypes other than genotype 1 could reduce the need for new therapies.[151,153,155] Daklinza/Sovaldi, Technivie, and grazoprevir/elbasvir show promise for treating genotype 3, 4, or 6 infections, some experts thought,[118,142] although others commented these interventions may have a larger impact in countries other than the United States, where incidence of these genotypes is higher.[114,114,153] One research expert noted that pan-genotypic regimens such as Sovaldi/velpatasvir may simplify treatment guidelines by providing a DAA option that could be effective in treating all patients infected with HCV.[132]

Acceptance and adoption: Experts expect clinician and patient acceptance of all-oral HCV drugs to remain high because of their high efficacy, safety, and short treatment duration. Although the high estimated cost of DAA therapy could pose a barrier to patient and prescriber acceptance, the upfront cost is expected to be offset by cost savings to the health care system by preventing the need for additional treatment, HCV complications, and health monitoring in the future, some experts commented.[119,127,138,139,152,153] Experts noted that, other than Harvoni, several DAAs are approved or are being developed for treating HCV genotype 1 infection (e.g., grazoprevir/elbasvir, Sovaldi/velpatasvir, Viekira Pak); patient adoption in this competitive space will likely be influenced by prices negotiated for the drugs by third-party payers, as well as payers' coverage policies.[114,117,118,147,151]

Health care delivery infrastructure and patient management: Some experts thought that all-oral, more tolerable DAA treatment options might entice more patients to seek HCV testing and treatment.[124,155] Improved treatment outcomes could reduce hospitalizations from liver disease and ease the burden on infrastructure and staffing for HCV inpatient treatments, some experts stated, but other experts expected minimal disruptions to infrastructure and management. Several experts stated that treatment facilities could spend more time acquiring prior approval from payers than they did previously.[117,142,149]

Health disparities: The anticipated high cost of emerging HCV therapies could provide barriers to treatment for patients, the experts noted; they thought that patients of low socioeconomic status may not be able to afford co-pays for these DAAs.[127,129,130,150,155] Patients with private insurance are more likely to have difficulty obtaining these new HCV drugs than are patients with Medicaid; however, coverage also varies greatly by State, one clinical expert noted.[143] Two experts with research and clinical perspectives thought that the practice of limiting coverage to those patients with severe liver disease by third-party payers may increase health disparities.[128,135]

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