

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. HHS290201000006C). 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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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 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 report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Contents

Executive Summary	ES-1
Background.....	ES-1
Methods	ES-1
Results.....	ES-2
Discussion.....	ES-3
Health Care-Acquired and Bacterial Infection Interventions.....	1
Antimicrobial Copper Surfaces in the Intensive Care Unit for Prevention of Hospital-Acquired Infections	2
Bedaquiline (TMC207) for Treatment of Multidrug-Resistant Tuberculosis	6
Fecal Microbiota Transplantation for Treatment of Recurrent <i>Clostridium Difficile</i> Infection.....	10
Fidaxomicin (Difcid) for Treatment of <i>Clostridium Difficile</i> Infection.....	14
Xpert MTB/RIF Test for Simultaneous Detection and Drug- Sensitivity Testing of <i>Mycobacterium Tuberculosis</i>	17
Hepatitis C Virus Infection Intervention.....	21
Boceprevir (Victrelis) and Telaprevir (Incivek) for Treatment of Chronic Hepatitis C Infection.....	22
HIV/AIDS Interventions	26
Collaborative Care Model for Comorbid HIV and Major Depressive Disorder	27
Emtricitabine/Tenofovir (Truvada) for Prevention of HIV Infection.....	30
Routine Anal Pap Smear Screening at HIV Clinics to Prevent Anal Cancer	34
References	37

Figures

Figure 1. Overall high-impact potential: antimicrobial copper surfaces in the intensive care unit for prevention of hospital-acquired infections	4
Figure 2. Overall high-impact potential: bedaquiline (TMC207) for treatment of multidrug-resistant tuberculosis	8
Figure 3. Overall high-impact potential: fecal microbiota transplantation for treatment of recurrent <i>Clostridium difficile</i> infection	12
Figure 4. Overall high-impact potential: fidaxomicin (Difcid) for treatment of <i>Clostridium difficile</i> infection	15
Figure 5. Overall high-impact potential: Xpert MTB/RIF test for simultaneous detection and drug-sensitivity testing of <i>Mycobacterium Tuberculosis</i>	19

Figure 6. Overall high-impact potential: boceprevir (Victrelis) and telaprevir (Incivek) for treatment of chronic hepatitis C infection24

Figure 7. Overall high-impact potential: collaborative care model for comorbid HIV and major depressive disorder.....28

Figure 8. Overall high-impact potential: emtricitabine/tenofovir (Truvada) for prevention of HIV infection32

Figure 9. Overall high-impact potential: routine anal Pap smear screening at HIV clinics to prevent anal cancer35

Executive Summary

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 identifying 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 7 years out on the horizon and then to follow them for up to 2 years after initial entry into the health care system. Since that implementation, review of more than 15,000 leads about potential topics has resulted in identification and tracking of about 1,600 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 950 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 annually. Topics eligible for inclusion are those interventions expected to be within 0–4 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 350 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 seven or 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 potential high-impact 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 10 topics for which (1) preliminary phase III data on drugs, phase II or III data on devices and procedures were available, or programs were being piloted; (2) information was compiled before September 21, 2012, in this priority area; and (3) we received six to nine sets of comments from experts between February 3, 2011, and October 19, 2012. (A total of 117 topics in this priority area were being tracked in the system as of October 19, 2012.) For this report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). We present 9 summaries of 10 topics (indicated below with an asterisk) that emerged as having potentially high impact on the basis of experts’ comments and their assessment of potential impact. The material on interventions in this Executive Summary and report is organized alphabetically by disease state and then by intervention. 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. * Antimicrobial copper surfaces in the intensive care unit for prevention of hospital-acquired infections	High
2. * Bedaquiline (TMC207) for treatment of multidrug-resistant tuberculosis	Moderately high
3. * Boceprevir (Victrelis) for treatment of chronic hepatitis C infection	High
4. * Collaborative care model for comorbid HIV and major depressive disorder	Lower end of the potential high-impact range
5. * Emtricitabine/tenofovir (Truvada) for prevention of HIV infection	High
6. * Fecal microbiota transplantation for treatment of recurrent <i>Clostridium difficile</i> infection	High
7. * Fidaxomicin (Dificid) for treatment of <i>Clostridium difficile</i> infection	Moderately high
8. * Routine anal Pap smear screening at HIV clinics to prevent anal cancer	Moderately high
9. * Telaprevir (Incivek) for treatment of chronic hepatitis C infection	High
10. * Xpert MTB/RIF Test for simultaneous detection and drug-sensitivity testing of <i>Mycobacterium tuberculosis</i>	Moderately high

Discussion

Health Care-Acquired and Bacterial Infections

Experts identified five interventions involving health care-acquired and bacterial infections as having potential for high impact: antimicrobial copper surfaces fitted to intensive care unit (ICU) equipment to reduce hospital-acquired infections, two treatments for recurrent *Clostridium difficile* infection, an antibiotic to treat multidrug-resistant TB, and a rapid test to determine whether a patient has a drug-resistant form of TB.

Antimicrobial Copper Surfaces in the Intensive Care Unit for Prevention of Hospital-Acquired Infections

- **Key Facts:** About 2 million health care-acquired infections (HAIs) are documented in the United States annually and result in 100,000 deaths. Additionally, the U.S. Centers for Disease Control and Prevention (CDC) has estimated that HAIs add \$28 billion to \$45 billion to U.S. health care costs annually. On average, HAIs add an estimated 19.2 hospital days per patient contracting an HAI at a per-patient cost of \$43,000. Further, patients contracting an HAI have a 1-in-20 chance of dying if the infection is acquired while hospitalized and a 1-in-4 chance of dying if the infection was contracted in the ICU. According to estimates by the International Copper Association, about 80% of infectious diseases are transferred by touch. Despite common infection-control practices, including hand-washing and frequent surface disinfection, the number of HAIs each year continues to rise. Hospital surfaces in patient rooms, including the ICU, typically consist of stainless steel and plastics that possess no antibacterial properties and serve as fomites for disease transmission in time periods between disinfection procedures in many health care settings.

The intrinsic antimicrobial properties of copper and copper alloys (brasses and bronzes) for touch surfaces on hospital hardware and equipment might add another safeguard against disease transmission between cleanings. Antimicrobial Copper (International Copper Association, Ltd., New York, NY) touch surfaces can be incorporated into a wide variety of components, including bedrails, handrails, door handles, grab bars, IV poles, food trays and carts, sinks, faucets, shower and lavatory components, work surfaces, computer keyboards, equipment adjustment knobs, and face plates. Copper's antimicrobial properties are purported to remain effective for the product's lifetime. These surfaces are purported to continuously reduce bacterial contamination and achieve 99.9% reduction of gram-negative and gram-positive bacteria within 2 hours of exposure. More than 350 alloys, such as brass and bronze, have been registered to be antimicrobial, providing options to fit various clinical and aesthetic demands. Copper surfaces are purported by the manufacturer association to exert their antibacterial activity in two sequential steps. First, antimicrobial copper is purported to disrupt the integrity of bacterial cell membranes through oxidation and disrupt physiologic functions such as electrostatic potential. Second, antimicrobial copper ions are purported to penetrate compromised cells and alter cell metabolism by interacting with numerous enzymes crucial for normal metabolic activity. Copper surfaces are intended to be used in combination with standard infection control procedures. Studies have shown that antimicrobial copper surfaces can significantly reduce the microbial burden found on surfaces in the ICU as well as reduction in infection rates in patients staying in copper-fitted rooms.

In July 2012, AHRQ awarded an interdisciplinary research collaboration at the University of California, Los Angeles, \$2.5 million to conduct a 4-year, randomized study to determine whether reductions of surface bacteria due to the use of copper surfaces lead to decreased HAI rates, improved treatment outcomes, and reduced costs. The study will evaluate copper, plastic, or sham stainless steel surfaces to better understand their role as fomites.

- **Key Expert Comments:** Overall, experts commenting on this intervention stated that antimicrobial copper touch surfaces could have a significant impact on reducing HAIs and associated morbidity, mortality, and costs. Although a significant capital investment may be required to retrofit frequently touched surfaces in ICUs, the intervention is expected to quickly accrue savings. Except for a one-time disruption in patient management, antimicrobial copper is not expected to alter hospital operations. Although antimicrobial copper surfaces may reduce pathogens, experts warn that infection rates may not decline as much as expected if an HAI is contracted from bacteria already colonizing the patient's body and, thus, not transmitted from a caregiver's hand or contaminated fomites.
- **Potential for High Impact:** High

Bedaquiline (TMC207) for Treatment of Multidrug-Resistant Tuberculosis

- **Key Facts:** TB prevalence has resurged since 1985, attributed mostly to the increase in HIV infection and development of multidrug-resistant TB (MDR-TB) organisms. In 2011, the TB rate in the United States was 3.4 cases per 100,000 individuals. California, Florida, New York, and Texas accounted for half of all new TB cases in 2010. Although TB rates in the United States are relatively low, 62% of U.S. TB cases occur in patients who were born outside the country, a case rate that is about 11 times higher than for U.S.-born people. Additionally, in the United States, drug-resistant TB is relatively rare. About 1.3% of patients in the United States with TB were found to have drug-resistant disease. However, although the percentage of U.S.-born patients with MDR-TB has remained at or below 1.0% since 1997, the proportion of reported primary MDR-TB cases occurring in foreign-born persons increased from 25.3% in 1993 to 82.7% in 2011. The possibility of new drug-resistant strains is ongoing, and new agents to combat evolving resistance patterns are needed. Treatment guidelines for MDR-TB recommend using four to five different antibacterials for 18–24 months. Treatments are needed that are effective against resistant TB strains; effective treatments can also shorten the duration of therapy, further limiting the potential to develop future resistance.

Bedaquiline (TMC207, Janssen Research & Development division of Johnson & Johnson, New Brunswick, NJ) is an oral diarylquinolone antibacterial in clinical development for treating MDR-TB with a novel mechanism of action that targets energy metabolism by inhibiting mycobacterial ATP synthase. Bedaquiline has the potential to be the first anti-TB drug brought to market in more than 40 years that has a new mechanism of action. In clinical trials, the drug was given to patients in whom multidrug-resistant pulmonary tuberculosis was newly diagnosed at a dose of 400 mg daily for 2 weeks, followed by 200 mg 3 times a week for 6–22 weeks in addition to the patient's optimized standard treatment regimen. In a prospective, randomized, early bactericidal activity (EBA) study, patients (n=85) admitted to hospitals with drug-susceptible uncomplicated pulmonary TB who had no prior treatment were randomly treated with bedaquiline; bedaquiline and pyrazinamide; PA-824 and pyrazinamide; bedaquiline and PA-824; PA-824, moxifloxacin, and pyrazinamide; or unmasked standard anti-tuberculosis

treatment as a positive control. Patients were assessed using a 14-day measure of the daily fall of *Mycobacterium tuberculosis* per milliliter of sputum in daily overnight sputum collections. The mean 14-day measure of PA-824-moxifloxacin-pyrazinamide (n=13, 0.233) was significantly higher than that of bedaquiline (n=14, 0.061), bedaquiline-pyrazinamide (n=15, 0.131), bedaquiline-PA-824 (n=14, 0.114), but not PA-824-pyrazinamide (n=14, 0.154) or standard treatment (n=10, 0.140). Treatments were generally well tolerated. The company submitted a new drug application to the U.S. Food and Drug Administration (FDA) on June 29, 2012, based on phase II data, with a request for priority review. In September 2012, FDA granted priority review status, and a decision was expected by the end of December 2012. Drug cost and third-party payer information is not available, but given the unmet need, payers will likely reimburse for the drug as a specialty pharmaceutical requiring prior authorization.

- **Key Expert Comments:** Overall, experts commenting on this intervention stated that although the evidence base for bedaquiline is limited to phase II data, the treatment looks promising for this difficult-to-treat infection. Although rare in the United States, MDR-TB has a long and complicated treatment regimen which patients do not always complete and does not always result in a clinical cure. Bedaquiline could meet a significant unmet need as an oral therapy that can be added to the current treatment regimen, which could significantly improve treatment outcomes and reduce the duration of treatment, effects that could lead to cost savings. By treating MDR-TB more quickly and effectively, the drug could also have significant benefits from a public health perspective by reducing disease transmission.
- **Potential for High Impact:** Moderately high

Fecal Microbiota Transplantation for Treatment of Recurrent *Clostridium Difficile* Infection

- **Key Facts:** More than 300,000 U.S. hospitalizations are complicated each year by *Clostridium difficile* infections (CDIs), with associated annual costs estimated at \$431 million to \$3 billion. Recurrent CDI is increasingly common and challenging to treat effectively. About 20% of patients have a recurrence. Vancomycin or metronidazole is commonly used after a second CDI recurrence, but when vancomycin therapy is stopped, up to 60% of these patients develop recurrence, which suggests that other therapeutic options are needed.

Fecal microbiota transplantation (FMT), or fecal transplantation, is intended to recolonize a patient's intestinal flora with beneficial bacteria that will "crowd out" or otherwise make the environment in the bowel unfavorable for *C. difficile* colonization. Shortly before the procedure, which can be delivered by several methods (e.g., colonoscopy, nasogastric tube, enema), healthy donors submit fresh stool, which is mixed with saline into a solution and tested for pathogens, including syphilis, HIV, and hepatitis A, B, and C (the exact pathogens depend on the center). Centers collecting and processing the stool also typically screen transplant recipients for similar diseases to prevent disease transmission. If colonoscopy is the fecal-saline solution delivery method, the treating clinician introduces it into the intestines using a colonoscope to enter the right cecum, and the rest is introduced distally as the colonoscope is withdrawn. Typically, this procedure is required only once in a patient. Researchers who analyzed data on more than 77 patients with recurrent CDI from five treatment centers across the United States who received FMT reported that CDI was cured in 91% of patients after one treatment. Other, smaller trials have reported similar success rates. Some news reports have stated that facilities offering the procedure inform patients that a 90% success rate can be assumed. The procedure is being implemented in a

small number of research and gastrointestinal specialty centers. The procedure can be readily adopted at medical facilities because it is not subject to FDA regulation, and the material is collected and prepared at the facility or physician office administering the treatment. Four ongoing comparative trials are listed at the National Clinical Trials database and are comparing FMT to oral vancomycin for recurrent CDI. A clinical working group on FMT was established in late 2011 to create guidance on appropriate indications, for donors and for methods of delivery.

Specific cost information on the various modalities for administering the treatment is scarce at this time. Reported costs associated with screening donor blood and stool for contagious agents, preparation of the donor fecal sample, and placement of a nasogastric tube or retention enema tube can exceed \$2,500. If the procedure is done by colonoscopy, the average cost of colonoscopy is about \$3,000. Screening, collection, and preparation of the stool would be additional costs. However, costs of multiple regimens of antibiotic therapy for recurrent CDI, physician office visits, and hospitalizations from complications of recurrent CDI can easily exceed the reported costs of one FMT.

- **Key Expert Comments:** Overall, experts concluded that results from the small number of FMT studies completed thus far are very promising. However, experts were eager to see larger comparative studies to better determine the role of FMT in clinical practice. Experts noted several potential societal barriers to acceptance of the procedure and a lack of standardized protocols, which could slow diffusion; however, they also noted that the severity of recurrent CDI and its impact on patient quality of life might prompt patients to seek out the procedure.
- **Potential for High Impact:** High

Fidaxomicin (Dificid) for Treatment of *Clostridium Difficile* Infection

- **Key Facts:** Fidaxomicin (Dificid™, Optimer Pharmaceuticals, Inc., San Diego, CA) is a new, narrow-spectrum oral macrolide taken twice daily that is poorly absorbed by the body, allowing the drug to exert its activity in the gastrointestinal tract. Fidaxomicin is purported to be highly selective for *C. difficile* and, thus, leaves the normal intestinal flora intact. In clinical trials, fidaxomicin was reported to have similar cure rates to vancomycin but lower rates of CDI recurrence, persistent diarrhea, and death. In June 2011, FDA approved fidaxomicin for treating *C. difficile*-associated diarrhea. According to one U.S.-based online pharmacy, a 10-day course of fidaxomicin costs about \$3,625 compared with \$1,400 for a 10-day course of vancomycin. Our searches of 11 representative, private, third-party payers that publish coverage policies online found 7 with coverage determinations for fidaxomicin for treating *C. difficile*-associated diarrhea; 6 cover fidaxomicin for members with *C. difficile*-associated diarrhea. However, preauthorization is required (after failed therapy with prior antibiotic regimens), and patient copayments are said to be high. Pharmacies are also said to not routinely stock the drug because of its high cost, so once prescribed, patients may have to wait a day or two to obtain it.
- **Key Expert Comments:** The experts commenting on this topic stated that recurrent CDI can persist for a long time, be very costly to treat, and have high morbidity and mortality. The lack of new medications for CDI treatment has created an unmet need for an agent that can treat and minimize recurrent infections. Although fidaxomicin is more expensive than vancomycin, experts thought the antibiotic would be cost saving if it prevents CDI recurrence. Diffusion of fidaxomicin as a first-line treatment could depend largely on

whether patients have prescription drug coverage and on the formulary status of the drug on the patient's prescription drug plan.

- **Potential for High Impact:** High

Xpert MTB/RIF Test for Simultaneous Detection and Drug-Sensitivity Testing of *Mycobacterium Tuberculosis*

- **Key Facts:** According to the World Health Organization, *M. tuberculosis* infection is highly underdiagnosed because of current TB testing methods that require weeks to deliver a definitive result. During those weeks, infected patients go untreated or may be placed on ineffective therapies, thereby continuing to spread TB and creating a significant public health concern. Thus, the need for effective, rapid diagnostics and new treatments to address resistant strains that are emergent globally is significant. The Xpert MTB/RIF (*M. tuberculosis*/rifampicin) test (Cepheid, Sunnyvale, CA) is a nucleic-acid-based test that is run on Cepheid's GeneXpert[®] real-time polymerase chain reaction (PCR) system. The test is intended to simultaneously detect *M. tuberculosis* complex species and determine whether the identified bacterium is susceptible to rifampicin, a first-line therapy for TB. The assay is intended to yield results in about 2 hours, which would enable relatively rapid initiation of treatment. The test is available in the United States as a research-use-only reagent. The company anticipated filing a submission for marketing approval by the end of 2012 with U.S. marketing approval of a test kit anticipated in 2013 and product launch in 2013 or 2014.
- **Key Expert Comments:** Overall, experts thought that this test has potential as a rapid, sensitive, and specific diagnostic test to address the unmet need for more rapid diagnosis and better initial management of this form of TB, thus improving patient health outcomes and reducing spread of disease. By knowing the patient's TB status when he or she leaves the physician's office, more appropriate treatment could be given and proper infection control measures could begin to be implemented. Xpert MTB/RIF test detects resistance only to rifampin, which is a common first-line antibacterial agent. Susceptibility to other agents would still need to be guided by traditional testing methods. Nevertheless, the Xpert MTB/RIF test could replace other PCR methods of detection and provide an improved approach to diagnosis and treatment, which could improve outcomes for patients, especially those with limited access to care, and reduce disease transmission.
- **Potential for High Impact:** Moderately high

Hepatitis C Virus Infection

Hepatitis C virus (HCV) is a major public health concern, the primary cause of death from liver disease, and the leading cause for liver transplantation in the United States. According to CDC, an estimated 3.2 million Americans have chronic HCV infection. From 50% to 80% of infected people are reportedly unaware they are infected. Additionally, about 50,000 of the 1 million people with chronic HIV infection in the United States also have chronic HCV infection. Some calculations suggest that HCV-related mortality will continue to increase over the next 2 decades without effective new treatment. Also, total U.S. annual medical costs for HCV-infected people are expected to almost triple, from \$30 billion in 2009 to about \$85 billion by 2029.

Chronic HCV infection is considered clinically “curable”—that is, the virus can be suppressed to undetectable levels. The current standard of care is an initial regimen of pegylated-interferon alpha-2a (Pegasys[®], F. Hoffmann-La Roche, Ltd., Basel, Switzerland) and ribavirin (Copegus[®], Roche), a combination known as IFN/RBV. However, about 60% of HCV-infected patients who undergo and complete the IFN/RBV treatment for 48 weeks do not achieve a viral cure. Additionally, fewer than 10% of people who have a diagnosis of chronic HCV infection and attempt therapy actually complete it, leaving them at risk for relapse. Factors affecting treatment completion include the long course of therapy, poor cure rates, and poor quality of life during therapy.

Thus, intensive research has been ongoing, and dozens of drugs are in development in new drug classes. The relatively recent explosion in HCV drug development has come about because of effective and efficient in vitro methods that enable developers to quickly screen and evaluate potential candidates.

Boceprevir (Victrelis) and Telaprevir (Incivek) for Treatment of Chronic Hepatitis C Infection

- **Key Facts:** In May 2011, two new agents in a new class known as protease inhibitors became the first medications approved in 20 years to treat HCV infection: oral telaprevir (Incivek[™], Vertex Pharmaceuticals, Inc., Cambridge, MA) and oral boceprevir (Victrelis[™], Merck & Co., Inc., Whitehouse Station, NJ). Researchers reported that these protease inhibitors increased efficacy so that 65% to 75% of patients with the most common genotype, HCV genotype 1, who were given one of these agents in combination with IFN/RBV, achieved a sustained virologic response (referred to in clinical trials as a “clinical cure”). The availability of these new agents could improve treatment outcomes for many patients. However, more options are needed because of side effects and because some populations have been more challenging to treat than others (i.e., African-American patients have lower clinical response than whites to HCV therapy; patients co-infected with HIV or genotype 4 and patients who are prior nonresponders to IFN/RBV with other comorbid conditions, such as nonalcoholic fatty liver disease, need new effective options). However, side effects reported with the new protease inhibitors might affect full patient adherence.

IFN/RBV and telaprevir therapy has caused severe rashes that respond poorly to steroids in some patients; in treatment with boceprevir, a significantly higher incidence of anemia was reported. Physicians must also combine protease inhibitors with other antiviral agents because monotherapy with protease inhibitors has led to drug-resistant HCV strains. Lessons learned from HIV treatment suggest that combination therapy, with several distinct compounds with differing mechanisms of action, could minimize emergence of drug-resistant strains. The IFN/RBV component of an HCV treatment regimen seems to mitigate development of resistance and is expected to remain a mainstay of treatment in the near term

along with its side effects. Additionally, patients co-infected with HCV and HIV must be closely monitored for drug interactions, particularly when taking some ritonavir-boosted HIV protease inhibitors in combination with HCV protease inhibitors. Boceprevir has been shown to lower serum concentrations of the HIV drugs, and the HIV protease inhibitors have been shown to lower serum concentrations of telaprevir.

Many companies have been developing strategies to eliminate interferon or IFN/RBV in the treatment regimen and may include combinations of protease, polymerase inhibitors, NS5A inhibitors, or HCV polymerase inhibitors alone. In anticipation of protease inhibitors, it has been documented, clinicians held up initiating treatment of IFN/RBV-only regimens in HCV-infected patients to enable them to have what clinicians believed would be a better chance of clinical success once protease inhibitors became available. Although many of these patients are now seeking treatment with a protease inhibitor in combination with IFN/RBV, there is evidence that some patients are still waiting for an interferon-free regimen to become available, because of preference or contraindication for existing therapies. Some in the HCV community are hopeful that nucleoside polymerase inhibitors and or/ NS5A inhibitors in some combination may provide an interferon-free regimen with improved efficacy and tolerability and shorter treatment regimen. Many of these drugs are tracked in the horizon scanning system, but have not reported results from a phase III trial as of this writing.

Boceprevir's average wholesale price is \$15.71 per 200 mg capsule, or \$5,280 when sold by the package of 336 capsules (a 28-day supply). Merck stated that the wholesale acquisition cost is about \$1,100 per patient per week of treatment. Merck has a patient-assistance program to defray costs for those without insurance or whose insurance does not cover the drug.

The current average wholesale price of a course of telaprevir treatment is about four times as high as boceprevir (\$117.14 per 375 mg capsule); the company set the average wholesale price at \$49,200 for a 12-week regimen, or \$4,100 per week.

Our searches of 11 representative, private, third-party payers that publish 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 that all list coverage determinations for protease inhibitors to treat chronic HCV genotype 1 infection. In general, payers cover protease inhibitor therapy for treating chronic HCV infection; however, preauthorization is required, and quantity limits are generally imposed. One third-party payer stated that telaprevir is the preferred brand and that boceprevir is the nonpreferred brand.

- **Key Expert Comments:** Overall, experts saw all the protease inhibitors as having significant potential to address the unmet need of effective treatment for chronic HCV infection. They thought that fulfilling this need could provide a large benefit from the public health perspective and that these drugs could significantly reduce morbidity, mortality, cost of chronic infection, and demands on the health care system in the long term. However, they speculated that these benefits might be offset by high costs of protease-inhibitor treatment and the development of adverse events, which could require expensive treatment and followup. As the first class of new therapies for HCV treatment in 20 years and the first class of direct-acting antivirals for this condition, NS3/4A protease inhibitors were expected by experts commenting on this intervention to have a high impact on health care.
- **Potential for High Impact:** High

HIV/AIDS

HIV infection continues to be a major public health concern, continuously challenging physicians, researchers, and public health officials to find the best practices to contain the epidemic. HIV prevention measures remain crucial in controlling the disease. However, as HIV management has transitioned from a deadly fatal infection to a chronic illness, more attention has shifted toward effectively controlling the infection and the numerous accompanying comorbidities. Three interventions for management of HIV infection have been identified for this report as having high potential impact—one for prevention of HIV infection and the other two for managing comorbidities associated with infection.

Collaborative Care Model for Comorbid HIV and Major Depressive Disorder

- **Key Facts:** HIV and major depressive disorder (MDD) frequently co-occur in patients with HIV. MDD is the most common mental illness that these patients experience, yet MDD is both underdiagnosed and undertreated in this patient population. Feelings of severe, persistent sadness and hopelessness can lead to negative behaviors associated with HIV management and treatment adherence, which can lead to disease progression and even increased mortality. According to the National Institute of Mental Health (NIMH), MDD should be treated as a separate illness for patients with HIV. Common interventions for MDD include psychotherapy and prescription antidepressant medications. NIMH notes that MDD treatment in the context of HIV should be managed by a mental health professional, especially when antidepressant pharmacotherapy is prescribed, to avoid drug interactions.

To improve MDD diagnosis and management as well as HIV outcomes, a collaborative care team consisting of a registered nurse depression care manager, a clinical pharmacist, and a psychiatrist can be formed with protocols in place to facilitate communication and appropriate treatment. As part of the program, patients with HIV are screened for MDD at the HIV clinic during regular visits. The care team convenes once weekly and can communicate via electronic medical record progress notes. The registered nurse depression care manager also communicates with patients via telephone on an ongoing basis to deliver participant education and activation, assesses treatment barriers and possible resolutions, monitors depression symptoms, treats any substance abuse, and provides instruction in self-management. Referrals can be made to specialty mental health care providers at any time. Investigators in one study conducted in three Veterans Affairs clinics reported that patients infected with HIV (n=249) and with depression who were treated with collaborative care were more likely than patients treated with usual care to report treatment response and remission at 6 months. Patients treated with collaborative care reported more depression-free days during a 12-month period than patients treated with usual care. Patients treated with collaborative care had a significant reduction in HIV symptom severity at 6 months and 12 months compared with usual care. In a retrospective analysis, charts from patients (n=124) with HIV and comorbid depression who were referred for depression treatment at a psychiatric facility located within an infectious diseases outpatient clinic were also analyzed. In the posttreatment period, significant reductions in depression and HIV RNA were observed, and significant increases in CD4 T-cell count and antidepressant prescriptions were observed compared with the pretreatment period.

- **Key Expert Comments:** Overall, experts commented that a collaborative care model to treat MDD in patients with HIV could lead to improved diagnosis of MDD in more patients with HIV. They believed that better MDD management might lead to improved treatment

adherence and improved health outcomes. They also speculated that patients can gain a better understanding of their infection and how to better manage it. Experts pointed out that establishing a collaborative care group might result in a need for additional staff, facilities, and information technology as well communication sessions that might change care processes. Additionally, increased diagnosis of MDD is expected to increase demand for mental health services. Experts thought clinicians would accept the intervention because of the minimal training required and the potential to improve treatment adherence and outcomes. Experts were concerned that some patients might not accept the intervention because of a perceived stigma from the diagnosis of depression.

- **Potential for High Impact:** Lower end of the potential high-impact range

Emtricitabine/Tenofovir (Truvada) for Prevention of HIV Infection

- **Key Facts:** CDC estimates that as many as 50,000 people are newly infected with HIV in the United States annually; 61% and 23% of new infections occur in men who have sex with men (MSM) and men who have sex with women, respectively. Women are twice as likely to be infected with HIV through heterosexual contact. In 2011, Truvada[®] (emtricitabine/tenofovir, Gilead Sciences, Inc., Foster City, CA), in phase III development for preventing HIV infection, gained traction as a potential option for HIV prophylaxis in high-risk males and females seeking effective prevention against HIV. This was based on researchers' reports of data from a trial that high-risk MSM who took emtricitabine/tenofovir once daily were 44% less likely to become infected with HIV-1 than MSM given placebo. However, researchers later reported evidence that emtricitabine/tenofovir failed to protect high-risk females from contracting HIV. Experts speculated that the lack of efficacy in protecting women might be due to the drug's inability to concentrate sufficiently in vaginal tissue, which is where transmission occurs during intercourse, or might be related to problems with treatment adherence. Others hypothesized that in one preexposure prophylaxis trial, females may have given their HIV medication to their infected partners. These results dampened some enthusiasm and added to the controversy because treatment adherence has been shown to greatly improve efficacy of prophylactic emtricitabine/tenofovir. Additionally, more recent data from two other preexposure prophylaxis studies in serodiscordant couples have shown emtricitabine/tenofovir to be 73% to 78% effective in males and females. Emtricitabine/tenofovir is also controversial because some believe that the costly therapy might only buy time until infection occurs, even if the patient adheres to the recommended treatment regimen. In July 2012, FDA approved emtricitabine/tenofovir once-daily in combination with safer sex practices to reduce the risk of sexually acquired HIV-1 infection in adults at high risk. The retail cost of a 30-day supply of emtricitabine/tenofovir is roughly \$1,100. Our searches found no third-party payers with a coverage determination for this indication at this time.
- **Key Expert Comments:** Overall, experts commenting on this topic thought that prophylactic use of this drug has a high potential to address an important unmet need as the first pharmacologic agent approved to reduce the risk of acquiring HIV-1 infection in high-risk patients. Currently, no other preventive options are available other than abstinence and condom use, which are not employed by all individuals at high risk for infection. Experts thought that emtricitabine/tenofovir could have a significant impact on health promotion by reducing the number of HIV-infected individuals. However, experts noted that early trials have shown that this intervention would not protect everyone who attempts the regimen.

Experts speculated that this, combined with high treatment costs and likely high out-of-pocket costs to patients and frequent followup for something that is not a disease (i.e., unprotected sex) and that can be prevented with behavior interventions, would be controversial as the role of prophylactic emtricitabine/tenofovir evolves.

- **Potential for High Impact:** High

Routine Anal Pap Smear Screening at HIV Clinics to Prevent Anal Cancer

- **Key Facts:** Patients with HIV have a higher risk of developing anal cancer, possibly due to impaired T-cell function, yet no national or international guidelines for anal dysplasia screening are available for this patient population. The incidence of anal cancer rates in individuals infected with HIV increased from 19.0 per 100,000 person-years for the period 1992–1995, to 72.2 for 2000–2003. One cohort study showed that as many as 49% of HIV-infected MSM developed high-grade anal dysplasia within 4 years, compared with 17% of MSM not infected with HIV. Additionally, cross-sectional studies revealed anal dysplasia in 26% of women and 34% of men infected with HIV who did not report a history of anal intercourse. Before anal cancer develops, precancerous lesions can usually be detected and excised before progressing to anal cancer. Anal Papanicolaou (Pap) screening incorporated into routine visits for treatment and monitoring at HIV clinics for all patients, regardless of history of anal intercourse, might help reduce the incidence, morbidity, and mortality of anal cancer in patients with HIV. In a pilot study, 82% of HIV-infected patients approached during routine clinic visit agreed to participate in the study requiring an anal Pap smear collection. Fifty-three percent of patients had abnormal cytology results; among those undergoing high-resolution anoscopy with biopsy, 55% of patients had high-grade anal intraepithelial neoplasia, including two cases of carcinoma in situ.
- **Key Expert Comments:** Overall, experts stated a significant unmet need exists for earlier anal cancer detection in patients with HIV. The experts theorized that anal Pap screening is an effective tool to improve patient health outcomes and that screening in HIV clinics could be an effective way to implement standardized processes. Once educated about the importance of screening, patients seem to be receptive to the procedure. However, more studies are needed to fully understand the role that anal Pap screening may have on treatment and survival outcomes in this patient population. A greater body of evidence, once obtained, would help to increase diffusion via clinician acceptance and reimbursement.
- **Potential for High Impact:** Moderately high

Health Care-Acquired and Bacterial Infection Interventions

Antimicrobial Copper Surfaces in the Intensive Care Unit for Prevention of Hospital-Acquired Infections

Health care-associated infections (HAIs) are a significant cause of mortality, morbidity, and added cost in the U.S. health care system.¹ According to estimates by the International Copper Association, about 80% of infectious diseases are transferred by touch.² About 2 million HAIs are documented in the United States annually and result in 100,000 deaths.³ In addition, the U.S. Centers for Disease Control and Prevention (CDC) estimates that HAIs add between \$28 billion and \$45 billion to annual U.S. health care costs.⁴ On average, HAIs add an estimated 19.2 hospital days and \$43,000 in additional costs for each patient who contracts an HAI.⁵ Further, patients contracting an HAI have a 1-in-20 chance of dying if the infection is acquired while hospitalized and a 1-in-4 chance of mortality if the infection is contracted in the ICU.⁶ Hospital surfaces in patient rooms, including the intensive care unit (ICU), typically consist of stainless steel and plastics that purportedly possess no antibacterial properties and serve as fomites for disease transmission between disinfection procedures in many health care settings. In some cases, these surfaces can be colonized with live microbes for days or weeks, providing a contamination source to the hands and equipment of health care workers, professionals, visitors, and patients. The intrinsic antimicrobial properties of copper and copper alloys (brasses and bronzes) for touch surfaces on hospital hardware and equipment could add another safeguard against disease transmission between cleanings.⁷

Antimicrobial Copper (International Copper Association, Ltd., New York, NY) touch surfaces can be incorporated into a wide variety of components, including bedrails, handrails, door handles, grab bars, IV poles, food trays and carts, sinks, faucets, shower and lavatory components, work surfaces, computer keyboards, equipment adjustment knobs, and face plates. Copper's antimicrobial properties are purported to remain effective for the product's lifetime, and they do not rely on coatings or impregnated surfaces that may wear off or wash away, limiting their lifetime of service.⁷ The manufacturer association claims that copper touch surfaces continuously reduce bacterial contamination, achieving 99.9% reduction of gram-negative and gram-positive bacteria within 2 hours of exposure and that the surface delivers continuous antibacterial activity between routine cleaning and sanitizing steps.⁸ Antimicrobial copper consists of copper alloys such as brass and bronze, copper nickels, and copper-nickel-zincs.^{1,9} Manufacturers intend these alloys to have strength comparable to stainless steel. Copper alloys are purported to be durable. Natural tarnishing does not impair the surface's efficacy, and copper touch surfaces have been deemed to not be harmful to people or the environment.^{1,10}

The manufacturer purports that copper surfaces exert their antibacterial activity in two sequential steps. First, antimicrobial copper is purported to disrupt the integrity of bacterial cell membranes through oxidation and disrupt physiologic functions such as electrostatic potential. Second, copper ions are purported to penetrate compromised cells and alter cell metabolism by interacting with numerous enzymes crucial for normal metabolic activity.¹¹ The use of antimicrobial copper is intended to supplement and not substitute for standard infection control practices, and users are advised to continue to follow all current infection control practices.⁸ Antimicrobial copper is commercially available in certain hospital settings, such as on door knobs and door push plates. Thirteen companies are positioning to manufacture products containing the Antimicrobial Copper mark.¹²

Antimicrobial Copper is the only hospital touch surface with a U.S. Environmental Protection Agency (EPA) public health registration, allowing the manufacturer to claim that copper surfaces can kill specific bacteria (*Staphylococcus aureus*, methicillin-resistant *S. aureus* [MRSA],

vancomycin-resistant *Enterococcus* [VRE], *Enterobacter aerogenes*, *Pseudomonas aeruginosa*, and *Escherichia coli* O157:H7) that cause infections and pose a threat to human health.⁸ Although the manufacturer association makes no claims of efficacy against other organisms, the literature has shown that the copper might also be effective against viruses, other bacteria, and fungal pathogens.^{7,13} More than 350 antimicrobial copper alloys are EPA-registered public health antimicrobial products available to address various practical and aesthetic demands.¹⁴

The additional cost of manufacturing a copper sink for a hospital room is estimated at \$40–\$60 each, which might be considered marginal considering the cost for a hospital sink of approximately \$7,500.¹⁵ Additionally, copper rails are expected to add approximately \$100 to the cost of a standard \$30,000 hospital bed.¹⁵ According to the manufacturer, equipping each U.S. hospital room with antimicrobial copper products could cost from \$1.5 billion to \$2.5 billion, and a return on investment might be realized within 1.0 to 1.5 years after implementation.¹⁵

An analysis of antimicrobial copper touch surfaces compared with standard surfaces in the ICUs of three U.S. hospitals revealed that the median microbial burden observed on copper surfaces was 97% less than on control surfaces, and investigators have reported a significant reduction (40.4%) in the number of infections reported in patients treated in copper-fitted rooms.^{15,16}

In another analysis, investigators sampled copperized (Cu) objects (n=282) in 32 ICU rooms and non-Cu objects (n=288) in 27 ICU rooms to examine the ability of antimicrobial copper to lower the microbial burden (MRSA and VRE) on commonly touched objects (bed rails [99.99% Cu alloy], tray tables [90% Cu alloy], chair arms [90% Cu alloy], call buttons [70% to 95% Cu alloy], monitors [90% Cu alloy], and IV poles [75% to 95% Cu alloy]) and mitigate the acquisition of HAIs. Use of copper significantly reduced the total mean microbial burden in the ICU room by 87.4% (p=0.003). Copper was also effective in reducing the mean microbial burden on four of the six objects (bedrails [99%, p=0.0003], chair arms [38%, p=0.11], call buttons [90%, p=0.003], and IV poles [67%, p=0.11]). Use of copper showed no reduction in the mean microbial burden on tray tables or monitors. *Staphylococcus* was the predominant organism isolated from each object regardless of the surface composition and comprised 78.7% of the mean microbial burden of Cu rooms and 55.5% of non-Cu rooms. According to investigators, MRSA and VRE were frequently isolated from non-Cu objects but were not isolated from Cu objects.¹⁷

Another study examined the ability of copper trays and arms on phlebotomy chairs to reduce mean microbial burden compared with standard materials. The authors reported the following:¹⁸

Microbial burden was decreased on phlebotomy chairs fitted with copper trays and arms. No such reduction was found on standard chairs. The antimicrobial activity of the copper arms of the chairs also created a microbicidal “halo effect,” evident in the reduction of bacteria on adjacent, noncopper, surfaces of the chairs.

In a crossover study in an acute medical ward, a toilet seat, set of tap handles, and a ward entrance-door push plate, each containing copper, were compared with equivalent standard, noncopper items in the same ward. Samples were taken once weekly for 10 weeks; after 5 weeks, the copper-containing and noncopper items were interchanged. The median microbial burdens of copper-containing items were from 90% to 100% lower than their control equivalents. The authors reported that all but one item sampled had a statistically significant reduction in microbial burden.¹⁹

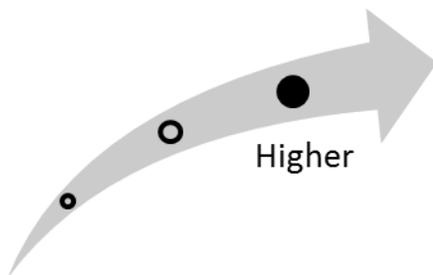
In July 2012, a research collaboration involving teams from the David Geffen School of Medicine at University of California, Los Angeles (UCLA), the UCLA Fielding School of Public Health, and the Henry Samueli School of Engineering and Applied Science at UCLA announced that they were awarded \$2.5 million from the Agency for Healthcare Research and Quality (Rockville, MD) to conduct a 4-year, randomized study to determine whether reductions of surface bacteria due to the use of copper surfaces lead to decreased HAI rates, improved treatment

outcomes, and reduced costs. The study will evaluate copper, plastic, or sham stainless steel surfaces to determine their role in HAI transmission.²⁰

Clinical Pathway at Point of This Intervention

ICUs typically contain stainless steel and plastic surfaces that are disinfected with standardized terminal cleaning procedures when patients are discharged from a room. Antimicrobial copper touch surfaces might help prevent the accumulation of pathogens between cleanings.²¹

Figure 1. Overall high-impact potential: antimicrobial copper surfaces in the intensive care unit for prevention of hospital-acquired infections



Overall, experts commenting on this intervention stated that antimicrobial copper touch surfaces might significantly reduce HAIs and associated morbidity, mortality, and costs. Although a significant capital investment may be required to retrofit frequently touched surfaces in ICUs, the intervention is expected to quickly provide durable cost savings and improved patient outcomes. Except for a one-time disruption in patient management, using antimicrobial copper is not expected to alter hospital operations. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered comments on this intervention.²²⁻²⁸ Overall, the experts agreed that HAIs lead to significant morbidity, mortality, and costs in health care facilities. The unmet need to reduce these infections is significant because current infection-control practices and education have not lowered these rates adequately in many cases. Overall, the experts stated, using copper surfaces might help address the unmet need by reducing the frequency of HAIs.

The experts stated that implementing copper touch surfaces in ICUs would create only a minimal, one-time disruption in infrastructure and patient management when some rooms would be unavailable during retrofitting with copper surfaces. Implementing copper surfaces into new infrastructure and equipment purchased is expected to be easier than retrofitting existing surfaces.

The experts believe that using antimicrobial copper surfaces in ICUs would be widely accepted by both patients and physicians because this intervention might be a simple, nontoxic way help to solve a complex and burdensome problem in health care. One expert representing a clinical perspective stated that physicians are more likely to accept this intervention if they will not personally bear the cost of fitting facilities with antimicrobial copper. Experts stated that patients will likely accept an intervention that is expected to improve their health outcome. One expert representing a health systems perspective stated that acceptance by clinicians or patients will be secondary to acceptance by health systems administrators, whose acceptance will be crucial to implement the intervention. The experts also stated that although a one-time capital investment for

new copper fixtures (which are slightly more expensive than current fixtures) is required, they are likely to be cost-saving within a year or two because extended ICU admissions can be among the most expensive occurrences in health care.

Bedaquiline (TMC207) for Treatment of Multidrug-Resistant Tuberculosis

Tuberculosis (TB) is a disease that occurs typically in the lungs and is characterized by the formation of tubercles and caseous necrosis in the affected tissues.²⁹ Patients with pulmonary TB may exhibit a bad cough that lasts 3 weeks or longer, chest pain, cough that produces blood or sputum, weakness or fatigue, weight and appetite loss, chills, fever, and night sweats.³⁰ TB prevalence has resurged since 1985, attributed mostly to the increase in HIV infection and development of drug-resistant TB organisms. In 2011, the TB rate in the United States was 3.4 cases per 100,000 individuals.³¹ California, Florida, New York, and Texas accounted for half of all new TB cases in 2010.³² Although TB rates in the United States are relatively low, 62% of TB cases occur in patients who were born outside the country, a case rate that is about 11 times higher than for U.S.-born people.³³

Additionally, in the United States, drug-resistant TB is relatively rare. About 1.3% of patients in the United States with TB were found to have drug-resistant TB. However, although the percentage of U.S.-born patients with multidrug-resistant TB (MDR-TB) has remained at 1% or less since 1997, the proportion of reported primary MDR TB cases occurring in foreign-born persons increased from 25.3% (103 of 407) in 1993 to 82.7% (81 of 98) in 2011.³³ The introduction of new drug-resistant strains is a constant possibility and new agents to combat evolving resistance patterns are needed. The most common reason for treatment failure is poor treatment adherence, which can lead to the development of drug resistance.³⁴ Treatment guidelines for MDR-TB recommend using four to five different antibacterials for 18–24 months.³⁵ Treatments are needed that are effective against resistant TB strains; effective treatment can also shorten the duration of therapy, further limiting the potential of developing resistance.

Bedaquiline (TMC207, Janssen Research & Development division of Johnson & Johnson, New Brunswick, NJ) is an oral diarylquinolone antibacterial in clinical development for treating MDR-TB with a novel mechanism of action that targets energy metabolism by inhibiting mycobacterial ATP synthase.³⁶ Bedaquiline has been shown to potently inhibit drug-sensitive and drug-resistant *Mycobacterium tuberculosis* in vitro and showed bactericidal activity in patients with drug-susceptible pulmonary tuberculosis.³⁷ The diarylquinolones are a new drug class intended to increase therapeutic options for patients with MDR-TB, a population for which treatment options are few, largely ineffective, and often very toxic.³⁶ In trials, the drug was given to patients in whom multidrug-resistant pulmonary TB was newly diagnosed at a dose of 400 mg daily for 2 weeks, followed by 200 mg three times a week for 6–22 weeks in addition to the patient's optimized standard treatment regimen.^{37,38}

In a phase II, randomized, controlled trial, patients (n=47) with newly diagnosed, pulmonary MDR-TB were treated with either bedaquiline (n=23; 400 mg daily for 2 weeks, followed by 200 mg three times a week for 6 weeks) or placebo (n=24), both in combination with a standard five-drug, second-line TB regimen.³⁷ Patients treated with bedaquiline besides standard therapy had a reduced time to conversion to a negative sputum culture, compared with patients treated with placebo and the standard five-drug regimen (hazard ratio, 11.8; 95% confidence interval [CI], 2.3 to 61.3; p=0.003 by Cox regression analysis).³⁷ Bedaquiline also increased the proportion of patients with conversion of sputum culture compared with placebo (48% vs. 9%, respectively). The mean log(10) count of colony-forming units (CFUs) in the sputum declined more rapidly in patients given bedaquiline than in patients given placebo. Bedaquiline was generally well tolerated with only nausea occurring significantly more frequently among patients receiving the active drug than in those given placebo (26% vs. 4%, p=0.04).³⁷

In a prospective, randomized, early bactericidal activity (EBA) study, patients (n=85) admitted to hospitals with drug-susceptible, uncomplicated, pulmonary TB who were treatment naïve were randomly treated with bedaquiline; bedaquiline and pyrazinamide; PA-824 and pyrazinamide; bedaquiline and PA-824; PA-824, moxifloxacin, and pyrazinamide; or unmasked standard anti-TB treatment as a positive control. Patients were assessed using the 14-day EBA measuring the daily fall in (CFU) of *M. tuberculosis* per milliliter of sputum in once-daily overnight sputum collections. The mean 14-day EBA of PA-824-moxifloxacin-pyrazinamide (n=13, 0.233) was significantly higher than that of bedaquiline (n=14, 0.061), bedaquiline-pyrazinamide (n=15, 0.131), and bedaquiline-PA-824 (n=14, 0.114) but not PA-824-pyrazinamide (n=14, 0.154) or standard treatment (n=10, 0.140). Treatments were generally well tolerated.³⁹

In June 2012, the manufacturer submitted a new drug application (NDA) to the U.S. Food and Drug Administration (FDA) based on phase II data and requested priority review. Priority review can be requested under the Prescription Drug User Fee Act for medicines that may offer major advances in care or provide a treatment option for diseases for which no adequate therapy exists.⁴⁰ Priority review also means that FDA attempts to render a decision within 6 months of the NDA submission. In September 2012, FDA granted the manufacturer priority review for bedaquiline,⁴⁰ and, given that the NDA was submitted June 29, 2012, a decision was anticipated by the end of December 2012.

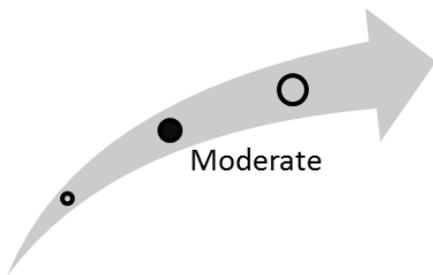
No information is available regarding costs or coverage of bedaquiline by third-party payers. Because bedaquiline is a highly specialized antibiotic used to treat a difficult infection that requires lengthy treatment, payers will likely cover bedaquiline as a specialty pharmaceutical with preauthorization requirements, including documentation that the patient has MDR-TB and possibly that the infection is resistant to one or more agents commonly used to treat MDR-TB.

Clinical Pathway at Point of This Intervention

Patients with active TB are typically given several medications that are to be taken over 6–9 months. These include 2 months with isoniazid, rifampin, and pyrazinamide combination (Rifater[®]), 4 months of isoniazid and rifampin combination (Rifamate[®], Rimactane[®]), and ethambutol (Myambutol[®]) or streptomycin added until the patient's drug sensitivity is known after bacterial culturing of sputum. The most common reason for treatment failure is lack of adherence with the regimen, which can cause drug resistance to develop.³⁴ Treatment guidelines for MDR-TB recommend using four to five different antibacterials for 18–24 months.³⁵ If approved for marketing, bedaquiline could be added to these regimens or be used in place of other oral antibacterials in cases of MDR-TB that are resistant to multiple oral agents. The drugs include the following:

- First-line oral agents: pyrazinamide or ethambutol
- Injectable agents: kanamycin (or amikacin), capreomycin, or streptomycin
- Fluoroquinolones: levofloxacin, moxifloxacin, or ofloxacin
- Second-line oral bacteriostatic agents: p-aminosalicylic acid, cycloserine or terizidone, or ethionamide or prothionamide
- Drugs of unclear role in MDR-TB treatment (optional): clofazimine, linezolid, amoxicillin/clavulanate, thioacetazone, imipenem/cilastatin, high-dose isoniazid, or clarithromycin

Figure 2. Overall high-impact potential: bedaquiline (TMC207) for treatment of multidrug-resistant tuberculosis



Overall, experts commenting on this intervention stated that although the evidence base for bedaquiline is from only phase II data, the treatment looks promising. Although rare in the United States, MDR-TB has a long and complicated treatment regimen, which patients do not always adhere to or complete and which does not always result in a clinical cure even when treatment is complete. Bedaquiline could address a significant unmet need as an oral therapy that can be added to the current treatment regimen, which might significantly improve treatment outcomes and reduce the treatment duration.

As an additive therapy, bedaquiline is not expected to cause a large shift in infrastructure or patient management. However, the long treatment duration and the need for directly observed treatment for MDR-TB is associated with significant costs. Bedaquiline could reduce these demands on personnel and the associated costs. Although the experts expect bedaquiline to be more expensive than available antibacterials, the drug could save money by reducing therapy duration, and it could reduce direct and indirect costs of MDR-TB from a public health and societal perspective. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered comments on this intervention.⁴¹⁻⁴⁷ The experts agreed that although MDR-TB is rare in the United States, when it does occur, successful treatment is difficult and the disease can cause significant morbidity and mortality in immunocompromised patients, including those with HIV. MDR-TB also requires a lengthy treatment regimen. Thus, a significant unmet need exists for effective, well-tolerated agents that can reduce the duration of treatment.

Overall, experts commenting on this topic thought that the novel mechanism of action for bedaquiline could be beneficial and that the available phase II data are encouraging. However, experts called for additional studies to better understand bedaquiline's impact on improving outcomes in patients with MDR-TB.

Bedaquiline is added to the current TB regimen and is not expected to disrupt how patients are treated or managed. However, if the drug can reduce the time needed to clear the infection, it could reduce the demands on facilities and staff that treat MDR-TB. The reduced resource demand could be significant, because TB treatment is administered as "directly observed treatment," meaning that caregivers observe the patient during medication administration. The need to do this is time consuming for health care workers. Also, bedaquiline use could shift the care setting by making more patients eligible for outpatient treatment. Because bedaquiline is a new antibacterial agent, hospitals will need to establish protocols for bedaquiline-resistance testing.

The experts opined that bedaquiline would likely cost more than current TB treatments, but that these costs might be offset by reductions in both hospital stays and the duration other TB therapies.

TB therapy has high personnel costs, which could be reduced with bedaquiline therapy. Experts postulated that bedaquiline would be accepted by patients and clinicians as an additional pill added to an existing treatment regimen. However, one clinical expert stated that high rates of gastrointestinal side effects could reduce patient acceptance, and other experts thought it would be difficult for patients to know which part of the regimen was causing side effects and, thus, which part of the regimen to discontinue.

Experts differed in perspectives on bedaquiline's impact on health disparities. In the United States, TB is more likely to affect patients who are of low income, poverty level, foreign-born, or HIV infected. These populations are less likely than others to have access to care. However, by reducing the treatment duration, experts stated, having programs in place to make bedaquiline available to these patients could help reduce disparities. Some experts stated that bedaquiline could have a positive public health impact by effectively treating MDR-TB and reducing treatment duration, which, in turn, could reduce transmission rates.

Fecal Microbiota Transplantation for Treatment of Recurrent *Clostridium Difficile* Infection

In 2006, an estimated 300,000 U.S. hospitalizations were complicated by *Clostridium difficile* infections (CDIs), with estimated costs of \$431 million to \$3 billion annually.⁴⁸ Inappropriate use of antibiotics can result in a disturbance of the normal bacterial flora of the colon, colonization with *C. difficile*, and release of toxins that cause mucosal inflammation and damage. Patients infected with *C. difficile* typically have watery diarrhea, fever, appetite loss, nausea, and abdominal pain or tenderness.⁴⁹ Chronic and relapsing CDIs are increasingly common and a challenge to treat effectively; about 20% of patients have a recurrence.⁵⁰ Although vancomycin (Vancocin[®]) or metronidazole (Flagyl[®]) is typically used after a second CDI recurrence, up to 60% of these patients develop further recurrence after vancomycin therapy is stopped, which suggests that other therapeutic options are needed.⁵¹

Colonoscopic fecal bacteriotherapy, or fecal microbiota transplantation (FMT), is intended to recolonize a patient's intestinal flora with beneficial bacteria that will "crowd out" or otherwise make the environment in the bowel unfavorable for *C. difficile* colonization.⁵¹ The treatment can be delivered by any of several methods: colonoscopy, nasogastric tube, or enema.⁵² Method standardization is lacking at this time. For the colonoscopic FMT procedure, healthy donors may submit fresh stool on the day of the procedure, and it is mixed with saline into a solution and tested for pathogens, including syphilis, HIV, and hepatitis A, B, and C (the exact pathogens depend on the center). Prospective donors are excluded if they recently used antibiotics or had a bout of diarrhea. The fecal-saline solution is introduced into the patient's right cecum in the intestine by a gastroenterologist, who uses colonoscope. The remainder of the solution is introduced distally as the colonoscope is withdrawn. Approximately 300–500 mL is infused into the patient; the dose varies by patient weight. Typically, this procedure is required only once in a patient.^{50,53}

In the largest analysis to date from five treatment centers across the United States, FMT was reported to be 91% effective in patients (n=77) with recurrent CDI. The mean age of the patient population was 65 years, and 40% of these patients were hospitalized, homebound, or in a specialized nursing facility at the time of the procedure. The median time of illness before therapy was 11 months, and the mean number of courses of antibiotic therapy was five before treatment. Patients treated with FMT had a mean time to resolution of diarrhea of 6 days. During long-term followup, only patients who were treated later with antibiotics (n=7) had a CDI recurrence. Two of these patients were successfully re-treated with FMT after an unsuccessful course of vancomycin. Additionally, 53% of patients in this study stated they would have preferred FMT as their first-line treatment.⁵⁴

In another trial, patients (n=70) with recurrent CDI were treated with colonoscopic FMT. All patients had a favorable response except those infected with strain type 027 CDI, who had an 89% favorable response rate. Four patients who did not respond to FMT had preexisting serious conditions caused by chronic diarrhea or a comorbidity, and all subsequently died of colitis. Within the first year after FMT, four patients previously treated had a relapse after later treatment with antibiotics. Two of these patients were successfully treated with another FMT, and two were treated with antibiotics for CDI.⁵⁵

In another retrospective study, patients (n=49) with either moderate and recurrent, or severe refractory CDI were treated with FMT via nasogastric tube (74%) or colonoscopy (26%).⁵⁶ Ninety-four percent of patients resolved symptoms within 1–4 days. Three patients whose symptoms did not respond to therapy were concurrently taking antibiotics. Four patients had recurrence after FMT

and eventually died; however, the deaths were not attributed to recurrent CDI. No adverse events were reported in patients who underwent FMT.⁵⁶

In another trial, prospective data were collected from three different centers performing FMT on 37 patients with recurrent CDI.⁵⁷ Patients received one or two FMTs. Ninety-two percent (75% to 100%) of patients were cured. Two experienced a recurrence 5–12 months after receiving subsequent antibiotic treatment and were successfully retreated with FMT. One noncured patient died after 1 month due to toxic megacolon. He had refused the suggested operative treatment before the FMT.⁵⁷

In a retrospective study of 12 consecutive patients (9 women and 3 men, mean age 66 years) with refractory/recurrent CDI who were symptomatically ill for a mean of 351 days before colonoscopic FMT, 100% experienced an immediate and durable clinical response to FMT. No adverse events were reported from FMT.⁵⁸

FMT is being implemented in a small number of research and gastrointestinal specialty centers. This procedure can be readily adopted by clinicians, even in an office setting, and is not subject to FDA regulation because the material is collected and prepared within the facility or physician's office where it is administered.

Four trials are under way and registered at the National Clinical Trials database and the International Clinical Trials Registry Platform to assess colonoscopic FMT in patients with recurrent, relapsing, or refractory CDI.⁵⁹⁻⁶² In one phase II/III, randomized, open-label trial, patients with recurrent CDI (n=126) will be treated with either 2 weeks of oral vancomycin pretreatment followed by a single FMT procedure administered by rectal enema or 2 weeks of oral vancomycin pretreatment followed by a 6-week taper of the drug. Patients will be assessed for CDI recurrence up to 120 days following treatment. This trial is expected to be completed in December 2013.⁵⁹

In another phase II, randomized, double-blind, crossover trial, patients with recurrent or refractory CDI (n=120) will be treated with either three FMT retention enemas (days 1, 5, and 12) and 14 days of oral placebo or oral vancomycin for 14 days with a saline enema (days 1, 5, and 12).⁶⁰ Patients will be assessed for clinical cure, treatment failure, and relapse rate over 14 days. This trial is expected to be completed in June 2013.⁶⁰

In a third, nonrandomized, open-label trial, patients with recurrent CDI whose disease has not responded to standard therapy (n=30) will be treated with “synthetic stool” or pure cultures of intestinal bacteria derived from healthy donor stool administered by rectal enema.⁶¹ Patients will be assessed for clinical cure for up to 6 months after treatment. This trial is expected to be completed in January 2013.⁶¹

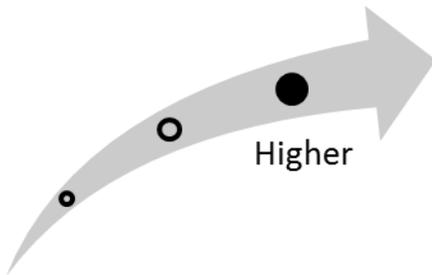
Finally, in a randomized, single-blind trial, patients with recurrent CDI (n=120) will be treated with oral vancomycin for 14 days, oral vancomycin for 14 days and bowel lavage with KleanPrep[®] on day 4, or oral vancomycin for 4 days followed by bowel lavage and FMT administered via nasoduodenal tube on day 5.⁶² Patients will be assessed for diarrhea and *C. difficile* toxin in stool 10 weeks after therapy. No completion date was reported for this trial.⁶²

Specific cost information on the procedure is scarce because it has been performed infrequently by a limited number of clinicians at a few centers. Reported costs associated with screening donor blood and stool for contagious agents, preparing the donor fecal sample, and placing a nasogastric tube or retention enema tube can exceed \$2,500. If the procedure is done by colonoscopy, the average cost of colonoscopy is about \$3,000. Screening, collecting, and preparing the stool would be additional costs. However, costs of multiple regimens of antibiotic therapy for recurrent CDI, physician office visits, and hospitalizations from complications of recurrent CDI can easily exceed the reported costs of one FMT.

Clinical Pathway at Point of This Intervention

According to CDC, once CDI is confirmed, patients are taken off the antibiotic that created the environment for the infection to occur. In some patients (20%, within 2–3 days) the infection may resolve without further treatment. If it does not, the patient is typically treated with either oral metronidazole or vancomycin for 10 days.⁶³ FMT is intended to treat recurrent CDI.

Figure 3. Overall high-impact potential: fecal microbiota transplantation for treatment of recurrent *Clostridium difficile* infection



Overall, experts concluded that results from FMT studies completed thus far are very promising. They thought that the procedure has significant potential to address the unmet need for effective treatment for CDI recurrence by providing a relatively low-cost, effective treatment, preventing antibacterial resistance, reducing the probability of CDI transmission, and lowering CDI-associated mortality. However, experts were eager to see larger studies to better determine the role of FMT in clinical practice and whether it should be first-line therapy for CDI. Experts noted that several societal barriers to acceptance of the procedure may slow diffusion; however, they also noted that hesitation on the part of patients might be mitigated by poor quality of life and ongoing illness in patients with recurrent CDI. Experts stated that clinicians will have greater acceptance of the procedure once donor screening, testing, and transplant processing protocols are established. Experts thought that FMT has high potential to significantly improve health outcomes in patients with difficult-to-treat, recurrent CDI. As the potential role of this intervention continues to be defined by clinicians using it, the procedure's unconventional and controversial nature could continue to provide catchy headlines for the media, they opined. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, provided comments on this intervention.⁶⁴⁻⁷⁰ All the experts concurred that recurrent CDI causes great morbidity, mortality, and costs to patients and the health care system. Emerging antibacterial resistance associated with these infections represents an important unmet need. A general consensus arose among the experts that FMT has the potential to address the unmet need for effective treatment for recurrent CDI without using antibiotics, which could lead to a significant impact on health outcomes and quality of life. In general, the experts accepted the underlying theory of FMT and were somewhat certain that it could be highly effective, although larger trials are needed to bear this out.

The experts mentioned that health care facilities generally have the staffing and equipment needed to perform the procedure and expect minimal disruptions to infrastructure and patient management. Potential disruptions cited would include shortened duration of inpatient stays, reduction in ICU admissions for toxic megacolon, and transition from inpatient to outpatient treatment with FMT.

Experts generally viewed the procedure as cost neutral or cost saving compared with the cost of multiple failed courses of antibiotics and resultant complications. The experts thought that clinicians would accept the procedure increasingly as donor selection, screening, and transplant processing protocols become standardized. Patients with long-term CDI recurrence, as well as their treating physicians, might be eager to try any therapy that has a high likelihood of efficacy. However, psychological factors or religious beliefs may preclude some patients from seeking the treatment. One expert representing a clinical perspective thought that even a different name for the procedure might be needed to increase acceptance.

Fidaxomicin (Dificid) for Treatment of *Clostridium Difficile* Infection

Fidaxomicin (Dificid™, Optimer Pharmaceuticals, Inc., San Diego, CA) is a narrow-spectrum, oral macrolide antibiotic that is microbiologically active against *C. difficile*.⁷¹ Fidaxomicin inhibits RNA polymerase, a bacterial enzyme, resulting in the death of the bacteria; the drug is also purported to inhibit bacterial toxin production.^{72,73} Fidaxomicin is purported to be poorly absorbed by the body, allowing the intervention to exert its activity in the gastrointestinal tract.⁷¹ Additionally, fidaxomicin is purported to be highly selective to *C. difficile*, allowing it to leave the normal intestinal flora intact.^{73,74}

Two randomized controlled trials with identical protocols compared oral fidaxomicin (200 mg twice daily) to oral vancomycin (Vancocin®, 125 mg 4 times daily) for 10 days in adults with acute CDI symptoms and a positive stool toxin test (n=1,105). In a combined analysis, the authors presented results showing cure rates of 91.9% and 90.2% with fidaxomicin and vancomycin, respectively. CDI recurrence rates were significantly lower in patients treated with fidaxomicin (13%) compared with patients treated with vancomycin (24.6%; p<0.001). Global cure rates were 78.6% and 66.4%, respectively (p<0.001), in patients treated with fidaxomicin and vancomycin. Adverse events were similar in both trials and not different among the treatments.⁷⁵

In another trial, patients (n=128) with one prior CDI episode and recurrence within 28 days were treated with oral fidaxomicin (200 mg twice daily) or vancomycin (125 mg 4 times daily) for 10 days. After treatment, 19.7% of patients receiving fidaxomicin experienced another recurrence compared with 35.5% of patients receiving vancomycin (p=0.045).⁷⁶ Early recurrence (within 14 days) was reported in 8% of patients given fidaxomicin and 27% of patients given vancomycin (p=0.003).⁷⁶

In a combined analysis of two phase III, randomized, controlled, blinded trials, adults with active CDI were randomly assigned to receive either fidaxomicin (200 mg twice daily) or vancomycin (125 mg 4 times daily) for 10 days. Fidaxomicin was noninferior for clinical cure and superior for reducing CDI recurrence compared with vancomycin. In an intent-to-treat analysis of the combined data of patients (n=1,164), fidaxomicin was reported to reduce persistent diarrhea, recurrence, or death by 40% (p<0.0001) compared with vancomycin overall through day 40. Investigators stated, “A 37% (95% CI, 2%-60%; P = .037) reduction in persistent diarrhea or death was evident through day 12 (heterogeneity P = .50 vs 13-40 days), driven by 7 (1.2%) fidaxomicin versus 17 (2.9%) vancomycin deaths at <12 days.” Low albumin and eosinophil counts and using metronidazole (Flagyl®)/vancomycin before randomization were risk factors for persistent diarrhea or death through 12 days, and CDI in the previous 3 months was a risk factor for recurrence (all p<0.01).⁷⁷

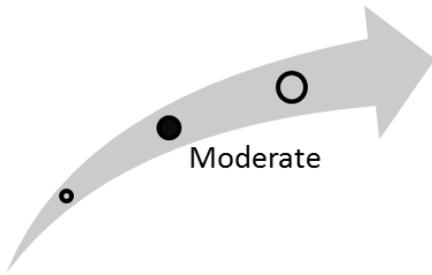
In June 2011, FDA approved fidaxomicin for treating *C. difficile*-associated diarrhea (CDAD).⁷⁸ It is taken twice daily for 10 days. Optimer Pharmaceuticals announced a 2-year agreement with Cubist Pharmaceuticals, Inc. (Lexington, MA), to copromote fidaxomicin under the brand name Dificid in the United States.⁷⁹ For the manufacturing, Optimer entered into an agreement with Biocon, Ltd. (Bangalore, India), in 2010.⁸⁰ According to one U.S.-based online pharmacy, a 10-day course of fidaxomicin costs about \$3,625.⁸¹ A 10-day course of vancomycin costs about \$1,400.⁸¹ 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 7 that list coverage determinations for fidaxomicin for treating CDAD.⁸²⁻⁸⁸ The majority, six

payers, cover fidaxomicin for members with CDAD; however, preauthorization is typically required, and fidaxomicin often has tier 3 or 4 formulary status.

Clinical Pathway at Point of This Intervention

Two interventions have been the standard treatment options for CDI over the past 25 years. Mild to moderate CDI is typically treated with metronidazole, although this is given only for the initial episode because of neurotoxicity concerns. For more severe CDI, vancomycin, currently the only FDA-approved antibiotic for treating CDI, is the standard treatment, either alone or in combination with metronidazole.⁴⁹ Fecal microbiota transplantation is also emerging as a CDI treatment. Fidaxomicin offers an alternative antibiotic treatment for CDI, with the possibility of less recurrence than is seen with vancomycin.

Figure 4. Overall high-impact potential: fidaxomicin (Dificid) for treatment of *Clostridium difficile* infection



Experts noted that CDI persistence is common and costly, with high morbidity and mortality in patients with recurrent infection, which responds poorly to antibiotic therapy. Experts thought that clinicians and patients would welcome a new, effective, antibiotic treatment for recurrent CDI that is well tolerated and reduces recurrence rates. Fidaxomicin could address some of these needs, experts believe, because it has been shown to have comparable efficacy to vancomycin with fewer CDI recurrences and side effects, which might improve quality of life for many patients by shortening the infection duration. Although fidaxomicin is more expensive than vancomycin, experts thought that the antibiotic could reduce costs by preventing CDI recurrence. However, diffusion as a first-line treatment would depend largely on the drug's formulary status at third-party payers; thus far, payers require prior authorization and a stepped therapy approach. Based on this input, our overall assessment is that this intervention is in the moderate end of the high-potential-impact range.

Results and Discussion of Comments

Seven experts, clinical, research, and health systems backgrounds, offered perspectives on this intervention.⁸⁹⁻⁹⁵ Experts agreed that CDI can be prolonged and costly, with high morbidity and mortality in patients with recurrent infection that responds poorly to antibiotic therapy. Clinical experts agreed that CDI is on the rise and is becoming more difficult to treat and that few treatment options exist and availability of effective treatments that are well tolerated could fill a significant unmet need. The experts agreed that fidaxomicin is an effective, localized therapy for treating CDI. Although vancomycin is effective as a first-line agent in many patients, experts generally agreed that fidaxomicin will have the greatest impact by reducing and resolving recurrent infections, improving patient quality of life and their ability to work and perform normal daily activities.

The experts did not think that fidaxomicin would disrupt health care delivery, infrastructure, or patient management because one antibiotic replaces another. However, they thought that using this

option to cure CDI could lessen patient need for health care resources and demand on both outpatient and inpatient facilities and staff. Experts stated that clinicians would be highly accepting of fidaxomicin because of the global efficacy of the treatment and the labeled indication for treating CDI, which metronidazole does not have. Barriers to acceptance include cost and the preauthorization required from third-party payers. Patients were also expected to opt for fidaxomicin treatment if cost is not an issue for them, because CDI-associated diarrhea and hospitalization are significant quality-of-life issues. All the experts agreed that although fidaxomicin is more than twice as expensive as vancomycin, the antibiotic's costs are expected to be offset by a reduced frequency of recurrent infections, which would save significant costs. Third-party payers may eventually make fidaxomicin the preferred therapy for CDI if they see convincing longer-term data that it lowers the rate of hospital readmissions, resolves CDI, and shortens duration of infections.

Xpert MTB/RIF Test for Simultaneous Detection and Drug-Sensitivity Testing of *Mycobacterium Tuberculosis*

According to the World Health Organization, TB is considered to be highly underdiagnosed. This is a direct result of current TB testing methods, which require weeks to deliver a definitive result. During that time, patients are untreated or placed on ineffective therapies. These patients may also continue to spread TB to others in the community, creating a significant public health concern.⁹⁶

The *M. tuberculosis*/rifampicin test (Xpert[®] MTB/RIF, Cepheid, Sunnyvale, CA) is a nucleic-acid-based test run on Cepheid's GeneXpert[®] real-time polymerase chain reaction (PCR) system.⁹⁶ The test simultaneously detects the presence of *M. tuberculosis* complex species and determines whether the identified bacterium is susceptible to rifampicin, the first-line TB drug.⁹⁷ In the assay, a real-time hemi-nested PCR reaction is performed to amplify and detect a portion of the *rpoB* gene, a genetic marker that is specific for a subunit of an RNA polymerase essential to TB viability.⁹⁶ The antibiotic activity of rifampicin targets the subunit encoded by the *rpoB* gene to inhibit the RNA polymerase, inhibiting bacterial survival.⁹⁶ Research has demonstrated that the portion of the *rpoB* gene amplified in the Xpert MTB/RIF assay harbors mutations in the majority of rifampicin-resistant TB strains.⁹⁸

In the assay, the detection of TB DNA in the patient sample is accomplished by five separate real-time PCR fluorescent probes, which are specifically activated in the presence of amplified *rpoB* DNA and detected by the GeneXpert system.⁹⁷ Each of the five probes overlaps a different site known to be mutated in rifampicin-resistant TB if rifampicin resistance can be determined based on the binding signal given from the probes.⁹⁷

To perform the test, a technician first treats a patient sputum sample with a solution containing sodium hydroxide and isopropanol (isopropyl alcohol) to reduce the viability of any *M. tuberculosis*, thereby preventing contamination. Subsequent processing and detection are performed on the GeneXpert system using a single-use, closed Xpert MTB/RIF cartridge that contains all the reagents necessary for testing.^{96,97} The procedure's automated nature and the fact that it does not require handling of PCR amplicons are intended to ensure optimal accuracy of the assay by limiting interoperator variability and reducing the potential for false positives caused by amplicon contamination.⁹⁷ The assay is intended to yield results for both the presence of *M. tuberculosis* and antibiotic resistance for positive samples in about 2 hours.⁹⁶ For a clinician to fully determine an effective treatment regimen, full drug-susceptibility testing would still need to be performed in patients with rifampicin-resistant TB for a clinician to fully determine an effective treatment regimen.

In a diagnostic sub-study of a TB prevalence survey conducted in gold mining companies in South Africa, participants' sputum (n=6,893) was tested using liquid culture (reference comparator), Xpert MTB/RIF, and smear microscopy. Sputum samples tested positive for *M. tuberculosis* (MTB) in 2.7%, 2.1%, and 1.3% of samples tested by culture, Xpert MTB/RIF test, and microscopy, respectively. Sensitivity, specificity, positive predictive value, and negative predictive value for the Xpert MTB/RIF test were 62.6%, 99.6%, 81.3%, and 98.9%, respectively. Agreement between Xpert and culture was 98.5%. Sensitivity of microscopy was 17.6%. When individuals with a history of TB treatment were excluded from the analysis, Xpert MTB/RIF specificity was 99.8% and the positive predictive value was 90.6% for detecting MTB. Costs for testing the 7,000 specimens, with 2.7% of specimen cultures positive for MTB, were \$165,690 for Xpert MTB/RIF and \$115,360 for the combination of microscopy and culture.⁹⁹

In a large multicenter trial, patients (18 years of age or older) suspected of having TB or MDR-TB (n=6,648) presenting with cough lasting at least 2 weeks were tested for TB using Xpert MTB/RIF, culture, and microscopy detection methods. The investigators reported, “One-off MTB/RIF testing detected 933 (90.3%) of 1033 culture-confirmed cases of tuberculosis, compared with 699 (67.1%) of 1041 for microscopy. MTB/RIF test sensitivity was 76.9% in smear-negative, culture-positive patients (296 of 385 samples), and 99.0% specific (2846 of 2876 non-tuberculosis samples).” The sensitivity and specificity of the MTB/RIF test for rifampicin resistance were 94.4% and 98.3%, respectively. As observed with microscopy, MTB/RIF test sensitivity was not significantly lower in patients co-infected with HIV. Median time to detection of TB was 0 days for the MTB/RIF, 1 day for microscopy, 16 days for liquid culture, and 30 days for solid culture. Using the MTB/RIF test reduced the median time to treatment of patients with smear-negative TB from 56 days to 5 days.¹⁰⁰

In an international clinical trial, investigators collected three sputum samples each from patients suspected of having TB or drug-resistant TB (n=1,730).¹⁰¹ Samples were analyzed by a combination of acid-fast smear, solid culture, liquid culture, and Xpert MTB/RIF tests.¹⁰¹ Among culture-positive patients, the Xpert MTB/RIF test gave a positive TB result for 551 of 561 smear-positive patients (98.2%) and for 124 of 171 smear-negative patients (72.5%).¹⁰¹ Additionally, among 609 culture-negative patients, the Xpert MTB/RIF test correctly identified 604 patients as negative for TB infection (99.2%).¹⁰¹ As for susceptibility testing, compared with conventional culture-based susceptibility testing, the Xpert MTB/RIF test correctly identified 200 of 205 patients with TB as having a rifampicin-resistant infection (97.6%) and 504 of 514 patients with TB as having a rifampicin-sensitive infection (98.1%).¹⁰¹

In an additional study, Xpert MTB/RIF was compared to culture and microscopy detection methods using samples from pediatric patients with suspected TB (n=164).¹⁰² Xpert MTB/RIF detected 100% of the smear-positive cases and 66.6% of culture-positive cases that were smear negative. In the per-sample analysis, Xpert displayed a similar sensitivity to culture methods and detected three-fold more confirmed TB cases than microscopy in a similar amount of time. Four additional culture-negative cases with clinical TB (8.5%) were diagnosed by Xpert MTB/RIF. Xpert MTB/RIF demonstrated 100% specificity when TB was reliably excluded; accuracy was not affected by HIV infection in these patients.¹⁰²

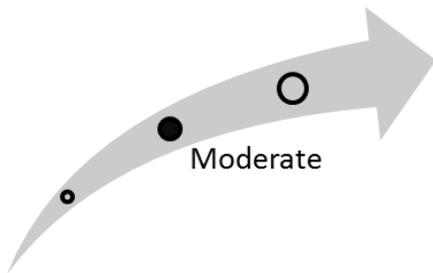
Cepheid has received a Conformité Européene (CE) mark for marketing the test in Europe.¹⁰³ The test is available in the United States as a research-use-only reagent.¹⁰⁴ The manufacturer expected to make a submission and file for U.S. regulatory approval by the end of 2012, with an expected launch in 2013 or 2014.¹⁰⁵ Pricing for the Xpert MTB/RIF test is not available; however, other test-cartridge-based assays running on the GeneXpert system cost approximately \$20 per assay.¹⁰⁶ Additionally, to run the Xpert MTB/RIF test, a facility would need to have a GeneXpert system, which could represent a capital equipment purchase of more than \$100,000 for higher throughput versions.^{96,107} According to one source, standard basic testing for TB costs about \$20–\$40, and more advanced testing to determine rifampicin resistance can add another \$20–\$30.¹⁰⁶

Clinical Pathway at Point of This Intervention

A patient initially presents with symptoms that indicate a possible case of pulmonary TB based on his or her medical history, physical examination, symptoms, TB infection test results (e.g., tuberculin skin test, QuantiFERON-TB Gold test), and/or chest radiographs.^{108,109} The current recommended diagnostic procedure for laboratory confirmation of TB is to obtain a respiratory sputum sample from the patient and test the sample simultaneously with a nucleic acid amplification test, an acid-fast bacteria smear test, and liquid or solid media culture.¹⁰⁸ The Xpert

MTB/RIF test would be used in place of current nucleic acid amplification tests. Besides identifying the presence of TB, the Xpert MTB/RIF test would also give a preliminary indication of potential antibiotic resistance, which would normally be determined following a positive culture isolate by assaying the isolate's in vitro susceptibility to antibiotics.^{96,108}

Figure 5. Overall high-impact potential: Xpert MTB/RIF test for simultaneous detection and drug-sensitivity testing of *Mycobacterium Tuberculosis*



Overall, experts commenting on this intervention thought that the Xpert MTB/RIF test has potential to be a rapid, sensitive, and specific diagnostic that could address the unmet need for more rapid diagnosis and better initial management of TB. If it shows sufficient efficacy, they thought, it has potential to improve patient health outcomes and reduce the spread of TB. By knowing the patient's TB status when he or she leaves the physician's office, experts noted, more appropriate treatment could be given and proper infection control measures could be implemented. However, the Xpert MTB/RIF test detects resistance only to rifampin, which is a common first-line antibacterial agent. Susceptibility to other agents would still need to be guided by traditional testing methods. Nevertheless, the Xpert MTB/RIF test could replace other PCR detection methods and provide an improved approach to diagnosis and treatment, which could reduce problems with followup for patients with limited access to care. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.¹¹⁰⁻¹¹⁶ Overall, the experts concurred that current TB diagnostic methods are lengthy, taking days to weeks to confirm or rule out the presence of TB and antibiotic susceptibility. This presents a significant unmet need for more rapid diagnostic testing to direct appropriate therapy and implement infection control measures for patients, the community, and health care providers. Experts agreed that the test is fast and accurate, which allows health care practitioners to implement infection control procedures almost immediately. Additionally, Xpert MTB/RIF also provides early detection of rifampicin resistance to guide appropriate antibiotic selection, which could improve health outcomes.

The experts stated that Xpert MTB/RIF could improve health disparities because it is inexpensive for patients, and most experts thought that Xpert MTB/RIF testing would be offered in most emergency departments and public health clinics. However one expert representing a research perspective stated the GeneXpert system may be too costly in some underserved areas, which could create disparities.

In general, the experts thought the Xpert MTB/RIF test would not have a large impact on how the disease is treated or diagnosed but that it would allow current treatment strategies to be employed earlier and, therefore, potentially reduce disease transmission. Although experts expected impact on staffing and training to be minimal, a significant capital investment of \$100,000 is required to

purchase the GeneXpert system if the facility has not purchased it for other testing. Although most experts thought that clinicians would readily embrace Xpert MTB/RIF testing, one expert representing a research perspective stated that facilities using other PCR methods may resist early adoption because only 1% of the TB cases in U.S.-born patients are MDR-TB. Patients were also expected to embrace rapid diagnosis. The expert stated that Xpert MTB/RIF testing will likely be cost effective. However, initial costs of the GeneXpert system could lead to more centralized TB testing centers.

Hepatitis C Virus Infection Intervention

Boceprevir (Victrelis) and Telaprevir (Incivek) for Treatment of Chronic Hepatitis C Infection

Unlike infections with HIV and hepatitis B virus, chronic hepatitis C virus (HCV) infection is considered “curable.” However, about 60% of people who undergo treatment with the current standard of care—an initial regimen of pegylated interferon alfa plus ribavirin (IFN/RBV) for 48 weeks—do not achieve a sustained virologic response (SVR) or viral cure, leaving them at risk for future liver disease.^{117,118} Because of recent advances allowing researchers to screen HCV drugs more effectively in vitro, many new HCV drug therapies are in clinical development. The class of agents furthest along in development is the direct-acting antiviral NS3/4A protease inhibitor. The protease activity of the HCV NS3 protein is required for HCV maturation and replication.¹¹⁹ The NS4A peptide functions as a cofactor for NS3 and plays a key role in increasing the processing rate of the viral polypeptide. Additionally, the activity of NS3/4A protease appears to be associated with HCV’s ability to evade the host’s innate immune response to the virus, further demonstrating the importance of NS3/4A as a target for HCV therapy.¹¹⁹ Inhibiting NS3/4A results in production of immature, noninfectious HCV virions, leading to an SVR.^{120,121}

Boceprevir

Boceprevir (Victrelis[™], Merck & Co., Inc., Whitehouse Station, NJ) is orally administered. In May 2011, FDA granted marketing approval for treating chronic HCV genotype 1 (HCV-1) infection in combination with IFN/RBV, which is a combination of pegylated interferon alfa-2a (Pegasys[®]) and ribavirin (Copegus[®]).¹²² Boceprevir was the first new drug approved in 20 years for treating HCV. It has been indicated for oral administration, 800 mg three times daily (every 7–9 hours) with food.¹²³

In one of several phase III clinical trials, treatment-naïve patients with chronic HCV-1 infection (n=1,099) were given boceprevir in combination with IFN/RBV in one of two treatment regimens (48 weeks of boceprevir plus IFN/RBV or 24 weeks of boceprevir plus 24 or 48 weeks of IFN/RBV) or 48 weeks of placebo plus IFN/RBV.¹¹⁷ Overall, SVR at 48 weeks was achieved by 65% of patients in the boceprevir groups compared with 38% of patients in the control group with no significant difference observed between the two boceprevir groups.¹¹⁷

In a second, phase III trial, treatment-experienced patients (n=404) with chronic HCV-1 infection whose infection persisted despite prior treatment with IFN/RBV were given boceprevir in combination with IFN/RBV or placebo in combination with IFN/RBV.¹²⁴ In the boceprevir group, 66% of patients achieved an SVR at 48 weeks compared with 21% of patients in the control group.¹²⁴

Boceprevir therapy costs an estimated \$1,100 per week (wholesale acquisition cost).¹²⁵ The therapy’s total cost depends on whether response-guided therapy is appropriate for a patient, which would shorten the treatment duration from 44 weeks to 28 or 36 weeks.¹²⁶ Merck has a patient-assistance program to defray costs for those without insurance or whose insurance does not cover the drug.

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 that all list coverage determinations for protease inhibitors to treat chronic HCV-1 infection.¹²⁷⁻¹³⁸ In general, payers cover boceprevir therapy for treating chronic HCV infection; however, preauthorization is required and monthly quantity limits are generally imposed. One third-

party payer stated that telaprevir (see below) is the preferred brand and that boceprevir is the nonpreferred brand.¹³²

Telaprevir

Telaprevir (Incivek™, Vertex Pharmaceuticals, Inc., Cambridge, MA) is orally administered and received FDA approval in May 2011 for treating chronic HCV-1 infection in combination with IFN/RBV.¹³⁹ Telaprevir is indicated for oral administration, 750 mg three times daily (every 7–9 hours) with food (not low fat) and is being evaluated for 1,125 mg twice-daily dosing.^{140,141}

In a phase III trial, treatment-naïve patients infected with HCV-1 (n=1,088) were given telaprevir in one of two dose regimens in combination with IFN/RBV or placebo.¹¹⁸ After receiving a 12-week telaprevir-based combination regimen followed by IFN/RBV alone, 75% of patients achieved an SVR at 24 weeks. After receiving an 8-week telaprevir-based combination regimen, followed by IFN/RBV alone, 69% of patients achieved an SVR. In the control arm, 44% of patients achieved an SVR after 48 weeks of IFN/RBV.¹¹⁸

In a second phase III trial, treatment-experienced patients with genotype-1 HCV infection whose disease had failed to achieve an SVR with prior IFN/RBV therapy (n=663) were given telaprevir or placebo in combination with IFN/RBV.¹⁴² At 24 weeks, 65% of patients given telaprevir achieved an SVR compared with 17% in the control group.¹⁴²

Telaprevir has also been evaluated in phase II trials as part of an interferon-free regimen in combination with VX-222, a nonnucleoside HCV NS5B polymerase inhibitor, and ribavirin.¹⁴³ Interim data have shown undetectable HCV in 83% of patients at week 12.¹⁴³

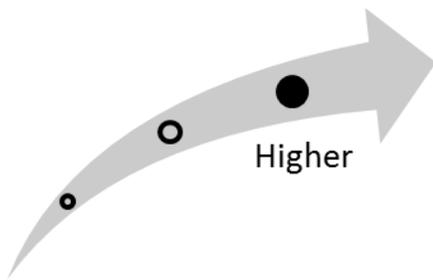
Nine other HCV protease inhibitors are being tracked in the Horizon Scanning System that have not yet reported phase III data. We will continue to monitor these interventions for at least 2 years from the point of diffusion of boceprevir and telaprevir to determine whether the drugs in development add any benefit or risk compared with drugs already approved in this class.

Telaprevir, when added to current IFN/RBV therapy, is expected to double the treatment cost. The current average wholesale price is about \$117 per 375 mg capsule; the company set the price at \$49,200 for a 12-week regimen.¹²⁶ The company introduced a copayment assistance program for patients who have to pay out of pocket for telaprevir irrespective of income (Co-Pay Assistance Program). Patients with government insurance are not eligible for this benefit.¹⁴⁴

Clinical Pathway at Point of This Intervention

Patients who test positive for antibodies to HCV and HCV RNA may be considered to have acute or chronic HCV infection, depending on the context. Additionally, a patient who tests negative for antibodies to HCV and positive for HCV RNA might be chronically infected if immunosuppressed.¹⁴⁵ Subsequent HCV genotype testing is performed to determine the therapy regimen and the likelihood of a positive clinical outcome.¹⁴⁵ Rest and hydration are typically prescribed. In 2011, the American Association for the Study of Liver Diseases updated its clinical practice guidelines to recommend treating patients with HCV-1 infection with a protease inhibitor (boceprevir or telaprevir) in combination with the previous standard of care, IFN/RBV.¹⁴⁶

Figure 6. Overall high-impact potential: boceprevir (Victrelis) and telaprevir (Incivek) for treatment of chronic hepatitis C infection



Overall, experts commenting on this intervention saw the NS3/4A protease inhibitors as having significant potential to address the unmet need of effective treatment for chronic HCV infection. They stated that fulfilling this need could provide a large benefit from the public health perspective and that these drugs could significantly reduce morbidity, mortality, cost of chronic infection, and demands on the health care system in the long term. However, they speculated that these benefits might be offset by high costs of protease inhibitor treatment and the development of adverse events, which could require expensive treatment and followup and could lead to treatment discontinuation. Because NS3/4A inhibitors are the first class of new therapies for HCV infection in 20 years and the first class of direct-acting antivirals for this condition, experts commenting on these drugs expected the drugs to have a higher potential impact on health care, especially if they are eventually used in an interferon-free regimen. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, commented on telaprevir for treating chronic HCV infection, and seven experts, with clinical, research, and health administration backgrounds commented on boceprevir for treating HCV infection.¹⁴⁷⁻¹⁶⁰ Overall, these experts agreed that current treatment with IFN/RBV is ineffective in most patients, resulting in significant morbidity, mortality, and costs. The current ineffective therapy regimens present a significant unmet need for better treatment strategies for chronic HCV infection. Additionally, experts generally concurred that the underlying theory for the protease inhibitors is sound. Experts were relatively certain that NS3/4A protease inhibitors have the potential to greatly improve health outcomes, although some experts still interpreted these therapies as additive to IFN/RBV because the approved regimens of telaprevir and boceprevir include IFN/RBV. However, one expert representing a research perspective was concerned about the frequency of adverse events observed with protease inhibitors in combination with IFN/RBV and stated, “if you survive the treatment you could be cured.”¹⁵⁵

Some experts stated that patients with HCV are disproportionately members of underserved populations. Additionally, African-American patients have a higher incidence of HCV but are less likely to respond to therapy with IFN/RBV only. Thus, protease inhibitor therapy may improve outcomes for these patients and reduce health disparities. Dissenting experts stated that the high cost of protease inhibitors and the need for regular interferon injections can represent significant barriers for patients who already have limited access to care and could increase health disparities.

Experts who generally interpreted HCV protease inhibitors as add-on therapies also did not think these treatments would significantly shift treatment or management models. Although patients and clinicians are eager to have new treatment options with increased SVR rates, physician

acceptance is expected to be influenced by adverse events and the need to avoid drug interactions while patients are taking HCV therapy. One clinical expert stated that the ability to manage adverse events will be a crucial factor determining continued patient acceptance of these new agents.

As an adjunctive therapy, protease inhibitors are expected to add significantly to the already high costs of HCV therapy. However, some experts suggested that costs could be offset by reduced duration of therapy. Effective treatment could also reduce the long-term costs of complications such as liver cirrhosis and liver failure associated with IFN/RBV inefficacy or nontreatment.

Overall, experts stated protease inhibitors have significant potential to address the unmet need for effective treatment for chronic HCV infection. By significantly increasing SVR rates, protease inhibitors are expected to reduce morbidity, mortality, cost of chronic infection, and demands on the health care system in the long term. However, experts speculated that these benefits might be mitigated by high costs of protease inhibitor treatment and the development of adverse events, which could require expensive treatment and followup and could lead to treatment discontinuation.

HIV/AIDS Interventions

Collaborative Care Model for Comorbid HIV and Major Depressive Disorder

Major depressive disorder (MDD) is a psychiatric condition characterized by severe, persistent feelings of sadness and hopelessness that interfere with routine daily activities such as work, sleep, or study.¹⁶¹ MDD is the most common mental illness that patients with HIV experience, yet MDD is both underdiagnosed and undertreated in this patient population.^{162,163} Patients with comorbid MDD and HIV are likely to have accelerated HIV disease progression, decreased immune functioning, increased failure to adhere to HIV medication regimens, and increased risk of mortality. Because MDD is a modifiable risk factor for HIV progression, effective MDD treatment might improve self-management, adherence behaviors, and HIV outcomes.¹⁶³

Using a collaborative care model might facilitate collaboration between primary care and specialty mental health care providers to improve depression diagnosis, care, and treatment outcomes. The model could also allow patients to receive care in more accessible and less stigmatizing settings.¹⁶³ Collaborative care models have been successfully used in patients with depression (without comorbid HIV), depression and diabetes, and depression and cancer.

The intervention as implemented in the Veterans Affairs health care system (HIV Translating Initiatives for Depression into Effective Solutions [HITIDES]) involves using an HIV-specific depression care team consisting of a registered nurse depression care manager, a clinical pharmacist, and a psychiatrist. As part of the program, patients with HIV are screened for MDD at the HIV clinic during regular visits.¹⁶³ The care team convenes once weekly (or additionally as needed) and makes treatment suggestions to HIV treating and mental health clinicians via electronic medical record progress notes.^{163,164} The registered nurse depression care manager also communicates with patients via telephone on an ongoing basis (i.e., every 2 weeks, then monthly), delivering the following intervention components: participant education and activation, assessment of treatment barriers and possible resolutions, monitoring of depression symptoms and substance abuse, and instruction in self-management.^{163,164} At any time during the intervention, HIV health care providers are free to refer patients directly to specialty mental health care providers.¹⁶³

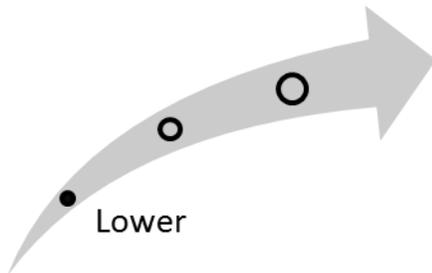
In an analysis of patients infected with HIV (n=249) and with MDD, patients were randomly assigned to the intervention (HITIDES; n=123) and to usual care (n=126).¹⁶³ Patients treated through the collaborative care model were more likely than patients treated with usual care to report treatment response (33.3% vs. 17.5%; odds ratio (OR), 2.50; 95% CI, 1.37 to 4.56) and remission (22.0% vs. 11.9%; OR, 2.25; 95% CI, 1.11 to 4.54) at 6 months but not 12 months. Patients treated through the collaborative care reported more depression-free days during the 12 months than patients treated with usual care (beta=19.3; 95% CI, 10.9 to 27.6; p<0.001). Patients treated through collaborative care had a significant reduction in HIV symptom severity at 6 months compared with patients treated with usual care (beta=-2.6; 95% CI, -3.5 to -1.8; p<0.001) and 12 months (beta=-0.82; 95% CI, -1.60 to -0.07; p = 0.03).¹⁶³

Current Approach to Care

According to the National Institute of Mental Health (NIMH), MDD should be treated as a separate illness for patients with HIV.¹⁶⁵ Common interventions for MDD include psychotherapy and prescription antidepressant medications (e.g., selective serotonin reuptake inhibitors), which NIMH declares generally well tolerated and safe for people with HIV.¹⁶⁵ NIMH notes that MDD treatment in the context of HIV should be managed by a mental health professional, especially when antidepressant pharmacotherapy is prescribed, so that drug interactions can be avoided.¹⁶⁵ A

collaborative care model is intended to facilitate this collaboration between mental health specialists and clinicians treating patients for HIV to improve depression- and HIV-treatment outcomes.¹⁶³

Figure 7. Overall high-impact potential: collaborative care model for comorbid HIV and major depressive disorder



Overall, experts commenting on this intervention thought a collaborative care model to treat MDD in patients with HIV might lead to improved diagnosis of MDD in more patients with HIV. Better management of MDD is expected to improve patient treatment adherence and health outcomes. Effective MDD treatment might also enable patients to gain a better understanding of their infection and how to better manage it. Establishing a collaborative care group might require additional staff, facilities, and information technology as well communication sessions that, in turn, might change care processes. Increased diagnosis of MDD is expected to increase demand for mental health services. Some experts stated that an onsite collaborative care model would be more likely to reduce barriers to care. Based on this input, our overall assessment is that this intervention is in the lower end of the high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, commented on this intervention.¹⁶⁶⁻¹⁷² Overall, the experts agreed that HIV and MDD are comorbid conditions with poor treatment outcomes that together can exacerbate both of these conditions and that using a collaborative care model can effectively manage both conditions simultaneously, improving treatment outcomes more than if the conditions were diagnosed and treated separately. Additionally, most of the experts agreed that combining mental health services with HIV care, which frequently affects underserved groups, might improve diagnosis rates and access to care. However, coordinating care between two separate sites was seen by two experts with research and clinical perspectives as potentially increasing disparities for patients with poor access to reliable transportation.

Establishing a collaborative care model for treating HIV and MDD could require additional staff, facilities, and information technology as well as communication sessions, and these requirements could change processes of care. By increasing MDD diagnosis rates, experts thought, mental health services would be in greater demand. Third-party payers would also have added costs brought about by the increased number of patients seeking mental health treatment. Some cost offset from the program might be achieved through better adherence to antiretroviral therapy and improved treatment outcomes. One expert with a clinical perspective stated that patients with depression frequently use additional medical resources; thus, effective treatment could reduce this demand in the longer-term.

Clinicians are expected to accept this model due to the minimal training required to implement the program and the potential to increase treatment adherence. While some experts thought many patients would be receptive to the program, they pointed out that some patients might be reluctant

because of concerns about the stigma of a depression diagnosis. More data will be needed to fully understand the benefits of this collaborative care model.

Emtricitabine/Tenofovir (Truvada) for Prevention of HIV Infection

An estimated 1.2 million people in the United States are living with HIV infection, and 20% of those individuals are unaware of their HIV status.¹⁷³ CDC estimates that as many as 50,000 people are newly infected with HIV in the United States annually; 61% and 23% of new infections occur in men who have sex with men (MSM) and women, respectively;¹⁷⁴ and women are twice as likely as men to be infected with HIV through heterosexual contact.¹⁷³ One estimate of the HIV transmission risk during receptive anal sex without a condom—the highest-risk sexual activity—indicates that it may be as high as 3% to 5% for each occurrence. The risk is estimated to be lower for receptive vaginal intercourse and even lower for oral sex, each in the absence of a latex barrier (condom or dental dam). Although no single sexual exposure carries a high risk of contagion, HIV infection can occur following the first sexual exposure; therefore, use of latex barriers during each sexual encounter is recommended.¹⁷⁵ Although behavior-change programs have resulted in dramatic reductions in HIV transmission in the United States, there remains no truly effective means to prevent HIV infection among populations at high risk for infection, including male prostitutes who have sex with men. Preexposure chemoprophylaxis (i.e., pretreating uninfected individuals at risk for HIV infection with antiretroviral therapies [ARTs]) is an emerging intervention for reducing HIV transmission.¹⁷⁶ Evidence has accumulated to support the theory that ART, taken regularly, can reduce the risk of HIV infection.¹⁷⁶⁻¹⁷⁹

Emtricitabine/tenofovir (Truvada[®], Gilead Sciences, Inc., Foster City, CA), which initially received FDA approval in 2004 for treating HIV, was recently approved to be part of a comprehensive strategy for preventing HIV in adults at high risk of infection.^{176,177} According to CDC, many researchers believe that the daily use of an antiviral drug such as emtricitabine/tenofovir is one of the most important new prophylactic measures under investigation for HIV to help decrease infection in individuals at high risk.¹⁷⁷ Emtricitabine/tenofovir is a once-daily, oral, combination ART consisting of two HIV nucleoside reverse transcriptase inhibitors also made by Gilead Sciences, emtricitabine 200 mg (Emtriva[®]) and tenofovir disoproxil fumarate 300 mg (Viread[®]).¹⁸⁰ Emtricitabine and tenofovir are also available separately in single-agent tablets. However, the combination of two nucleoside reverse transcriptase inhibitors in a single tablet taken once daily decreases patient pill burden and is believed to result in higher adherence to medication regimens among patients with HIV.¹⁸¹ Treatment adherence is thought to be essential for high efficacy.¹⁷⁶

Nucleoside reverse transcriptase inhibitors suppress replication of retroviruses by blocking the activity of HIV-1 reverse transcriptase.¹⁸⁰ This results in premature termination of viral DNA replication.

In the Preexposure Prophylaxis Initiative (iPrEx) trial, HIV-seronegative men or transgender women who have sex with men (n=2,449) were prophylactically given emtricitabine/tenofovir or placebo once daily. The prophylactic use of emtricitabine/tenofovir was shown to lead to a 44% reduction in the incidence of HIV (95% CI, 15 to 63; p=0.005).¹⁷⁶

In another trial, daily prophylactic use of emtricitabine/tenofovir failed to prevent HIV-1 infection in high-risk women. The study was stopped early due to lack of efficacy, which could have been due to low treatment adherence.¹⁸²

In a different trial of HIV-1-uninfected heterosexual men and women in Botswana who were 18–39 years of age (n=1,219), daily prophylactic use of emtricitabine/tenofovir reduced the risk of acquiring HIV infection by roughly 62% compared with placebo.¹⁸³

An additional analysis that excluded HIV infections that occurred more than 30 days after a participant's last reported drug dose was conducted because these individuals could not have been

taking study pills at the time of infection. In this analysis, emtricitabine/tenofovir reduced the risk of HIV infection by 78% compared with placebo.¹⁷⁸

In another trial examining HIV-1 serodiscordant heterosexual couples in Kenya and Uganda (n=4,758), patients who took daily prophylactic tenofovir or emtricitabine/tenofovir had an average 67% (p<0.001) and 75% (p<0.001) fewer HIV infections, respectively, than those who received placebo. There was no significant difference between the protective effects of tenofovir and emtricitabine/tenofovir (p=0.23).¹⁸⁴

Patients prescribed preexposure prophylaxis (PrEP) must be confirmed to be HIV-negative immediately before initial use and periodically during use to prevent the development of drug resistance. The manufacturer says that PrEP should not be initiated if signs or symptoms of acute HIV infection are present unless negative infection status is confirmed.¹⁸⁵

The most common adverse events associated with emtricitabine/tenofovir for PrEP include abdominal pain, headache, and weight loss.¹⁸⁵ Patients should be tested for hepatitis B virus before initiating PrEP, because severe acute exacerbations of hepatitis B have occurred in patients co-infected with HIV-1 and hepatitis B virus who have discontinued emtricitabine/tenofovir.¹⁸⁵ Patients taking PrEP should be evaluated for new onset or worsening renal impairment. Emtricitabine/tenofovir use has also been associated with decreased bone mineral density and body fat redistribution or accumulation.¹⁸⁵

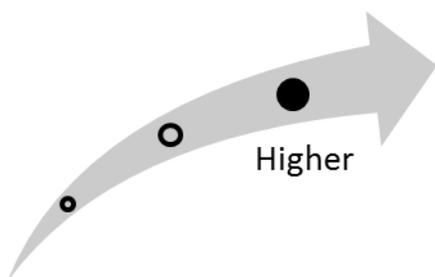
In December 2011, Gilead Sciences submitted a supplemental NDA to FDA for once-daily emtricitabine/tenofovir for PrEP to reduce the risk of HIV-1 infection among uninfected adults.¹⁷⁴ In February 2012, FDA granted the application priority review status and set a target decision date of June 15, 2012.¹⁸⁶ After extending the decision date to review the manufacturer's proposed Risk Evaluation and Mitigation Strategy,¹⁸⁷ FDA in July 2012 approved emtricitabine/tenofovir once-daily in combination with safer sex practices to reduce the risk of sexually acquired HIV-1 infection in adults at high risk.¹⁸⁸

The retail cost of a 30-day supply of emtricitabine/tenofovir is roughly \$1,100.¹⁸⁹ Our searches were unable to find any third-party payers with a coverage determination for PrEP. According to the manufacturer, patients with insurance who are prescribed emtricitabine/tenofovir for treating chronic HIV infection commonly have a \$10 copayment.¹⁹⁰

Clinical Pathway at Point of This Intervention

According to clinical practice guidelines, the most reliable way to avoid HIV transmission is to abstain from sexual contact or to be in a long-term, mutually monogamous relationship with an uninfected partner. For those entering a monogamous relationship, HIV screening before initiating sex may reduce the risk of future HIV transmission. Male latex condoms are also highly effective at preventing HIV-1 transmission. In people with latex allergy, nonlatex male condoms made of polyurethane or other synthetic material provide protection against HIV equal to that of latex condoms.¹⁹¹ Emtricitabine/tenofovir is a combination ART under clinical development for preventing HIV-1 transmission in patients at high risk for HIV infection.

Figure 8. Overall high-impact potential: emtricitabine/tenofovir (Truvada) for prevention of HIV infection



Overall, experts commenting on this intervention thought that prophylactic use of this drug has high potential to address an important unmet need as the first pharmacologic agent approved for reducing the risk of HIV-1 infection in high-risk patients. Currently, no preventive options are available other than abstinence and condom use, which are not employed by all individuals at high risk of infection. Experts thought that emtricitabine/tenofovir could have a large impact on health promotion by reducing the number of HIV-infected individuals. However, experts cited the early trials that have shown this intervention would not protect everyone who attempts the regimen. This, combined with high treatment costs and likely high out-of-pocket costs to patients for something that is not a disease (i.e., unprotected sex) and that can be prevented with behavior interventions, would be controversial as the role of prophylactic emtricitabine/tenofovir evolves. The experts stated that public-private partnerships will be essential for providing the medication, education, and followup necessary to effectively implement PrEP and improving health outcomes in all eligible patients. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, commented on this intervention.¹⁹²⁻¹⁹⁸ The experts stated that there remains a significant unmet need for effective measures to prevent HIV transmission in serodiscordant couples. Additionally, some individuals at high risk are not in a position to practice all safer sex measures during each sex act. Before approval of emtricitabine/tenofovir, no pharmacologic methods were available to reduce the risk of HIV infection, which represented a significant gap in HIV risk mitigation.

Overall, the experts were confident that PrEP could significantly reduce the risk of contracting HIV in patients at high risk, improving health outcomes. However, experts expressed some pessimism regarding the need for high treatment adherence for optimal protection.

Experts were divided on the ability of PrEP to reduce health disparities. Having an intervention such as PrEP allows patients at high risk who do not always follow all current risk mitigation strategies to have an additional safeguard for HIV prevention. However, experts suspect that many of the patients who could benefit most from PrEP are less likely to be able to afford the high cost of PrEP and are less likely to have the health insurance that could help to defray the costs of frequent followup, which are indicated for PrEP. Programs to address treatment cost and followup will be essential to reducing health disparities that could be caused by PrEP.

PrEP is expected to disrupt health care infrastructure and patient management by shifting HIV prevention to primary care physicians and obstetricians/gynecologists who are not familiar with prescribing PrEP, monitoring the side effects of emtricitabine/tenofovir, or performing HIV testing quarterly. Additionally, primary care physicians and obstetricians/gynecologists are not familiar

with educating their patients on HIV risk mitigation strategies, which could require some training. If PrEP is successful, less demand on staff and facilities to treat HIV infection could be realized.

Experts were divided regarding patient and clinician acceptance of PrEP. One clinical expert stated that primary care physicians rarely ask sex and sexuality questions of their patients, which would make it difficult to identify patients at high risk of infection. These physicians could also be reluctant to familiarize themselves with the protocols necessary to properly implement PrEP. The expert also stated that it has been documented that patients routinely underestimate their personal level of exposure risk, which would make them less likely to seek PrEP. Other barriers to patient acceptance include being stigmatized for seeking HIV therapy and inability to adhere to quarterly followup. Other experts thought clinicians could be reluctant to recommend PrEP because they think it could increase risky behavior, that it could cause side effects in otherwise healthy patients, or that their patients would be unable to afford it. Cost was also cited as a barrier to patient acceptance. However some experts stated that in the appropriate patient population, PrEP could be highly accepted by both patients and clinicians.

The experts stated that PrEP is a costly intervention. However, it could be cost saving in some populations. If found to be cost saving and if third-party payers cover PrEP in the future, some patients could still be reluctant to admit that they are at high risk for HIV infection, because this admission could increase their insurance premiums.

Overall, experts stated that PrEP with emtricitabine and tenofovir could fill a significant unmet need because it is the first approved pharmacotherapy intended to reduce the risk of acquiring HIV in patients at high risk of infection. Although the high cost of PrEP and the use a pharmaceutical to prevent a disease that can be addressed with behavior interventions makes the intervention controversial, the experts stated that this is a major step forward in the battle against HIV/AIDS. The experts stated that public-private partnerships will be essential to providing the medication, education, and followup necessary to effectively implement PrEP and in improving health outcomes in all eligible patients.

Routine Anal Pap Smear Screening at HIV Clinics to Prevent Anal Cancer

Patients with HIV have a higher risk of developing anal cancer, possibly due to impaired T-cell function, yet no national or international guidelines for anal dysplasia screening are available for this patient population.¹⁹⁹ The incidence of anal cancer in people infected with HIV increased from 19.0 per 100,000 person-years for the period 1992–1995 to 72.2 for the period 2000–2003. One cohort study showed that as many as 49% of HIV-infected MSM developed high-grade anal dysplasia within 4 years, compared with 17% of MSM not infected with HIV.¹⁹⁹ Before anal cancer develops, precancerous lesions can usually be detected and excised before they progress to anal cancer.²⁰⁰ Anal Papanicolaou (Pap) screening incorporated into routine visits for treatment and monitoring at HIV clinics for all patients, regardless of history of anal intercourse, might help reduce the incidence, morbidity, and mortality of anal cancer in patients with HIV.¹⁹⁹

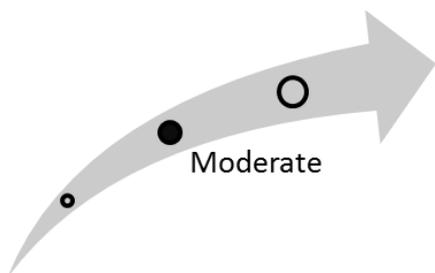
A pilot screening program for anal intraepithelial neoplasia in patients positive for HIV-1 attending the Miami Veterans Affairs HIV clinic was developed because for many patients with HIV-1, HIV clinics are the only place where they receive routine care, but these facilities do not have the infrastructure and processes in place to perform routine anal Pap screening in a patient population that is at increased risk for anal cancer.¹⁹⁹ Physicians and nurse practitioners are trained to perform specimen collection by watching a DVD.^{199,201} Specimen collection and cytology reading for an anal Pap smear are similar to those for a cervical Pap smear. Anal Pap smears are collected using the ThinPrep[®] system (Hologic, Inc., Bedford, MA).¹⁹⁹ Anal cytology is performed, and all samples are read by a pathologist.

In the pilot study, 82% of patients with HIV approached during routine clinic visit agreed to participate in the study requiring an anal Pap smear collection. Fifty-three percent of patients had abnormal cytology results, and among those undergoing high-resolution anoscopy with biopsy, 55% had high-grade anal intraepithelial neoplasia, including two cases of carcinoma in situ. According to investigators, anal cytology was well accepted, and incorporating it into HIV primary care practice is feasible.¹⁹⁹

Current Approach to Care

Anal cancer can be detected as part of a digital rectal examination, which is typically part of a routine pelvic exam for women and can occur during regular prostate screening for men older than 50 years of age. However, patients not in these populations may not receive routine screening for anal cancer. The American Cancer Society states that some experts recommend anal cytology (Pap) screening every 2–3 years in patients at high risk for abnormal anal cytology, including MSM (homosexual and bisexual men), women who have had cervical or vulvar cancer, patients with HIV, and organ transplant recipients. If an abnormality is discovered during screening, anal cancer can be diagnosed using various methods, including endoscopy, anoscopy, and rigid proctosigmoidoscopy, followed by biopsy and diagnostic imaging to determine the extent of disease progression. Anal cancer is usually treated with a combination of surgery, radiation, and chemotherapy.²⁰⁰ Patients with HIV frequently receive routine care only at HIV clinics. Some clinical investigators have proposed that patients attending HIV clinics for routine treatment and monitoring can be screened for anal cancer with anal Pap smears to reduce the incidence of anal cancer in this population.

Figure 9. Overall high-impact potential: routine anal Pap smear screening at HIV clinics to prevent anal cancer



Overall, experts commenting on this intervention noted a significant unmet need for earlier anal cancer detection in patients with HIV. The experts theorized that anal Pap screening is an effective tool to improve patient health outcomes, and screening in HIV clinics may be an effective way to implement standardized processes. Once educated about the importance of screening, patients are receptive to the procedure. However, more studies are needed to fully understand the role that anal Pap screening could have on treatment and survival outcomes in this patient population. Experts noted that a larger body of evidence that demonstrates a benefit for this approach would help to increase diffusion via clinician acceptance and reimbursement. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

Results and Discussion of Comments

Eight experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.²⁰²⁻²⁰⁹ Overall, the experts agreed that the burden of anal cancer in patients with HIV has increased and that a significant unmet need exists to detect these malignancies early to improve treatment outcomes. If these patients do not receive regular care in another setting, screening for anal cancer in HIV clinics could be appropriate. However, some of the experts thought that too little evidence exists to determine how effective anal Pap screening would be in reducing the burden of these cancers. Some disagreement arose regarding the impact of anal Pap screening at HIV clinics. Anal Pap smears are generally considered experimental and are not expected to be covered by third-party payers. However, because many patients with HIV have poor access to care, performing low-cost routine anal cancer screening, regardless of third-party payment, might improve access to care in a population at increased risk of developing anal cancer.

If further studies show anal Pap screening to significantly improve survival, experts thought, it could shift health care delivery infrastructure and management from chemotherapy, radiation, and surgery more frequently to early detection of precancer and excision, with improved outcomes. Additionally, staff would need to be trained on obtaining and handling specimens and counseling patients with abnormal anal Pap results, although the program is intended to cause only minor disruptions in management and infrastructure at the level of the HIV clinic.

If shown to significantly improve survival in patients with HIV, experts thought, anal Pap screening would likely be accepted by clinicians; however, some resistance may arise because many other comorbidities exist that clinicians must be aware of when treating patients with HIV. Thus, anal Pap screening may seem like “one more thing” clinicians must be concerned with, taking time and resources. Additional barriers to physician acceptance could include lack of consensus regarding the role of anal Pap screening for anal cancer detection and lack of reimbursement. However, a clinical expert stated that the New York State Department of Health AIDS Institute recommends annual screening in MSM who have HIV. Patients are expected to be generally receptive to anal Pap screening if it is recommended by a physician. Patients are also expected to be

more willing to be screened for anal cancer if they are aware they are at elevated risk. The experts stated that anal Pap screening is a low-cost screening method that could be cost saving to the health system.

Overall, experts stated, a significant unmet need remains for earlier anal cancer detection in patients with HIV. The experts theorize that anal Pap screening could be an effective screening tool to improve patient health outcomes and that screening in HIV clinics may be an effective way to implement standardized processes. However, more studies are needed to fully understand the role that anal Pap screening has on treatment and survival outcomes in this patient population. A greater body of evidence would help increase diffusion via clinician acceptance and procedure reimbursement.

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