AHRQ Healthcare Horizon Scanning System – Potential High Impact Interventions Report

Priority Area 09: Infectious Disease including HIV/AIDS

Potential High Impact Interventions

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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. HHSA29020100006C). 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 closer to diffusion into practice in the United States. Drafts of 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 those interventions that experts deem, 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 six 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 the horizon scanning, assessing the leads for topics, or provide opinions regarding potential impact of interventions.

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

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor target technologies and innovations in health care and to create an inventory of target technologies 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 the analysis of 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 utilization 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 e-mail to effectivehealthcare@ahrq.hhs.gov.

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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 identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 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, more than 7,000 leads about topics have resulted in identification and tracking of more than 900 topics across the 14 AHRQ priority areas.

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 to 4 years of potential diffusion (e.g., in phase III trials for pharmaceuticals or biotechnologies or in phase II or a trial with some preliminary efficacy data on the target population for devices and programs) 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 a profile on topics and issuing topic profile 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 (COI). 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 high impact potential designation. 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 potential 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 11 topics for which (1) preliminary phase III data on drugs, phase II data on devices and procedures were available, or programs were in pilot phase; (2) information was compiled by November 2011 in this priority area; *and* (3) we received six to eight sets of comments from experts between February 2011 and November 1, 2011. (A total of 88 topics in this priority area were being tracked in the system as of November 2011.) For purposes of the Potential High Impact Interventions Report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). The material on interventions in this Executive Summary and report is organized according alphabetically by disease state. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary. We present eight summaries of nine topics (indicated below with an asterisk) that emerged as potential high impact on the basis of experts' comments and their assessment of potential impact.

Priority Area 09: Infectious Disease Including HIV/AIDS
1. Bioabsorbable gentamicin surgical implant (CollaRx) to prevent postsurgical infection
2. *Collaborative care model for treatment of HIV and comorbid depression
3. *Copper surfaces in the ICU for prevention of hospital acquired infections
4. *Emtricitabine/tenofovir (Truvada) for prevention of HIV infection
5. *Fecal microbiota transplantation to treat recurrent *C. difficile* infection
6. *Fidaxomicin (Dificid) for treatment of *Clostridium difficile* infection
7. *NS3/4A protease inhibitor (boceprevir [Victrelis]) for treatment of chronic hepatitis C infection
8. *NS3/4A protease inhibitor (telaprevir [Incivek]) for treatment of chronic hepatitis C infection
9. Peramivir for treatment of influenza
10. *Routine anal Pap smear screening at HIV clinics to prevent anal cancer
11. *Xpert MTB/RIF test for simultaneous detection and drug sensitivity testing of *M. tuberculosis*

Discussion

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 U.S. According to the U.S. Centers for Disease Control and Prevention (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 U.S. are also chronically infected with HCV. 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 care is an initial regimen of pegylated-interferon alpha-2a (Pegasys®, Hoffmann-La Roche Inc., Basel Switzerland) and ribavirin (Copegus®, Hoffmann-La Roche), a combination known as IFN-RBV. However, about 60% of patients in whom HCV is diagnosed who undergo and complete the IFN-RBV treatment for 48 weeks do not achieve a viral cure. Additionally, less than 10% of people whose cases are diagnosed and who attempt therapy actually complete it, leaving them at risk for relapse. This is because of the long course of therapy, poor cure rates, and poor quality of life during therapy.

Thus, intensive research has been ongoing with dozens of drugs 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.

NS3/4A Protease Inhibitors for Treatment of HCV 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 with coinfections to 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). Unfortunately, side effects reported with the new protease inhibitors might affect full patient compliance.

  In therapy with IFN-RBV and telaprevir, severe rashes that respond poorly to steroids have occurred; 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, are essential to minimize emergence of drug-resistant strains.

IFN-RBV as part of a regimen seems to mitigate development of resistance, so it is expected to remain a mainstay of treatment in the near term along with its side effects.

Many companies have been developing strategies to eliminate IFN 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 that 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 IFN-free regimen to become available, due to 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 IFN-free regimen with improved efficacy, 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 higher than 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.

- **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 anemia, which would require its own 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 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 a crucial pillar 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 comorbidities that accompany chronic infection. Three interventions for management of HIV infection have been identified for this report as having high potential impact. One is for prevention of HIV infection, the other two for managing comorbidities associated with infection.

Collaborative Care Model for Comorbid HIV and Major Depressive Disorder

- **Key Facts**: Major depressive disorder (MDD) and HIV frequently coexist in HIV-infected patients. MDD is the most common mental illness that patients with HIV 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 leading to disease progression and even increased mortality. According to the U.S. 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 treatment for MDD 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 registered nurse depression care manager (DCM), a clinical pharmacist, and a psychiatrist can be formed with protocols in place to facilitate communication and appropriate treatment for the patient. 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 DCM also communicates with patients via telephone on an ongoing basis to deliver participant education and activation, assessment of treatment barriers and possible resolutions, monitor depression symptoms, treatment and substance abuse, and provide 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 diagnosed 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 a12-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.

- **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 expressed the view that better management of MDD is expected to lead to improved treatment adherence and improve 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 the need for additional staff, facilities, and information technology as well communication sessions that might change care processes. In addition, increased diagnosis of MDD is expected to increase demand for mental health services. However, experts noted that in many health care settings, there is little financial motivation for facilities to implement collaborative care for HIV and MDD, and they thought that the intervention will likely need significant grant funding for widespread diffusion.
- **Potential for High Impact**: Lower range of high impact

Truvada Combination Therapy for Prophylaxis in Population at High Risk of HIV

- **Key Facts**: Earlier this year, Truvada® (emtricitabine/tenofovir, Gilead Sciences, Inc., Foster City, CA), in phase III development for HIV, 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 men who have sex with men (MSM; homosexual and bisexual men) who took emtricitabine/tenofovir once daily were 44% less likely to become infected with HIV-1 than MSM given placebo. However, recently, researchers reported evidence 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 might spark some 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 has 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.

- **Key Expert Comments**: Overall, experts commenting on this topic thought that prophylactic use of this drug has a high potential to address an import unmet need in preventing 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 big 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 for something that is not a disease (i.e., unprotected sex) and that can be prevented with behavioral interventions, would be controversial as the role of prophylactic emtricitabine/tenofovir evolves.
- **Potential for High Impact**: High

Anal Pap Screening in HIV Clinics

- **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 persons 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.

  Screening and early treatment for colorectal cancer is crucial because patients treated surgically for localized colorectal cancer have a long-term survival of 91%, compared with patients diagnosed with advanced colon cancer, who have a 5-year survival rate of approximately 11% and must be treated with costly therapies such as adjuvant chemotherapy and monoclonal antibodies. 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 and among those undergoing high-resolution anoscopy with biopsy, 55% of patients had high-grade anal intraepithelial neoplasia, including 2 cases of carcinoma in situ.

- **Key Expert Comments**: Overall, experts stated there remains a significant unmet need for earlier anal cancer detection in patients with HIV. The experts theorize that anal Pap screening is an effective tool to improve patient health outcomes, and 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

Healthcare-Acquired and Bacterial Infections

Expert comments identified four interventions as having potential for high impact: Fitting intensive care unit (ICU) equipment and surfaces with antimicrobial copper to reduce hospital-acquired infections, two treatments for recurrent *Clostridium difficile* infection (CDI), and a rapid test to determine if a patient has a drug-resistant form of tuberculosis (TB).

Copper Surfaces in the ICU for Prevention of Hospital-Acquired Infections

- **Key Facts**: Approximately 2 million healthcare-acquired infections (HAIs) are documented in the U.S. annually and result in 100,000 deaths. According to CDC, more people are killed by HAIs than automobile accidents, fires, and drowning combined. Additionally, CDC has estimated that HAIs add $47 billion to U.S. health care costs, which represents an increase of an estimated 208% to each hospital bill. On average, HAIs are estimated to add 19.2 hospitals days totaling $43,000 to each patient who contracts a HAI. 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 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 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, New York, NY) touch surfaces can be incorporated into a wide variety of components including bed rails, food trays and carts, handrails, IV poles, sinks, faucets, shower and lavatory components, work surfaces, door handles, grab bars, computer keyboards, equipment adjustment knobs, and face plates. The antimicrobial properties of copper are purported to remain effective for the lifetime of the product; these surfaces continuously reduce bacterial contamination, achieving 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. Then 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 lead to a significant reduction in the microbial burden found on surfaces in the ICU as well as reduction in infection rates in patients staying in copper-fitted rooms.

- **Key Expert Comments**: Overall, experts commenting on this intervention stated that antimicrobial copper touch surfaces may 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 be cost-saving. Except for a one-time disruption in patient management, antimicrobial copper is not expected to alter hospital operations. Although antimicrobial copper may reduce the presence of pathogens on their surfaces, 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 was not transmitted from a caregiver's hand or contaminated fomites.
- **Potential for High Impact**: High

Fecal Microbiota Therapy for Recurrent *Clostridium difficile* Infection

- **Key Facts**: More than 300,000 hospitalizations in the U.S. are complicated each year by *C. difficile* infections (CDIs), with costs estimated to be from $431 million to $3 billion annually. Chronic relapsing CDIs are increasingly common and are challenging to treat effectively; about 20% of patients have a recurrence. Although vancomycin or metronidazole is commonly used after a second CDI recurrence, when vancomycin therapy is stopped, up to 60% of these patients develop further recurrence, which suggests that other therapeutic options are needed.

  Colonoscopic fecal microbiota therapy, 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. During the colonoscopic procedure, healthy donors submit fresh stool on the day of the procedure, which is mixed with saline into a solution and tested for pathogens, including hepatitis A, B, and C; syphilis; and HIV (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. Once prepared and tested, the fecal-saline solution is introduced into the intestines by a gastroenterologist 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. Other fecal microbiota therapy procedures have also been reported using enemas and nasogastric tubes. In an analysis of more than 77 patients with recurrent CDI from 5 treatment centers across the country, the procedure has been shown to be 91% effective. 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. Patients undergoing the procedure also appear unlikely to have a recurrence unless they take a course of antibiotics following the procedure. The procedure is being implemented in a limited number of research and gastrointestinal specialty centers. This medical procedure can be readily adopted by clinicians and is not currently subject to regulation by the U.S. Food and Drug Administration (FDA) because the material is prepared within the institution. Currently, only one registered phase III trial is under way to assess the therapy in patients with recurrent CDIs who will be treated with either oral vancomycin followed by fecal transplantation or a 6-week taper of oral vancomycin. This trial is expected to be completed in December 2013.

  Specific cost information on the procedure is scarce, because it has been performed infrequently by a limited number of clinicians at a small number of centers. 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.

- **Key Expert Comments**: Overall, experts concluded that results from the small number of fecal microbiota therapy studies completed thus far are very promising. However, experts were eager to see larger studies to better determine the role of fecal bacteriotherapy in clinical practice. Experts noted that several societal barriers to acceptance of the procedure could prevent 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 CDIs. Additionally, although recurrent CDI is quite difficult to treat, many early cases are effectively treated by changing antibiotics, so experts thought this procedure would likely be a second-line therapy used only after other treatments fail.
- **Potential for High Impact**: High

Fidaxomicin for Treatment of Recurrent *Clostridium difficile* Infection

- **Key Facts**: Fidaxomicin (Dificid™, Optimer Pharmaceuticals, Inc., San Diego, CA) is a narrow-spectrum oral macrolide taken twice daily that is purported to be poorly absorbed by the body, allowing the intervention to exert its activity in the gastrointestinal tract. However, because fidaxomicin is purported to be highly selective for *C. difficile*, the antibiotic is purported to leave the normal intestinal flora intact. In clinical trials, fidaxomicin has been shown to have similar cure rates to vancomycin, but lower rates of recurrence, persistent diarrhea, and death after the course of therapy. In June 2011, FDA approved fidaxomicin for treatment of *C. difficile*-associated diarrhea. A 10-day course of therapy costs about $2,800, which is about twice the cost of vancomycin.
- **Key Expert Comments**: The experts commenting on this topic stated that recurrent CDI can be prolonged and costly, with high morbidity and mortality. The lack of new medications for the treatment of CDI has created an unmet need for an agent that can treat and minimize recurrent infections. Although fidaxomicin is more expensive than vancomycin, experts expect the antibiotic to be cost saving because of the prevention of CDI recurrence. The diffusion of fidaxomicin as a first-line treatment might depend largely on whether patients have prescription drug coverage and formulary status of the drug on the patient's drug plan.
- **Potential for High Impact**: High

Rapid Test for Treatment-Resistant TB

- **Key Facts**: According to the World Health Organization, *Mycobacterium tuberculosis* infection is highly underdiagnosed because of current TB testing methods that require weeks to deliver a definitive result. During that time, patients are left untreated or may be placed on ineffective therapies, thereby continuing to spread TB, creating a significant public health concern. In the U.S., TB prevalence has resurged since 1985, attributed mostly to the increase in HIV infection and development of drug-resistant TB organisms. In 2009, the TB rate in the U.S. was 3.8 cases per 100,000 individuals, a slight decrease from 2008. The States of California, Florida, New York, and Texas accounted for half of all new TB cases in 2009. Thus, the need for effective, rapid diagnostics and new treatments to address resistant strains 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 the presence of *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 U.S. as a research-use-only reagent; U.S. marketing approval of a test kit is expected by 2012 or 2013.

- **Key Expert Comments**: Overall, experts thought that the Xpert MTB/RIF test could potentially be a rapid, sensitive, and specific diagnostic test with potential to address the unmet need for more rapid diagnosis and better initial management 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. However, one limitation of the Xpert MTB/RIF test is that it tests only for resistance to rifampin, which is a common first-line antibacterial agent. Susceptibility to other agents would still have 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 for smaller health care facilities, such as rural or public access clinics, which may have problems with followup.
- **Potential for High Impact**: Moderately high

Hepatitis C Virus Infection Intervention

Intervention

NS3/4A protease inhibitors (boceprevir and telaprevir) 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, approximately 60% of people who undergo treatment with the current standard of care, an initial regimen of IFN-RBV for 48 weeks, do not achieve a sustained virologic response (SVR) or viral cure, leaving them at risk for future liver disease. Because of recent advances allowing researchers to screen HCV drugs more effectively in vitro, there has been an explosion of HCV drug therapies 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.[1] 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 the ability of HCV to evade the host's innate immune response to the virus, further demonstrating the importance of NS3/4A as a target for HCV therapy.[1] Inhibition of NS3/4A results in production of immature, noninfectious HCV virions, leading to SVR.[2,3]

Boceprevir

Boceprevir (Victrelis™, Merck & Co., Inc., Whitehouse Station, NJ) is orally administered, and in May 2011 it was granted marketing approval from the U.S. Food and Drug Administration (FDA) for the treatment of chronic HCV genotype 1 infection in combination with IFN-RBV, which is a combination of pegylated-interferon alpha-2a (Pegasys®, Hoffmann-La Roche Inc., Basel Switzerland) and ribavirin (Copegus®, Hoffmann-La Roche).[4] Boceprevir was the first new drug approved for the treatment of HCV in 20 years. It has been used in clinical trials at a dosage of 800 mg three times per day, although doses may vary.[5]

In one of several phase III, clinical trials, treatment-naive patients with chronic HCV-1 (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 IFN-RBV for 24 or 48 weeks) or 48 weeks of placebo with IFN-RBV.[6] 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.[6] In a second phase III trial, treatment-experienced patients (n = 404) with chronic HCV-1 whose infection persisted despite prior treatment with IFN-RBV were given boceprevir in combination with IFN-RBV or placebo in combination with IFN-RBV.[7] In the boceprevir group, 66% of patients achieved SVR at 48 weeks compared with 21% of patients in the control group.[7]

Boceprevir 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 $,1100 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.

Telaprevir

Telaprevir (Incivek™, Vertex Pharmaceuticals, Inc., Cambridge, MA) is orally administered, and it received marketing approval in May 2011 from FDA for the treatment of chronic HCV genotype 1 infection in combination with IFN-RBV.[8] Telaprevir has been administered at 750 mg every 8 hours in clinical trials and is currently being evaluated for 1,125 mg twice-daily dosing.[9]

In a phase III clinical trial, treatment-naive patients infected with HCV genotype 1 (n = 1,088) were given telaprevir in one of two dose regimens in combination with IFN-RBV or placebo.[10] After receiving a 12-week telaprevir-based combination regimen followed by treatment with IFN-RBV alone, 75% of patients treated achieved an SVR at 24 weeks post-treatment. After receiving an 8-week telaprevir-based combination regimen, followed by treatment with IFN-RBV alone, 69% of patients achieved an SVR. In the control arm, 44% of patients achieved an SVR after 48 weeks of treatment with IFN-RBV.[10] In a second phase III clinical trial, treatment-experienced patients with genotype-1 HCV who had failed to achieve a SVR with prior IFN-RBV therapy (n = 663) were treated with telaprevir or placebo in combination with IFN-RBV.[11] At 24 weeks, 65% of patients with HCV infection treated with telaprevir achieved an SVR compared with 17% in the control group.[11] Telaprevir is also in phase II trials as part of a combination therapy with VX-222 (Vertex Pharmaceuticals), a nonnucleoside HCV NS5B polymerase inhibitor, plus IFN-RBV.[12] Interim data have shown undetectable HCV in 90% of patients at week 12.[12]

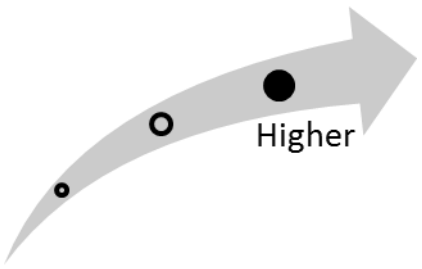
Currently, nine other HCV protease inhibitors are being tracked in the horizon scanning system that have not yet reported phase III data. These interventions will continue to be monitored for at least 2 years from the point of diffusion of boceprevir and telaprevir to determine if the drugs in development offer any benefit or risk that differs from those already approved in this class.

The therapy, when added to current IFN-RBV, is expected to double the cost of treatment. 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. The company introduced two tiers of payment assistance for patients with (Co-pay Assistance Program) and those without insurance or whose insurance does not cover telaprevir (Patient Assestance Program).

Clinical Pathway at Point of This Intervention

Patients who test positive for anti-HCV antibodies and HCV RNA may be considered to have acute or chronic HCV infection, depending on the context. Additionally, a patient negative for anti-HCV antibodies and positive for HCV RNA might be chronically infected if immunosuppressed.[13] Subsequent HCV genotype testing is performed to determine the therapy regimen and the likelihood of a positive clinical outcome.[13] Rest and hydration are typically prescribed. The treating clinician may also prescribe IFN-RBV. Boceprevir has recently been indicated for combination therapy with IFN-RBV for chronic HCV genotype 1 infection.

Figure 1. Overall High Impact Potential: NS3/4A protease inhibitors



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 anemia, which would require its own expensive treatment and followup. As the first class of new therapies for HCV-infection treatment in 20 years and the first class of direct-acting antivirals for this condition, NS3/4A inhibitors were expected by experts commenting on these drugs to have a higher potential impact on health care. 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

For these topics, a total of 15 sets of comments from experts were received: seven comment forms were received from experts on telaprevir, and eight comment forms from experts on boceprevir.[14-28] Experts offered perspectives from clinical, research, health systems, and health administration backgrounds.

Overall, these experts agreed that current treatment with IFN-RBV was 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 theoretically 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 treatment regimen for the first-approved drug in this class included IFN-RBV as a combination therapy, and it has been used adjunctively in most of the clinical trials. Experts who generally interpreted HCV protease inhibitors as add-on therapies also did not think these treatments would significantly shift treatment or management models.

However, some dissenting experts thought that the use of protease inhibitors could shorten the duration of therapy and reduce long-term complications such as cirrhosis and liver failure, which would have an impact on treatment and management paradigms, as well as reduce demands on staffing and infrastructure where patients with HCV are treated.

As an adjunctive therapy, HCV protease inhibitors were expected to have a large impact on costs. 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 cirrhosis and liver failure associated with IFN-RBV. Many patients and clinicians are eager to begin treatment with protease inhibitors. However, many of the experts saw high cost as a barrier to patient and clinician acceptance. One clinical expert was also quite concerned with the high incidence of anemia and need for erythropoietin in as many as 40% of patients in one clinical trial. This expert thought that the protease inhibitor with the highest efficacy and lowest anemia will gain the most acceptance and become the market leader.

HIV Interventions

Intervention

Collaborative care model for treatment of HIV and comorbid depression

Severe depression, or 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.[29] MDD and HIV are highly comorbid. MDD is the most common mental illness that patients with HIV experience, yet MDD is both underdiagnosed and undertreated in this patient population.[30,31] 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.[31] Because MDD is a modifiable risk factor, effective MDD treatment might improve self-management, adherence behaviors and HIV outcomes.[31]

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 may also allow patients to receive care in more accessible and less stigmatizing settings.[31] Collaborative care models have been successfully used in patients with depression (without HIV comorbid), 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, or HITIDES) involves the use of an HIV-specific depression care team, consisting of a registered nurse depression care manager (DCM), a clinical pharmacist, and a psychiatrist.[31] As part of the program, patients with HIV are screened for MDD at the HIV clinic, during their regular visits.[31] 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.[31,32] The DCM also communicates with patients via telephone on an ongoing basis (i.e., every two 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.[31,32] At any time during the intervention, HIV health care providers are free to refer patients directly to specialty mental-health care providers.[31]

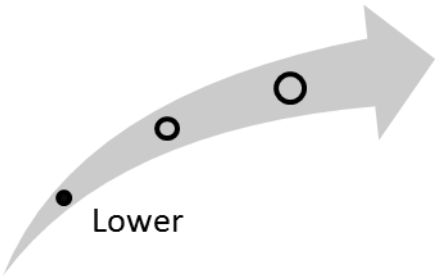
In an analysis of patients infected with HIV (n = 249) and diagnosed with depression, patients were randomly assigned to the intervention (HITIDES; n = 123) and to usual care (n = 126).[31] Patients treated with the collaborative care model were more likely than patients treated with usual care to report treatment response (33.3% vs. 17.5%; odds ratio, 2.50; 95% confidence interval [CI], 1.37 to 4.56) and remission (22.0% vs 11.9%; 2.25; 95% CI 1.11 to 4.54) at 6 months but not 12 months. Patients treated with 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 with collaborative care had a significant reduction in HIV symptom severity at 6 months compared with usual care (beta = -2.6; 95% CI, -3.5 to -1.8; $p < 0.001$) and 12 months (beta = -0.82; 95% CI, -1.6 to -0.07; $p = 0.03$).[31]

Current approach to care

According to the U.S. National Institute of Mental Health (NIMH), MDD should be treated as a separate illness for patients with HIV.[33] 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.[33] NIMH notes that treatment for MDD 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.[33] Use of 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.[31]

Figure 2. Overall High Impact Potential: Collaborative care model for HIV and Depression



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 lead to improved treatment adherence and improve health outcomes. Patients might also gain a better understanding of their infection and how to better manage it. Establishing a collaborative care group might result in the need for additional staff, facilities, and information technology as well communication sessions which may change process. Increased diagnosis of MDD is expected to increase demand for mental health services. Commenters thought that there would be little financial motivation for health care facilities to implement collaborative care for HIV and MDD and that the intervention would likely need significant grant funding in many areas for widespread diffusion. 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.[34-40] Overall, the experts agreed that HIV and MDD are comorbid conditions that both have poor treatment outcomes which can feed off each other to exacerbate both of these conditions. The use of a collaborative care model that can effectively manage both conditions simultaneously might improve treatment outcomes better than if the conditions were diagnosed and treated separately. In addition, most of the reviewers agreed that combining mental health services with HIV care, which frequently affects underserved groups, might improve diagnosis rates and access to care.

Establishing a collaborative care model for the treatment of HIV and MDD may result in the need for additional staff, facilities, and information technology as well communication sessions, which might change process. By increasing diagnosis rates of MDD experts thought, that there would be greater demand for mental health services. One expert representing a clinical perspective stated that implementing a collaborative care model could be costly without significant grant funding in many areas. Another clinical expert stated that although the cost of the services may be covered by third party payers, the cost of coordinating the program must be absorbed by the health care facility. Third-party payers will also have added costs brought about by increases in the number of patients seeking mental health treatment. There may be some cost offset from the program by having better adherence to antiretroviral therapy.

Overall, experts thought that a collaborative care model to treat MDD in patients with HIV might lead to increased diagnosis and management of MDD in patients with HIV. Better management of MDD is expected to improve treatment adherence and thus health outcomes. Patients would also gain a better understanding of their infection and how to better manage it. However, funding constraints in many health care settings may inhibit widespread adoption of this program and more data will be needed to fully understand the benefits of this collaborative care model.

Intervention

Emtricitabine/tenofovir (Truvada) for prevention of HIV infection

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. Pre-exposure chemoprophylaxis (i.e., pretreating uninfected individuals at risk for HIV infection with antiretroviral therapies [ARTs]) is emerging as a potential mechanism for reducing HIV transmission.[41] Evidence is mounting to suggest that ART, taken regularly, may prove effective in reducing risk of HIV infection.[41,42]

Emtricitabine/tenofovir (Truvada®, Gilead Sciences, Inc., Foster City, CA), which is approved for treatment of HIV, is currently being evaluated for the prevention of HIV in adults.[41-43] According to the U.S. Centers for Disease Control and Prevention (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 and could help decrease HIV infection in high-risk individuals.[42] Emtricitabine/tenofovir is a once-daily oral combination ART consisting of two HIV nucleoside reverse transcriptase inhibitors (NRTIs), emtricitabine 200 mg (Emtriva®, Gilead Sciences, Inc., Foster City, CA) and tenofovir disoproxil fumarate 300 mg (Viread®, Gilead Sciences).[44] NRTIs suppress replication of retroviruses by blocking the activity of HIV-1 reverse transcriptase.[43] 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% confidence interval, 15 to 63; $p = 0.005$).[41]

In an additional clinical 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. The results prompted a warning to doctors from CDC because there have already been reports of women using the drug off-label for HIV prevention.[45]

In an additional trial of HIV-1 uninfected heterosexual men and women in Botswana 18 to 39 years of age (n = 1,219), daily prophylactic use of tenofovir/emtricitabine reduced the risk of acquiring HIV infection by roughly 63% compared with placebo.

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 tenofovir/emtricitabine reduced the risk of HIV infection by 78% compared with placebo.[46]

In a another trial examining HIV-1 serodiscordant heterosexual couples in Kenya and Uganda (n = 4,758), patients who took daily prophylactic tenofovir or tenofovir/emtricitabine had an average 62% ($p = 0.0003$) and 73% ($p < 0.0001$) fewer HIV infections than those who received placebo.[47]

According to new clinical guidelines, long-term users of emtricitabine/tenofovir should be monitored for potential side effects.[48] Decline in renal function and proteinuria may be related to long-term use of emtricitabine/tenofovir, especially in African Americans.[48] Also, the long-term use has been associated with a decline in bone density, which is attributed to emtricitabine.[48]

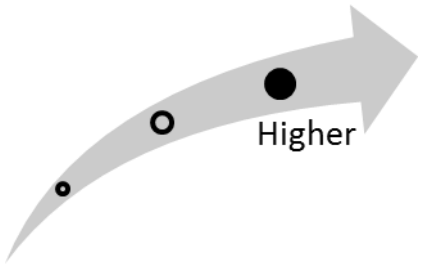
FDA approved emtricitabine/tenofovir (Truvada) in 2004 for use in combination with other antiretroviral agents for the treatment of patients with HIV-1 infection.[44] It is currently being tested in large-scale clinical trials in the U.S. and abroad for prevention of HIV in persons at high risk of infection.[43] It may be used off-label for HIV prophylaxis in patients at high risk for infection.

In June 2011, a letter from the AIDS Healthcare Foundation, signed by 55 physicians, was sent to FDA urging the regulatory body not to approve emtricitabine/tenofovir for HIV-1 pre-exposure prophylaxis before all data from ongoing clinical trials is analyzed.[49] The letter cited lack of efficacy in the iPrEx trial, lack of "real-world" adherence data, and potential "risk compensation" where patients may behave in ways more risky than they would without the drug.[49] However the letter supported an individual physician's choice to prescribe the drug for his or her patients off-label, and thus the ability to use the drug off-label should keep the FDA from feeling pressured to approve the drug prematurely.[49]

Clinical Pathway at Point of This Intervention

According to clinical practice guidelines, the most reliable way to avoid transmission of HIV is abstinence from sexual contact or to be in a long-term, mutually monogamous relationship with an uninfected partner.[50] For those entering a monogamous relationship, screening for HIV before initiating sex may reduce the risk of future transmission of HIV. Male latex condoms are also highly effective at preventing HIV-1 transmission.[50] 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.[50] Emtricitabine/tenofovir is a combination ART under clinical development for the prevention of HIV-1 transmission in men who have sex with men.

Figure 3. 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 a high potential to address an import unmet need in preventing 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 high-risk individuals. 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 behavioral interventions, would be controversial as the role of prophylactic emtricitabine/tenofovir evolves. 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.[51-56,57] Some of the comment forms from experts on this topic were received before the announcement that emtricitabine/tenofovir failed to protect women at high risk from contracting HIV-1.

All experts concurred there was a significant unmet need for new interventions to prevent HIV-1 transmission among high-risk individuals. Experts agreed that the underlying theory of prophylactic emtricitabine/tenofovir is sound, because the therapy has already been shown to be highly effective in controlling HIV-1 replication in infected individuals. In general, the experts were somewhat confident that daily emtricitabine/tenofovir use could significantly improve health outcomes. However, one expert with a health systems perspective expressed concern that getting a high-risk individual to take

any medication daily for any reason would be a challenge. It was also suggested that a 44% efficacy rate might be evidence of the drug's potential to offer only short-term efficacy.

Experts disagreed somewhat about whether emtricitabine/tenofovir would increase understanding of HIV, its treatment, management, and care models. Some experts thought that no change would come because some viewed this prophylactic treatment as not a far step from postexposure prophylaxis. Other experts thought that prophylactic emtricitabine/tenofovir use would shift care models from treatment to prevention of HIV-1. Physicians would need to know who needs to be prescribed prophylactic ART and may need additional training to properly implement this drug for prevention. One expert with a health systems perspective thought that this would involve a learning curve for physicians. One clinical expert stated that if physicians now have to determine who is at high risk for HIV-1 infection, it might increase the time needed for each patient visit. Experts also noted that prophylactic ART might reduce demands on the health care system by reducing the number of patients chronically infected with HIV-1. One expert with an independent research perspective stated that healthy individuals would now be considered "patients" and would have to be monitored for treatment side effects. One clinical expert stated that there could be a need to create a venue to treat the condition "unsafe sex." Two clinical experts also stated that through prophylactic use of ART we could learn more about what the side effects of the drugs are versus actual HIV-1 pathology.

There was some disagreement among the experts regarding the impact of emtricitabine/tenofovir on costs. Two experts with research backgrounds stated that the costs would be high but offset in part because of a reduced number of patients who would need to be treated. Another expert representing a health systems perspective stated that the costs of preventing HIV-1 infection could be half the lifetime costs of treating HIV-1 infection. Another expert representing a health systems perspective was alarmed by the high per-person cost of prophylactic ART therapy relative to condoms, potentially posing a strong impediment to acceptance or adherence to the regimen.

Cost considerations aside, prophylactic use of ART would be met with strong enthusiasm from many patients and clinicians, experts thought; however, other barriers to acceptance may include the frequency of adverse events and the need for faithful adherence to the treatment regimen for maximum efficacy. One expert with a health systems perspective stated that there will always be physicians who support only lifestyle modification for diseases such as HIV-1. An expert with a research perspective stated that regulatory approval would be needed for many physicians to fully accept this intervention, which could be hampered by early reports of inefficacy in women. This expert also stated that prophylactic use of the drug might spark controversy because of the debate about efficacy in women, and because some patients might engage in riskier behavior because they feel safer after using the drug. Another clinical expert stated that use of an expensive medication because of a failure of behavioral interventions may be highly controversial.

Intervention

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.[58] Screening and early treatment for colorectal cancer (CRC) is crucial. Patients treated surgically for localized CRC have a long-term survival of 91%, compared with patients diagnosed with advanced colon cancer (the tumor has penetrated beyond the bowel wall and there is evidence of metastasis to distant organs), who have a 5-year survival rate of approximately 11% and must be treated with costly therapies such as adjuvant chemotherapy and monoclonal antibodies.[59,60] 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.

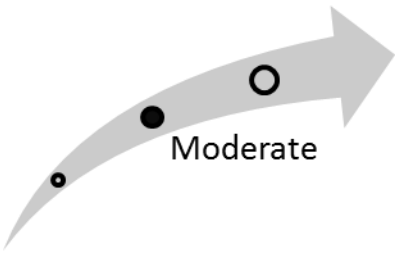
A pilot screening program for anal intraepithelial neoplasia in HIV-1 positive patients attending the Miami Veteran's Affairs HIV clinic was developed because for many patients with HIV-1, HIV clinics are the only place where they receive routine care, and these facilities currently do not have the infrastructure and processes in place to perform routine anal Pap screening in a patient population that is at increased risk for anal cancer.[58] Physicians and nurse practitioners are trained to perform specimen collection; training can be achieved by watching a DVD.[58,61] Specimen collection and cytology reading for an anal Pap smear is similar to that for a cervical Pap smear. Anal Pap smears are collected using the ThinPrep® system (Hologic, Inc., Bedford, MA).[58] Anal cytology is performed, and all samples are read by a pathologist.

In the mentioned pilot study, 82% of HIV-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 and among those undergoing high-resolution anoscopy with biopsy, 55% had high-grade anal intraepithelial neoplasia, including 2 cases of carcinoma in situ. According to the investigators, anal cytology was well accepted and incorporating it into HIV primary care practice is feasible.[58]

Current approach to care

Anal cancer falls under the overall category of CRC. No specific anal cancer screening guidelines currently exist for patients with HIV-1, although this population is at increased risk for anal cancer.[58] The American Cancer Society recommends that individuals at average to high risk undergo CRC screening beginning at 50 years of age, using colonoscopy and having polyps removed if they are detected.[62] Patients can also be screened using fecal occult blood tests as early as 40 years of age.[63] Patients who present with CRC in a routine exam or an exam prompted by common symptoms are confirmed with either barium enema radiography or colonoscopy.[64] Localized CRC can be treated definitively with surgical resection.[64] Patients with HIV frequently receive routine care only at HIV clinics. Patients attending HIV clinics for routine treatment and monitoring can be screened for CRC with anal Pap smears to reduce the incidence of advanced CRC.

Figure 4. Overall High Impact Potential: Routine anal Pap smear screening at HIV clinics



Overall experts commenting on this intervention stated there remains a significant unmet need for earlier anal cancer detection in patients with HIV. The experts theorize 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 on 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. Once a greater body of evidence is obtained, it will 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

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.[65-71] Overall, the reviewers agreed the burden of anal cancer in patients with HIV is increased, and there is a significant unmet need 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 felt there was not enough evidence to know how effective anal Pap screening would be in reducing the burden of these cancers and how the cost savings would compare to that of cervical cancer prevention. There was some disagreement 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 HIV patients have poor access to care, 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 have to be trained on obtaining and handling specimens and counseling patients with abnormal anal Pap results, and processes would have to be put into place to set alerts every 2 to 3 years that screening is needed.

If shown to significantly improve survival in patients with HIV, experts thought anal Pap screening would likely to be accepted by clinicians, however, there may be some resistance because there are many other comorbidities that clinicians must be aware of when treating patients with HIV and thus anal Pap screening may seem like "one more thing" clinicians must be concerned with, which takes time and resources. One expert representing a health systems perspective stated that barriers to physician acceptance would include lack of high-resolution anoscopy equipment for followup, lack of consensus regarding the role of anal pap screening for anal cancer detection, and lack of reimbursement. However, this expert also stated that the New York State Department of Health AIDS Institute currently recommends annual screening in HIV-positive men who have sex with men. Based on the data available, when patients are aware of their increased risk of anal cancer they become receptive to screening. Anal Pap screening is expected to cost approximately $45 to $60 per test, which may be affordable for patients with no insurance; some costs will be incurred by HIV clinics to implement training for testing. In some studies, anal cancer rates have been higher than some historical cervical cancer rates, which suggests the screening in this population would be cost-saving to the health care system over time.

Overall, experts stated, there remains a significant unmet need 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 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 would have on treatment and survival outcomes in this patient population. A greater body of evidence would help to increase diffusion via clinician acceptance and procedure reimbursement.

Hospital-Acquired and Bacterial Infection Interventions

Intervention

Copper surfaces in the ICU for prevention of hospital-acquired infections

Hospital-acquired infections (HAIs) are the fourth leading cause of death in the United States after heart disease, stroke, and cancer.[72] According to estimates by the International Copper Association, about 80% of infectious diseases are transferred by touch.[73] Despite common infection-control practices, including hand-washing and frequent surface disinfection, the number of HAIs each year continues to rise.[73] On average, each patient who contracts a HAI is estimated to add 19.2 hospitals days to their stay, totaling $43,000; patients have a 1-in-4 chance of mortality if the infection was contracted in the ICU.[72] Hospital surfaces in patient rooms, including the intensive care unit (ICU), typically consist of stainless steel and plastics that possess no antibacterial properties and serve as fomites for disease transmission between disinfection procedures in many health care settings.[74] In some cases, these surfaces can be colonized with live microbes for days or weeks, providing a source of contamination to the hands and equipment of health care workers, professionals, visitors, and patients.[74] The intrinsic antimicrobial properties of copper and copper alloys (brasses and bronzes) for touch surfaces on hospital hardware and equipment may add another safeguard against disease transmission between cleanings.[74]

Antimicrobial Copper (International Copper Association, New York, NY) touch surfaces can be incorporated into a wide variety of components including bed rails, food trays and carts, handrails, IV poles, sinks, faucets, shower and lavatory components, work surfaces, door handles, grab bars, computer keyboards, equipment adjustment knobs, and face plates.[74] The antimicrobial properties of copper are purported to remain effective for the lifetime of the product, and they do not rely on coatings or impregnated surfaces, which may wear away or wash away, limiting their lifetime of service.[74] 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.[75] Antimicrobial copper consists of copper alloys such as brass and bronze, copper nickels, and copper-nickel-zincs[72,76] These alloys are intended by manufacturers to have strength, comparable to stainless steel. Copper alloys are purported to be durable; natural tarnishing does not impair efficacy of the surface, and copper touch surfaces have been deemed to not be harmful to people or the environment.[72,77]

Copper surfaces are purported by the manufacturer 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. Then antimicrobial copper ions are purported to penetrate compromised cells and alter cell metabolism by interacting with numerous enzymes crucial for normal metabolic activity.[78] The use of antimicrobial copper is intended to be a supplement to and not a substitute for standard infection control practices, and users are advised to continue to follow all current infection control practices.[75] Antimicrobial copper is commercially available in certain hospital settings, such as on door knobs and door push plates. There are currently 13 companies positioning to manufacture products containing the Antimicrobial Copper mark.[79]

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.[75] Although the manufacturer association makes no claims of efficacy against other organisms, the literature has shown that the copper might also be effective against other viruses, bacterial, and fungal pathogens.[74,80] There are more than 350 antimicrobial copper alloys, such as brass and bronze, that are EPA-registered public health antimicrobial products available to address various practical and aesthetic demands.[81]

The additional cost of manufacturing a copper sink for a hospital room is estimated at $40 to $60 each, which might be considered marginal considering the cost for a hospital sink, which is currently approximately $7,500.[82] Additionally, copper rails are expected to add approximately $100 to the cost of a standard $30,000 hospital bed.[82] 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 to 1.5 years after implementation.[82]

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 a significant reduction (40.4%) in the number of infections reported in patients treated in copper-fitted rooms.[82,83]

In another analysis, copperized (Cu) objects (n = 282) in 32 ICU rooms and non-Cu objects (n = 288) in 27 ICU rooms were sampled to examine the ability of antimicrobial copper to lower the microbial burden (MRSA and/or 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. Copper significantly reduced the total mean microbial burden of 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 (bed rails [99%, p = 0.0003], chair arms [38%, p = 0.11], call buttons [90%, p = 0.003], and IV poles [67%, p = 0.11]. 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 the investigators, MRSA and VRE were frequently isolated from non-Cu objects, but were not isolated from Cu objects.[84]

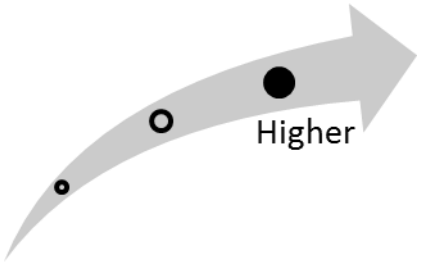
In another study, the ability of copper trays and arms on phlebotomy chairs to reduce mean microbial burden compared with standard materials was examined.[85] "Microbial burden was decreased on phlebotomy chairs fitted with copper trays and arms. No such reduction was found on standard chairs. The antimicrobial 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."[85]

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. All but one item sampled had a statistically significant reduction in microbial burden.[86]

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.[87]

Figure 5. Overall High Impact Potential: Antimicrobial copper surfaces in the ICU for prevention of HAI's



Overall, experts commenting on this intervention stated that antimicrobial copper touch surfaces might 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 be cost-saving. Except for a one-time disruption in patient management, antimicrobial copper is not expected to alter hospital operations. Although antimicrobial copper may reduce the presence of pathogens on their surfaces, it may not cause as great a decline in infection rates as expected if an HAI is contracted from bacteria already colonizing the patient's body and thus is not transmitted from a caregiver's hand or contaminated fomites, experts noted. 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

Eight experts, with clinical, research, and health systems backgrounds, offered comments on this intervention.[88-95] Overall, the experts agreed that HAIs lead to significant morbidity, mortality, and costs in health care facilities. There remains a significant unmet need to reduce these infections because current infection control practices and education have not lowered these rates adequately in many cases.

Overall, the experts stated, copper surfaces might be able to address the unmet need by reducing the frequency of HAIs. One expert representing a clinical perspective stated that copper touch surfaces might improve health disparities if implemented in settings such as schools, prisons, courts, nursing homes, public bathrooms, buses, and subways. However, one expert representing a clinical perspective stated the evidence base is too small to say with certainty copper surfaces will be effective, and an expert representing a research perspective stated concern that some pathogenic microbes may find a niche on copper surfaces or gain resistance. Additionally, one expert representing a clinical perspective stated that many HAIs are caused by bacteria colonizing the patients themselves and these infections cannot be prevented by any measure taken by health care personnel.

The experts stated that implementation of copper touch surfaces in ICUs would create only a minimal one-time disruption in infrastructure and patient management when some rooms would be closed to install sinks, or while patients are moved to another bed to retrofit a bed with copper rails. Installation of new door handles would not even require moving a patient. The experts suspect that 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 currently complex and burdensome problem in health care. The reviewers also stated that although a onetime capital investment for new copper fixtures (which are slightly more expensive than current fixtures) is required, they are likely to be cost-saving in with a year or two, because extended ICU visits can be among the most expensive occurrences in health care.

Overall, the experts 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 is required to retrofit frequently touched surfaces, the intervention is expected to quickly be cost-saving. However, both clinical experts cautioned that there are some people in the infectious disease community who believe patients serve as a significant reservoir for their own infections, such

as MRSA, and *Enterococcus* bacteria can be readily isolated from many patients without an active infection. Thus copper touch surfaces are expected to have some impact of the rate of HAIs, but the impact may not be as significant as would be expected if most HAIs were transmitted by contact with fomites. Additionally, the possibility of the bacterial resistance to copper should not be overlooked: some bacteria have gained resistance to heavy metals such as lead, cadmium, and silver.

Intervention

Fecal microbiota therapy for recurrent *Clostridium difficile* infection

In 2006, an estimated 300,000 hospitalizations in the U.S. were complicated by *Clostridium difficile* infections (CDIs), with estimated costs of $431 million to $3 billion annually.[96] 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.[97] Patients infected with *C. difficile* typically have watery diarrhea, fever, loss of appetite, nausea, and abdominal pain/tenderness.[97] Chronic and relapsing CDIs are increasingly common and a challenge to treat effectively; about 20% of patients have a recurrence.[98] Although vancomycin or metronidazole 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.[99]

Colonoscopic fecal bacteriotherapy, 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.[99] For the colonoscopic fecal bacteriotherapy procedure, healthy donors submit fresh stool on the day of the procedure, and it is mixed with saline into a solution and tested for pathogens, including hepatitis A, B, and C; syphilis; and HIV (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. Prospective donors are excluded if they recently used antibiotics or had a bout of diarrhea. Once the fecal-saline solution is prepared and tested, it is introduced into the right cecum in the intestine by a gastroenterologist using a colonoscope, and the rest is introduced distally as the colonoscope is withdrawn. Approximately 300 to 500 mL are in infused into the patient; the dose varies by patient weight. Typically, this procedure is required only once in a patient.[98] Other fecal transplantation procedures have also been reported using enemas and nasogastric tubes.[100]

In the largest analysis to date, fecal bacteriotherapy was 91% effective in patients (n = 77) with recurrent CDI from 5 treatment centers across the U.S. 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 prior to therapy was 11 months and the mean number of courses of antibiotic therapy was five prior to treatment. Patients treated with fecal bacteriotherapy had a mean time to resolution of diarrhea of 6 days. During long-term followup, only patients who were treated later with antibiotics (n = 8) had a CDI recurrence. Two of these patients were successfully treated again with fecal bacteriotherapy. In addition, 53% of patients in this study would prefer fecal bacteriotherapy as their first-line treatment.[101]

In an earlier clinical trial, patients (n = 12) with a mean CDI duration of 16.8 months were treated with colonoscopic fecal bacteriotherapy. No patients treated with fecal bacteriotherapy had a documented recurrence of CDI at a mean followup of 7.4 months, and 10 patients remained symptom free. Two patients had diarrhea after the procedure, but both were *C. difficile* negative. One of these patients responded to treatment with a fiber supplement, and the other patient resumed vancomycin.[99] In another earlier trial, 13 patients presenting with recurrent CDI were also treated with colonoscopic fecal bacteriotherapy. Patients with recurring CDI had experienced a mean of four prior episodes over a mean of 11.5 months. Twelve of 13 patients experienced resolution of diarrhea. One patient persisted with diarrhea and stool positive for *C. difficile* toxin (CDT). Stool for CDT was negative in 10 of 10 patients tested 30 or more days after transplantation. Patient followup of a mean of 5 months was reported. One patient relapsed at 7 months after therapy. Two patients required antibiotics during followup, with no diarrhea recurring.[102]

In another trial, prospective data were collected from three different centers performing the procedure on 37 patients with recurring CDI.[103] Patients received one or two fecal bacteriotherapy treatments. Ninety-two percent (range 75% to 100%) of patients were cured. Two relapsed 5 to 12 months after receiving subsequent antibiotic treatment and were successfully retreated with fecal bacteriotherapy. One noncured patient died after 1 month due to toxic megacolon. He had refused the suggested operative treatment before the fecal bacteriotherapy.[103]

In a retrospective study of 12 consecutive patients (nine women and three men, mean age 66 years) with refractory/recurrent CDI who were symptomatically ill for a mean of 351 days before colonoscopic fecal bacteriotherapy, 100% experienced an immediate and durable clinical response to fecal transplantation. No adverse events were reported from fecal transplantation.[104]

Fecal bacteriotherapy is being implemented in a limited number of research and gastrointestinal specialty centers. This medical procedure can be readily adopted by clinicians and is not currently subject to U.S. Food and Drug Administration regulation because the material is prepared within the institution.

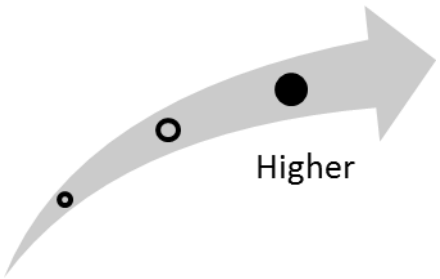
Currently, one registered phase III trial[105] is under way to assess colonoscopic fecal bacteriotherapy in patients with recurrent CDI who will be treated with either oral vancomycin followed by fecal transplantation or a 6-week taper of oral vancomycin. This trial is expected to be completed in December 2013.

Specific cost information on the procedure is scarce, because it has been performed infrequently by a limited number of clinicians at a small number of centers. 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.

Clinical Pathway at Point of This Intervention

According to the U.S. Centers for Disease Control and Prevention, once CDI is confirmed in patients, they are taken off the antibiotic that created the environment for the infection to occur, and in some patients (20%, within 2 to 3 days) the infection may resolve without further treatment. If it does not, the patient may be treated with either oral metronidazole or vancomycin for 10 days.[106] Fecal transplantation is intended to treat recurrent CDI.

Figure 6. Overall High Impact Potential: Fecal transplantation to treat recurrent *C. difficile* infection



Overall, experts concluded that results from the fecal transplantation studies completed thus far are very promising. They thought that the procedure has significant potential to address the unmet need by providing a low-cost, effective option to treat recurrent CDI, prevent antibacterial resistance, reduce the probability of CDI transmission, and lower CDI-associated mortality. However, experts were eager to see larger studies to better determine the role of fecal bacteriotherapy in clinical practice. Experts noted that several societal barriers to acceptance of the procedure may prevent 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. Additionally, although recurrent CDI is quite difficult to treat, many early cases are effectively treated by changing antibiotics, so experts thought this procedure would likely be a second-line therapy used only after other treatments fail. Experts thought that bacteriotherapy 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 unconventional and controversial nature of the procedure 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.[107-113] All 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. There was a general consensus among the experts that fecal transplantation has the potential to address the unmet need for effective treatment for recurrent CDI without the use of antibiotics, which could lead to a significant impact on health outcomes and quality of life. In general, the experts accepted the underlying theory of fecal transplantation and were somewhat certain that this intervention could be highly effective, although larger trials will be needed to bear this out.

Experts thought that fecal bacteriotherapy would affect the understanding of CDI and would be added to the current treatment model. However, experts representing a clinical perspective thought that fecal bacteriotherapy could greatly complicate the care model and process because of the colonoscopic method and associated laboratory work. Additionally, one of the experts mentioned that health care facilities may theoretically have the staffing and equipment needed to perform the procedure but are not prepared to confidentially tell a donor that he or she is unable to donate because he or she is carrying a type of disease that would prevent donation. However, processes are in place for other donated biologic tissue and matter to convey such information, and those procedures could be applied here.

Experts generally viewed the procedure as cost neutral or cost saving. The likelihood of patient and physician acceptance was questioned, and the procedure was viewed as likely to be controversial. The few data available, however, suggest high efficacy and safety thus far, so if larger studies confirm these data, the procedure would likely gain stronger acceptance. 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. The novelty of the procedure may gain acceptance by some physicians, while others would turn away from it for fear of liability due to disease transmission. There will also be patients with a barrier to acceptance due to psychological factors or religious beliefs that will not be overcome. One expert representing a clinical perspective thought that even a different name for the procedure might be needed to increase acceptance.

Intervention

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*.[114] Fidaxomicin inhibits RNA polymerase, a bacterial enzyme, resulting in the death of the bacteria.[115] Fidaxomicin is purported to be poorly absorbed by the body, allowing the intervention to exert its activity in the gastrointestinal tract.[114] In addition, fidaxomicin purported to be highly selective to *C. difficile*, allowing it to leave the normal intestinal flora intact.[116]

A combined analysis of two randomized controlled trials with identical protocols comparing oral fidaxomicin (200 mg twice daily) to oral vancomycin (125 mg four times daily) for 10 days in adults with acute CDI symptoms and a positive stool toxin test (n = 1,105) demonstrated that cure rates with fidaxomicin and vancomycin were 91.9% and 90.2% respectively. CDI recurrence rates were significantly lower in patients treated with fidaxomicin (13.0%) compared with vancomycin (24.6%; p <0.001). Global cure rates were 78.6% and 66.4%, respectively (p <0.001). Adverse events were similar in both trials and not different among the treatments.[117]

In another analysis, patients (n = 128) with one prior CDI episode and recurrence within 3 months were treated with oral fidaxomicin (200 mg twice daily) or vancomycin (125 mg four times daily) for 10 days. Following treatment, 19.7% of patients receiving fidaxomicin experienced another recurrence compared with 35.5% of patients receiving vancomycin (p =0.045), a 45% reduction in repeat recurrent events when patients were treated fidaxomicin.[118]

In a combined analysis of two phase III, blinded studies, adults with active CDI were randomly assigned to receive fidaxomicin (200 mg twice daily) or vancomycin (125 mg four times a day) for 10 days. Fidaxomicin was noninferior for clinical cure and superior for reducing CDI recurrence compared with vancomycin. In an ITT analysis of the combined data of patients (n = 1,164) showed fidaxomicin reduced persistent diarrhea, recurrence, or death by 40% (p <0.0001) compared with vancomycin overall through day 40. Investigators stated, "A 37% (P = 0.037) reduction in persistent diarrhea or death was evident through day 12 (heterogeneity p = 0.50 vs 13-40 days), driven by 7 (1.2%) fidaxomicin vs 17 (2.9%) vancomycin deaths through 12 days (exact p = 0.06)." Low albumin and eosinophil counts and the use of metronidazole/vancomycin before randomization were risk factors for persistent diarrhea/death through 12 days, and CDI in the previous 3 months was a risk factor for relapse (all p <0.01).[119]

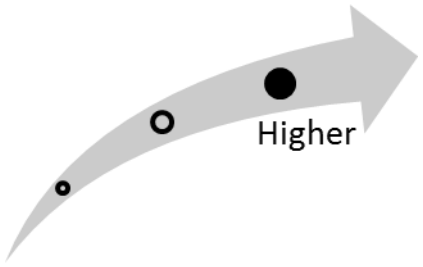
In June 2011, FDA approved fidaxomicin for treatment of *C. difficile*-associated diarrhea (CDAD).[120] It is taken twice daily for 10 days. Optimer Pharmaceuticals announced a 2-year agreement with Cubist Pharmaceuticals, Inc. (Lexington, MA), to copromote fidaxomicin to be sold as Dificid in the domestic market.[121] For the manufacture and supply of fidaxomicin, Optimer entered into an agreement with Biocon (Bangalore, India) in 2010.[115] The cost of a 10-day course of treatment is $2,800, which is estimated to be about twice the cost of vancomycin.

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 (Flagyl®, Pfizer, Inc., New York, NY), though this is only given for the initial episode because of neurotoxicity concerns. For more severe CDI, vancomycin (Vancocin®, ViroPharma Inc., Exton, PA), currently the only FDA-approved antibiotic for the treatment of CDI, is the standard treatment, either alone or in combination with

metronidazole.[122] Fidaxomicin offers an alternative treatment for CDI, with the possibility of less recurrence than with vancomycin.

Figure 7. Overall High Impact Potential: Fidaxomicin for treatment of *C. difficile* infection



Experts noted that CDI can be prolonged and costly, with high morbidity and mortality in patients with recurrent infection, which responds poorly to antibiotic therapy. Experts thought that the lack of new medications for effective treatment of recurrent CDI would make a new option that reduces recurrence rates welcomed by patients and clinicians. In addition, experts had some concern that treating patients with vancomycin for CDI might make them more likely to develop vancomycin-resistant enterococcus infections. Fidaxomicin could be used to ease some of those concerns, experts believed, because it has been shown to have comparable efficacy to vancomycin with fewer recurrences, 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 associated with the prevention of CDI recurrence. However the diffusion of fidaxomicin as a first-line treatment may depend largely on formulary status at third-party payers. 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 perspectives on this intervention.[123-129] The experts agreed that CDI can be prolonged and costly, with high morbidity and mortality in patients with recurrent infection, which responds poorly to antibiotic therapy. One expert representing a clinical perspective stated that there has been a lack of new medications for the treatment of recurrent CDI. Additionally, there is a need for improved tolerability of treatment for CDI. One clinical expert also stated that there is concern about using vancomycin to treat CDI because of the possibility that patients may develop vancomycin-resistant enterococcus infections. Based on current evidence, fidaxomicin might have comparable efficacy to vancomycin with fewer recurrences which could improve quality of life for many patients.

Fidaxomicin was not expected by the experts to cause a significant dislocation in health care delivery infrastructure or patient management, because one antibiotic will replace another. However, they thought that changes could include less demand on inpatient treatment facilities and staff because of a reduction in recurrent infections. Reduced demand on outpatient facilities and staff might also be observed because of shorter durations of infection. All of the experts agreed that although fidaxomicin is twice as expensive as vancomycin, the costs of the antibiotic are expected to be offset by a reduced frequency of recurrent infections, which would save significant costs.

Overall, fidaxomicin has the potential to address a significant unmet need by improving treatment outcomes in patients with CDI and more importantly lowering recurrence rates which are associated with the poorest outcomes. The experts were optimistic regarding the role of fidaxomicin as a first-line therapy to reduce CDI recurrence rates, and fidaxomicin could even gain support from patient advocacy groups. However the diffusion of fidaxomicin as a first-line treatment might depend largely on formulary status with third-party payers.

Intervention

Xpert MTB/RIF test for simultaneous detection and drug sensitivity testing of Mycobacterium tuberculosis

According to the World Health Organization, tuberculosis infection (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 left 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.[130]

The *Mycobacterium 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.[130] The test simultaneously detects the presence of *M. tuberculosis* complex species and determines whether the identified bacterium is susceptible to rifampicin.[131] 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 that is essential for TB viability.[130] The antibiotic activity of the first-line TB drug rifampicin targets the subunit encoded by the *rpoB* gene to inhibit the RNA polymerase, inhibiting bacterial survival.[130] 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.[132]

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.[131] 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.[131]

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.[130,131] 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.[130,131] The automated nature of the procedure and the fact that the procedure 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.[131] The assay is intended to yield results for both the presence of *M. tuberculosis* and antibiotic resistance for positive samples in about 2 hours.[130]

In an international clinical trial, three sputum samples were collected from patients suspected of having TB or drug-resistant TB (n = 1,730).[133] Samples were analyzed by a combination of acid-fast smear, solid culture, liquid culture, and Xpert MTB/RIF tests.[133] 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%).[133] Additionally, among 609 culture-negative patients, the Xpert MTB/RIF test correctly identified 604 patients as negative for TB infection (99.2%).[133] 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%).[133]

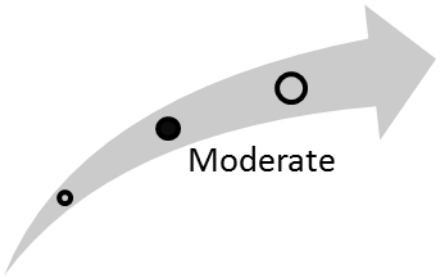
Cepheid has obtained a Conformité Européene (CE) mark for use of the test in Europe.[134] The test is also currently available in the U.S. as a research-use-only reagent; however, U.S. marketing

approval as a diagnostic test is not expected until 2012 or 2013.[135,136] A clinical trial of the Xpert MTB/RIF assay is ongoing in Cape Town, South Africa, enrolling 1,700 patients suspected of having TB or drug-resistant TB.[137]

Clinical Pathway at Point of This Intervention

A patient initially presents with symptoms that indicate a possible case of pulmonary TB based on the patient's medical history, physical examination, symptoms, TB infection test results (e.g., tuberculin skin test, QuantiFERON-TB Gold test), and/or chest x-ray results.[138,139] 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.[138] The Xpert MTB/RIF test would be used in place of current nucleic acid amplification tests. In addition to 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.[130,138]

Figure 8. Overall High Impact Potential: Xpert MTB/RIF test for detection and drug sensitivity testing of *M. Tuberculosis*



Overall, experts thought that the Xpert MTB/RIF test has potential to be a rapid, sensitive and specific diagnostic that might address the unmet need for more rapid diagnosis and better initial management of TB. If it does show efficacy, they thought, it has potential to improve patient health outcomes and reduce 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, experts noted that one limitation of the Xpert MTB/RIF test is that it tests for resistance only to rifampin, which is a common first-line antibacterial agent. Susceptibility to other agents would still have to be guided by traditional testing methods, experts noted. Nevertheless, the Xpert MTB/RIF test could replace other PCR methods of detection and provide an improved approach to diagnosis and treatment for smaller health care facilities, such as rural or public access clinics, which might have problems with followup. 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.[140-146] Overall, 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, particularly when dealing with immunosuppressed individuals. Experts agreed that the underlying theory of the test is sound and that it does not differ significantly from current molecular methods, other than the faster turnaround time. All but one expert thought the time saved in diagnosis using the Xpert MTB/RIF test could improve patient health outcomes. The remaining expert had a research perspective and was more skeptical of the test's potential.

In general, the experts though the Xpert MTB/RIF test would not make 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 transmission. One expert representing a clinical perspective stated that the most important aspect in diagnosing TB is still clinical suspicion of TB.

With regard to impact on patient management and care setting, the availability of the Xpert MTB/RIF test would allow smaller offices to do their own testing, which could lead to decentralization of testing, some experts thought. A greater availability of testing centers might also improve access to care and potentially reduce health disparities and promote health by avoiding transmission of the infection. 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. The per-patient test cost might be higher than for current methods but would not be prohibitive (about $50 per test). Faster turnaround time and high predictive values directing rapid treatment are expected to be readily accepted by patients and clinicians with little controversy.

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