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

Priority Area 09: Infectious Disease Including HIV/AIDS

Prepared for:
Agency for Healthcare Research and Quality
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Contract No. HHSA290201000006C

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June 2013

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. HHSA290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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

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

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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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Suggested citation: ECRI Institute. AHRQ Healthcare Horizon Scanning System Potential High-Impact Interventions: Priority Area 09: Infectious Disease Including HIV/AIDS. (Prepared by ECRI Institute under Contract No. HHSA290201000006C.) Rockville, MD: Agency for Healthcare Research and Quality. June 2013. http://www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

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

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

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

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identifying new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 4 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 16,000 leads about potential topics has resulted in identification and tracking of about 1,800 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 600 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice annually. Topics eligible for inclusion are those interventions expected to be within 0–4 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

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

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

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

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

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

Results

The table below lists the 10 topics for which (1) preliminary phase III data on drugs, phase II or III data on devices and procedures were available, or programs were being piloted; (2) information was compiled before May 16, 2013, in this priority area; and (3) we received five to nine sets of comments from experts between October 25, 2011, and May 18, 2013. (A total of 49 topics in this priority area was being tracked in the system as of May 18, 2013.) For this report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). We present eight summaries of eight topics (indicated below with an asterisk) that emerged as having higher impact potential on the basis of experts' comments and their assessment of potential impact. The material on interventions in this Executive Summary and report is organized alphabetically by disease state and then by intervention. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Priority Area 09: Infectious Disease Including HIV/AIDS

Topic	High-Impact Potential
1. *Antimicrobial copper surfaces in the intensive care unit for prevention of hospital-acquired infections	High
2. Bedaquiline (TMC207) for treatment of multidrug-resistant tuberculosis	No high-impact potential at this time
3. *Collaborative care model for comorbid HIV and major depressive disorder	Lower end of the high-impact-potential range
4. *Emtricitabine/tenofovir (Truvada) for prevention of HIV infection	High
5. *Fecal microbiota transplantation for treatment of recurrent *Clostridium difficile* infection	High
6. *OraQuick in-home rapid test for detection of HIV infection	Moderately high
7. *Routine anal Pap smear screening at HIV clinics to prevent anal cancer	Moderately high
8. *Sofosbuvir (GS-7977) for treatment of chronic hepatitis C infection	High
9. *Xpert MTB/RIF Test for simultaneous detection and drug-sensitivity testing of *Mycobacterium tuberculosis*	Moderately high
10. xTAG gastrointestinal pathogen panel for detecting gastroenteritis	No high-impact potential at this time

Discussion

Health Care–Acquired and Bacterial Infections

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

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

- **Key Facts**: About 2 million health care–acquired infections (HAIs) are documented in the United States annually and result in 100,000 deaths. The U.S. Centers for Disease Control and Prevention (CDC) has estimated that HAIs add $28 billion to $45 billion in costs to the U.S. health care system annually. On average, HAIs add an estimated 19.2 hospital days per patient contracting an HAI at a per-patient cost of $43,000. Patients contracting an HAI have a 1-in-20 chance of dying in the hospital and a 1-in-4 chance of dying if the infection was contracted in the ICU. About 80% of infectious diseases are transferred by touch, according to estimates by the International Copper Association, and despite common infection-control practices (hand-washing and frequent surface disinfection) the number of HAIs each year continues to rise. 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.

  The intrinsic antimicrobial properties of copper and copper alloys (brasses and bronzes) for touch surfaces on hospital hardware and equipment might add another safeguard against disease transmission between cleanings. Antimicrobial Copper (International Copper Association, Ltd., New York, NY) touch surfaces can be incorporated into a wide variety of components, including bedrails, handrails, door handles, grab bars, IV poles, food trays and carts, sinks, faucets, shower and lavatory components, work surfaces, computer keyboards, equipment adjustment knobs, and face plates. Copper's antimicrobial properties purportedly remain effective for the product's lifetime. These surfaces purportedly continuously reduce bacterial contamination and achieve a 99.9% reduction of gram-negative and gram-positive bacteria within 2 hours of exposure. As many as 479 alloys, such as brass and bronze, have been registered to be antimicrobial, providing options to fit various clinical and aesthetic demands. Copper surfaces purportedly exert their antibacterial activity in two sequential steps: (1) disruption of the integrity of bacterial cell membranes through oxidation and disruption of physiologic functions such as electrostatic potential and (2) antimicrobial copper ion penetration of compromised cells to 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. Published studies have shown that antimicrobial copper surfaces have reduced the microbial burden found on surfaces in the ICU and may lead to lower infection rates in patients staying in copper-fitted rooms. In one randomized controlled trial, patients (n=650) presenting for admission to three ICUs in the United States were randomly placed in rooms fitted with six copper alloy surfaces or standard surfaces. Patients admitted to copper rooms had a significant reduction in HAI or colonization with methicillin-resistant *Staphylococcus aureus* or vancomycin-

resistant enterococci infections compared with such infections in patients placed in standard rooms.

In July 2012, the Agency for Healthcare Research and Quality awarded a $2.5 million interdisciplinary research collaboration to the University of California, Los Angeles, to conduct a 4-year, randomized study to determine whether reducing surface bacteria through use of copper surfaces decreases HAI rates, improves treatment outcomes, and reduces costs. The study will evaluate copper, plastic, or sham stainless steel surfaces to better understand their role as fomites.

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

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

- **Key Facts**: In 2010, an estimated 500,000 individuals experienced *Clostridium difficile* infections (CDIs) in the United States, estimated to cost at least $1 billion annually. Recurrent CDI is increasingly common and challenging to treat effectively. About 15% to 30% of patients have a recurrence after treatment with metronidazole (Flagyl®) or vancomycin (Vancocin®). Vancomycin is commonly used after a second CDI recurrence, but when vancomycin therapy is stopped, up to 65% of patients develop recurrence, and other therapeutic options are needed.

  Fecal microbiota transplantation (FMT) from a healthy donor is intended to recolonize a patient's intestinal flora with beneficial bacteria that will "crowd out" or otherwise make the environment in the bowel unfavorable for *C. difficile* colonization. Shortly before the procedure, which can be delivered by any of several methods (e.g., colonoscopy, nasogastric tube, enema), healthy donors who have completed screening for other diseases (e.g., syphilis, HIV, hepatitis A, B, and C) submit fresh stool, which is mixed with saline into a solution and administered to the patient. Typically, this procedure is required only once in most patients to achieve a persistent resolution, although data have shown that a second administration for patients in whom CDI recurred after an initial FMT results in resolution in most of those patients. In a randomized trial of patients with recurrent CDI (n=43), 81% of patients treated with oral vancomycin followed by FMT administered through a nasoduodenal tube resolved *C. difficile*–associated diarrhea compared with 31% of patients treated with oral vancomycin alone and 23% of patients treated with vancomycin and bowel lavage ($p<0.001$ for both comparisons with the infusion group). Results were so compelling that the trial's Data and Safety Monitoring Board halted the trial early after an interim analysis. Researchers who analyzed data on more than 77 patients with recurrent CDI from five treatment centers across the United States who received FMT reported that CDI was cured in 91% of patients after one treatment. Other, smaller trials have reported similar

success rates. Some news reports have stated that facilities offering the procedure inform patients that a 90% success rate can be assumed.

In May 2013 at a public workshop on FMT and standards for the procedure, the U.S. Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER) announced that FMT falls within the agency's definition of a biological product and drug. Because CBER has not approved FMT for any therapeutic purpose, the agency is stated that it would require an investigational new drug (IND) application from any center intending to treat a patient with FMT for any condition. Several weeks later, FDA reconsidered this policy as a result of "subsequent communications, [in which] physicians and scientists have expressed concern to FDA that FMT is not appropriate for study under FDA's investigational new drug application (IND) regulations (21 CFR Part 312). Some health care providers have stated that applying IND requirements will make FMT unavailable…" FDA indicated that it "intends to exercise enforcement discretion regarding the IND requirements for the use of FMT to treat *C. difficile* infection not responding to standard therapies provided the treating physician obtains adequate informed consent from the patient or his or her legally authorized representative for the use of FMT products."

Six ongoing trials are listed at the National Clinical Trials database evaluating the safety and efficacy of FMT as well as the best practices to deliver the intervention. Specific cost information on the various modalities for administering the treatment is scarce at this time. Reported costs associated with screening donor blood and stool for contagious agents, preparation of the donor fecal sample, and placement of a nasogastric tube or retention enema tube can exceed $2,500. If the procedure is done by colonoscopy, the average cost of colonoscopy is about $3,000. Screening, collecting, and preparing the stool are done at additional cost. However, costs of multiple regimens of antibiotic therapy for recurrent CDI, physician office visits, and hospitalizations from complications of recurrent CDI can easily exceed the reported costs of one FMT. Third-party payers (Aetna for example) have started to cover the procedure for patients with CDI who did not respond to at least one course of metronidazole or vancomycin.

- **Key Expert Comments**: Overall, experts concluded that results from the small number of FMT studies completed thus far are very compelling. However, experts were eager to see larger comparative studies to better determine the role of FMT in clinical practice and the best processes and standards to ensure safety in screening and processing donor material. Experts noted several potential societal barriers to acceptance of the procedure and a lack of standardized protocols; however, they also noted that the severity of recurrent CDI and its impact on patient quality of life is prompting patients to seek out the procedure.
- **Potential for High Impact**: High

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

- **Key Facts**: According to the World Health Organization, *Mycobacterium tuberculosis* infection is highly underdiagnosed because current TB testing methods require weeks to deliver a definitive result. During that time, infected patients go untreated or may be placed on ineffective therapies, thereby continuing to spread TB and creating a significant public health hazard. Thus, the need for effective, rapid diagnostics and new treatments to address resistant strains that are emergent globally is significant. The Xpert MTB/RIF (*M. tuberculosis*/rifampicin) test (Cepheid, Sunnyvale, CA) is a nucleic acid–based test that is run on Cepheid's GeneXpert® real-time polymerase chain reaction (PCR) system. The test is

intended to simultaneously detect *M. tuberculosis* complex species and determine whether the identified bacterium is susceptible to rifampicin, a first-line therapy for TB. The assay is intended to yield results in about 2 hours, which would enable relatively rapid initiation of treatment. The test is available in the United States as a research-use–only reagent. The company anticipated filing a submission for marketing approval by the end of 2012 with U.S. marketing approval of a test kit anticipated in 2013 and product launch in 2013 or 2014. We were unable to find more recent information on the manufacturer's plans to file for marketing approval in the United States.

- **Key Expert Comments**: Overall, experts thought that this test has potential as a rapid, sensitive, and specific diagnostic test to address the unmet need for more rapid diagnosis and better initial management of this form of TB, thus improving patient health outcomes and reducing spread of disease. By knowing the patient's TB status before he or she leaves the physician's office, more appropriate treatment could be given and proper infection control measures could begin to be implemented. Xpert MTB/RIF test detects resistance only to rifampin, which is a common first-line antibacterial agent. Susceptibility to other agents would still need to be guided by traditional testing methods. Nevertheless, the Xpert MTB/RIF test could replace other PCR methods of detection and provide an improved approach to diagnosis and treatment, which could improve outcomes for patients, especially those with limited access to care, and reduce disease transmission.
- **Potential for High Impact**: Moderately high

Hepatitis C Virus Infection

Hepatitis C virus (HCV) is the primary cause of death from liver disease and the leading cause for liver transplantation in the United States. According to a CDC report published in August 2012, "Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945–1965," an estimated 3.2 million Americans have chronic HCV infection, 75% of those infected are in this age range, and 50% to 80% of infected people are unaware they are infected. Additionally, HCV is seen in patients with HIV. Of the 1 million people with chronic HIV infection in the United States, about 50,000 also have chronic HCV infection. Some calculations suggest that HCV-related mortality will continue to increase over the next two 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 with antiviral therapy. Intensive research has been ongoing, and dozens of drugs are in development in new drug classes. The relatively recent explosion in HCV drug development has come about because of effective and efficient in vitro methods that enable developers to quickly screen and evaluate potential candidates.

Sofosbuvir (GS-7977) for Treatment of Chronic Hepatitis C Infection

- **Key Facts:** In May 2011, the NS3/4a protease inhibitors boceprevir and telaprevir were approved by FDA for use in combination with interferon alfa (IFN) and ribavirin (RBV) for treating chronic hepatitis C virus (HCV) genotype 1 infection. Protease inhibitors were shown to improve cure rates for chronic hepatitis C, genotype 1, compared with cure rates of IFN and RBV alone. However, up to half of patients with chronic HCV infection are not able to tolerate IFN-containing treatment regimens, so the search is on for an IFN-free regimen. Also, protease inhibitors have been associated with significant side effects, including anemia and severe rash, and are effective against only HCV genotype 1 infection.

Thus, effective, well-tolerated, IFN-free options that are pan-genotypic are needed for chronic HCV infection.

Sofosbuvir (GS-7977; Gilead Sciences, Inc., Foster City, CA) is a uridine nucleotide analog HCV NS5B polymerase inhibitor under investigation for treating chronic HCV infection. Sofosbuvir purportedly targets the active site of the HCV RNA polymerase and inhibits elongation of the growing HCV RNA genomic transcript. Sofosbuvir is purported to have broad efficacy against multiple HCV genotypes and is being evaluated as part of multiple therapeutic regimens. In phase III clinical trials, sofosbuvir has been administered orally, once daily for 12 weeks in combination with RBV for patients infected with HCV genotype 2 or 3, and with IFN and RBV for patients infected with chronic HCV genotypes 1, 4, 5, or 6 whose disease is naïve to treatment. Sofosbuvir is also being investigated in combination with other direct-acting antiviral agents, including a once-daily fixed-dose combination with the NS5A inhibitor ledipasvir, with the intention of creating a convenient all-oral treatment that would eliminate the need for IFN and/or RBV in patients with chronic HCV genotype 1 infection. In phase III clinical trials, treatment with sofosbuvir and RBV was noninferior to treatment with IFN/RBV in patients with chronic HCV genotype 2 or 3 infection who had not had earlier treatment. In patients with chronic HCV genotype 2 or 3 infection for whom IFN treatment was not an option, sofosbuvir and RBV treatment resulted in a significantly higher sustained viral response at 12 weeks (SVR12) rate compared with such response with placebo. Additionally, patients infected with HCV genotype 1, 4, 5, or 6 and who had no prior treatment were given sofosbuvir in combination with RBV/IFN for 12 weeks and had a significantly higher SVR12 rate than did a predefined historic control group. In studies in which patients were given sofosbuvir and RBV, the most common side effects were dizziness, fatigue, headache, insomnia, and nausea. When patients were given sofosbuvir in combination with IFN/RBV, the most common side effects reported were anemia, fatigue, headache, insomnia, and nausea.

In April 2013, the company submitted a new drug application to FDA for sofosbuvir and RBV for treating HCV genotype 2 or 3 infection and for sofosbuvir plus IFN/RBV for patients with HCV genotype 1, 4, 5 or 6 who had had no prior treatment. In June 2013, FDA granted sofosbuvir priority review with a decision date of December 8, 2013. According to one estimate, sofosbuvir could cost about $75,000 to $85,000 per treatment course. For benchmarking purposes, a standard 12-week treatment regimen of the protease inhibitor telaprevir costs about $50,000. Boceprevir costs range from about $26,000 to about $48,000. Third-party payers typically cover HCV protease inhibitors as specialty tier drugs requiring prior authorization for coverage.

- **Key Expert Comments**: Overall, experts commenting on this intervention considered sofosbuvir as having high potential to address significant unmet needs for HCV treatment. Sofosbuvir, as part of an all-oral regimen, is purported to have high efficacy that is well-tolerated in patients who cannot tolerate IFN or do not want to use it. Sofosbuvir also provides a shorter and simpler dosing regimen compared with dosing for current treatment options. The high efficacy of sofosbuvir observed thus far in HCV genotypes other than genotype 1 is also perceived to be a significant advantage that will increase the drug's potential impact. Additional research will be needed to determine the long-term impact of sofosbuvir therapy on rates of cirrhosis, liver cancer, and liver transplantation. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.
- **Potential for High Impact**: High

HIV/AIDS

HIV infection continues to be a major public health concern, continuously challenging physicians, researchers, and public health officials to find the best practices to contain the epidemic. HIV prevention measures remain crucial in controlling the disease. CDC estimates that as many as 50,000 people are newly infected with HIV in the United States annually; 61% of new infections occur in men who have sex with men (MSM) and 23% of new infections arise in women. Women are twice as likely to be infected with HIV through heterosexual contact. According to a CDC study, about half of all new HIV infections occur from the approximate 20% of persons living with HIV who are unaware of their infection. As HIV management has transitioned from a deadly fatal infection to a chronic illness, more attention has shifted toward effectively controlling the infection and the numerous accompanying comorbidities. Four interventions for management of HIV infection have been identified for this report as having high potential impact—one for prevention of HIV infection, one for in-home HIV testing, and the other two for managing comorbidities associated with infection.

Collaborative Care Model (HITIDES) for Comorbid HIV and Major Depressive Disorder

- **Key Facts**: Major depressive disorder (MDD) frequently co-occurs in patients with HIV infection and is the most common mental illness that these patients experience. Yet MDD is both underdiagnosed and undertreated in this patient population and can adversely affect the efficacy of HIV management and treatment adherence, which can lead to HIV progression and increased mortality. According to the National Institute of Mental Health, MDD should be treated as a separate illness in patients with HIV infection and managed by a mental health professional, especially when antidepressant pharmacotherapy is prescribed, to avoid drug interactions.

  To improve MDD diagnosis and management as well as HIV outcomes, a collaborative care team consisting of a registered nurse depression care manager, a clinical pharmacist, and a psychiatrist can be formed with protocols in place to facilitate communication and appropriate treatment. As part of the HITIDES program (HIV Translating Initiatives for Depression into Effective Solutions), 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. A registered nurse acts as a depression care manager to communicate with patients by phone on an ongoing basis to deliver participant education and activation, assess treatment barriers and possible resolutions, monitor depression symptoms, treat any substance abuse, and provide instruction in self-management. Referrals are made to specialty mental health care providers as needed. Investigators in one study conducted in three Veterans Affairs clinics reported that patients (n=249) infected with HIV and with MDD who were treated with collaborative care were more likely than patients treated with usual care to report treatment response and remission at 6 months. The patients receiving collaborative care also reported more depression-free days during a 12-month period and a significant reduction in HIV symptom severity at 6 months and 12 months compared with those outcomes in patients receiving usual care. In a retrospective analysis, charts from patients (n=124) with HIV and co-occurring depression who were referred for depression treatment at a psychiatric facility located within an infectious diseases outpatient clinic were also analyzed. In the posttreatment period, significant reductions in depression and HIV RNA were observed, and significant increases

in CD4 T-cell count and antidepressant prescriptions were observed compared with those outcomes during the pretreatment period.

Veterans Affairs medical centers and community-based outpatient clinics reportedly are starting to integrate mental health services into primary care settings to screen for and treat HIV and comorbid depression.

- **Key Expert Comments**: Overall, experts commented that a collaborative care model to treat MDD in patients with HIV could lead to diagnosis and treatment of MDD in more patients with HIV. They believed that better MDD management might lead to improved treatment adherence and health outcomes for both disorders. They also speculated that patients whose MDD was well managed would be better able to understand HIV infection self-management. Experts pointed out that establishing a collaborative care group might result in a need for additional staff, facilities, and information technology as well communication sessions that could change care processes. Also, increased diagnosis of MDD is expected to increase demand for mental health services. Experts thought clinicians would accept the model because of the potential to improve treatment adherence and outcomes, but thought some patients might resist this model because of a perceived stigma about being given a diagnosis of MDD.
- **Potential for High Impact**: Lower end of the high-impact-potential range

Emtricitabine/Tenofovir (Truvada) for Prevention of HIV Infection

- **Key Facts:** Emtricitabine/tenofovir (Truvada®, Gilead Sciences, Inc., Foster City, CA) has gained traction as a potential option for HIV prophylaxis in high-risk males and females seeking effective prevention against HIV with its FDA approval for this patient population in July 2012. The approval was based on researchers' reports of data from a trial that reported that high-risk MSM who took emtricitabine/tenofovir once daily were 44% less likely to become infected with HIV-1 than MSM given placebo. However, researchers later reported evidence that emtricitabine/tenofovir failed to protect high-risk females from contracting HIV. Experts speculated that the lack of efficacy in protecting women might be due to the drug's inability to concentrate sufficiently in vaginal tissue, which is where transmission occurs during intercourse, or might be related to problems with treatment adherence. Others hypothesized that in one preexposure prophylaxis trial, females may have given their HIV medication to their infected partners. These results dampened some enthusiasm and added to the controversy because treatment adherence has been shown to greatly improve efficacy of prophylactic emtricitabine/tenofovir. Additionally, more recent data from two other preexposure prophylaxis studies in serodiscordant couples have shown emtricitabine/ tenofovir to be 73% to 78% effective in males and females. Emtricitabine/tenofovir is also controversial because some investigators believe that the costly therapy might only buy time until infection occurs, even if the patient adheres to the recommended treatment regimen. In July 2012, FDA approved emtricitabine/tenofovir once daily in combination with safer sex practices to reduce the risk of sexually acquired HIV-1 infection in adults at high risk. The retail cost of a 30-day supply of emtricitabine/tenofovir is about $1,300. Our searches found no third-party payers with a coverage determination for this indication at this time.
- **Key Expert Comments:** Overall, experts commenting on this topic thought that prophylactic use of this drug has high potential to address an important unmet need as the first pharmacologic agent approved to reduce the risk of acquiring HIV-1 infection in patients at high risk of contracting the infection. No other preventive options using

medication are available for these individuals. Experts thought that the drug could have a significant impact by reducing the number of HIV-infected individuals. However, experts noted that early trials have shown that this intervention would not protect everyone who attempts the regimen. Experts speculated that this, combined with high treatment costs and likely high out-of-pocket costs to patients and frequent followup for something that is not a disease (i.e., unprotected sex) and that can be prevented with behavior interventions, would be controversial as the role of prophylactic emtricitabine/tenofovir evolves.

- **Potential for High Impact:** High

OraQuick In-Home Rapid Test for Detection of HIV Infection

- **Key Facts**: Although an over-the-counter HIV test has been available since 1996, it requires that a blood sample be mailed to a laboratory for analysis; results are available the next business day at the earliest. A simple, rapid in-home test that patients can interpret might improve HIV screening rates by increasing the privacy and confidentiality of testing, empowering individuals about their health decisions, and providing a more rapid assessment of HIV status without the need for followup seronegative test results. Increased screening could reduce HIV transmission rates and improve disease management through earlier treatment.

  The OraQuick In-Home HIV Test (OraSure Technologies, Inc., Bethlehem, PA) is a rapid, home-based HIV test that is available over the counter. The test provides easy access to first-line testing that is affordable, safe, simple, rapid, painless, and anonymous. OraQuick is designed to detect HIV-specific antibodies found in a patient's saliva. The test kit includes a single-use testing device and a test tube containing testing reagent. The testing device is a lateral flow immunoassay with an integrated oral swab. The test is predicated on an oral swab–based test that has been available to health care professionals since 2004. Changes were made only to the packaging and instructions to create the home version of the test. To conduct the test, an individual collects his or her saliva sample from along the gum line using the oral swab, then places the swab end of the testing device in the test tube with reagent for 20 minutes. The testing device contains colloidal gold particles bound to protein A, which will bind antibodies from the saliva sample in solution and migrate along the device. The tube has two indicator lines toward the distal end that are viewed by the user to determine the result—one indicates test result and the other that the test was valid. The kit includes resources on HIV and HIV testing, including a hotline with 24-hour customer support to answer questions regarding testing and interpretation as well as referral to care if needed. A negative test result 3 months after the last risk event is likely to be a HIV negative result. An HIV positive test result requires followup testing by Western blot analysis to confirm infection. In a large clinical trial (n=5,662) used to support regulatory filing, the sensitivity of this in-home HIV test was 91.67% and specificity was 99.98%.

  A behavioral study was conducted of a cohort of ethnically diverse MSM (n=27) who were considered at risk of contracting HIV and never or rarely used condoms to determine if they would use the test to screen potential sexual partners. The authors reported 10 of 100 screened individuals received a positive test result. Sixty percent of those who screened positive were unaware of their HIV status. Most study participants purportedly expressed a strong desire to continue using the home test and would buy it. The manufacturer warns that the test should not be used to make decisions on behavior that may put one at increased risk for contracting HIV.

The test became commercially available in the United States in October 2012 after its July 2012 FDA approval for sale directly to consumers. The test can detect antibodies to both HIV-1 and HIV-2. The test is the first, and so far only, rapid over-the-counter test approved by FDA for detection of HIV or any other infectious disease.

The test costs about $40 when purchased directly from the manufacturer. Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found that only Aetna lists a coverage determination for the HIV home test kits, which states the payer does not cover home HIV test kits that do not require a physician's prescription.

- **Key Expert Comments**: Overall, experts commenting on this intervention thought that the OraQuick rapid in-home HIV test has potential to meet a significant unmet need by increasing HIV screening rates in patients who engage in high-risk behaviors but are reluctant to undergo HIV screening in clinics. In-home testing was thought to have potential to improve screening rates because of its relatively modest cost of $40 cost to purchase and perform testing. Experts cited that patients who know their HIV status are more likely to seek treatment and avoid high-risk behaviors, which could positively affect public health outcomes and reduce costs to the system. However, for patients with positive results, more patients would likely seek treatment, thereby increasing care costs to the health system. Experts theorized OraQuick's use could also affect patient management when patients with a positive home test present at health clinics for additional testing. They may have a high level of anxiety from a lack of pretest counseling. Experts believe that the test has the potential to reduce the number of "worried well" patients that clinicians encounter for testing.
- **Potential for High Impact**: Moderately high

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

- **Key Facts:** Patients with HIV have a higher risk of developing anal cancer, possibly due to impaired T-cell function, yet no national or international guidelines for anal dysplasia screening are available for this patient population. The incidence of anal cancer in individuals infected with HIV increased from 19.0 per 100,000 person-years for the period 1992–1995, to 72.2 for 2000–2003. One cohort study showed that as many as 49% of HIV-infected MSM developed high-grade anal dysplasia within 4 years, compared with 17% developing the disease in MSM not infected with HIV. Also, cross-sectional studies revealed anal dysplasia in 26% of women and 34% of men infected with HIV who did not report a history of anal intercourse. Before anal cancer develops, precancerous lesions can usually be detected and excised before progressing to anal cancer. Anal Papanicolaou (Pap) screening incorporated into routine visits for treatment and monitoring at HIV clinics for all patients, regardless of history of anal intercourse, might help reduce the incidence, morbidity, and mortality of anal cancer in patients with HIV. In a pilot study, 82% of HIV-infected patients approached during routine clinic visit agreed to participate in the study requiring an anal Pap smear collection. Fifty-three percent of patients had abnormal cytology results; among those undergoing high-resolution anoscopy with biopsy, 55% of patients had high-grade anal intraepithelial neoplasia, including two cases of carcinoma in situ.

- **Key Expert Comments:** Overall, experts stated a significant unmet need exists for earlier anal cancer detection in patients with HIV. The experts theorized that anal Pap screening is an effective tool to improve patient health outcomes and that screening in HIV clinics could be an effective way to implement standardized processes. Once taught 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 would likely increase adoption of this practice by clinicians and reimbursement by payers.
- **Potential for High Impact:** Moderately high

Health Care–Acquired and Bacterial Infection Interventions

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

Unmet need: Health care–associated infections (HAIs) are a significant cause of mortality, morbidity, and costs in the U.S. health care system.[1] About 80% of infectious diseases are transferred by touch, according to estimates by the International Copper Association.[2] About 2 million HAIs are documented in the United States annually and result in 100,000 deaths.[3] Additionally, the U.S. Centers for Disease Control and Prevention (CDC) estimates that HAIs add between $28 billion and $45 billion to annual U.S. health care costs.[4] On average, HAIs add an estimated 19.2 hospital days and $43,000 in additional costs for each patient who contracts an HAI.[5] Further, patients contracting an HAI have a 1-in-20 chance of dying if the infection is acquired while hospitalized and a 1-in-4 chance of mortality if the infection is contracted in the intensive care unit (ICU).[6]

Hospital surfaces in patient rooms, including the ICU, typically consist of stainless steel and plastics that purportedly possess no antibacterial properties and serve as fomites for disease transmission between disinfection procedures in many health care settings. In some cases, these surfaces can be colonized with live microbes for days or weeks, providing a contamination source to the hands and equipment of health care workers, professionals, visitors, and patients. The intrinsic antimicrobial properties of copper and copper alloys (brasses and bronzes) for touch surfaces on hospital hardware and equipment could add another safeguard against disease transmission between cleanings.[7]

Intervention: Antimicrobial copper touch surfaces can be incorporated into a wide variety of components, including bedrails, handrails, door handles, grab bars, intravenous (IV) poles, food trays and carts, sinks, faucets, shower and lavatory components, work surfaces, computer keyboards, equipment adjustment knobs, and face plates. Copper's antimicrobial properties are purported to remain effective for the product's lifetime, and they do not rely on coatings or impregnated surfaces that may wear off or wash away.[7] The manufacturer association claims that copper touch surfaces continuously reduce bacterial contamination, achieving 99.9% reduction of gram-negative and gram-positive bacteria within 2 hours of exposure and that the surface delivers continuous antibacterial activity between routine cleaning and sanitizing steps.[8]

Antimicrobial copper consists of copper alloys such as brass and bronze, copper nickels, and copper with nickel and zinc .[1,9] Manufacturers intend these alloys to have strength comparable to stainless steel. Copper alloys are purported to be durable. Natural tarnishing does not impair the surface's efficacy, and copper touch surfaces have been deemed to not be harmful to people or the environment.[1,10]

The manufacturer purports that copper surfaces exert their antibacterial activity in two sequential steps. First, antimicrobial copper purportedly disrupts the integrity of bacterial cell membranes through oxidation and disrupt physiologic functions such as electrostatic potential. Second, copper ions purportedly penetrate compromised cells and alter cell metabolism by interacting with numerous enzymes crucial for normal metabolic activity.[11] The use of antimicrobial copper is intended to supplement and not substitute for standard infection control practices, and users are advised to continue to follow all current infection control practices.[8]

Antimicrobial copper is commercially available in certain hospital settings, such as on door knobs and door push plates. Thirteen companies are positioning to manufacture products containing the Antimicrobial Copper mark.[12]

Clinical trials: In a randomized controlled trial, patients (n=650) admitted to three ICUs in the United States were randomly placed in rooms fitted with six copper alloy surfaces (bed rails,

overbed tables, IV poles, arms of the visitor's chair, and any two of the following items: nurses' call button, computer mouse, bezel of the touchscreen monitor, or palm rest of a laptop computer) or standard surfaces.[13] Patients admitted to copper rooms had a 45% reduction in HAI or colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant enterococci (VRE) compared with those infection rates in patients placed in standard rooms (p=0.020).[13] Additionally, patients assigned to rooms with copper surfaces had a 58% reduction in contracting an HAI alone compared with HAIs patients placed in standard rooms (p=0.013).[13]

In another analysis, investigators sampled copper-containing objects (n=282) in 32 ICU rooms and noncopper-containing objects (n=288) in 27 ICU rooms to examine the ability of antimicrobial copper to lower the microbial burden (MRSA and VRE) on commonly touched objects and mitigate the acquisition of HAIs. The copper content of the objects was as follows:

- Bed rails, 99.99% copper alloy
- Tray tables, 90% copper alloy
- Chair arms, 90% copper alloy
- Monitors, 90% copper alloy
- IV poles 75% to 95% copper alloy
- Call buttons, 70% to 95% copper alloy

Using copper significantly reduced the total mean microbial burden in the ICU room by 87.4% (p=0.003). Copper was also effective in reducing the mean microbial burden on four of the six objects (bedrails [reduced by 99%, p=0.0003], call buttons [by 90%, p=0.003], IV poles [by 67%, p=0.11], and chair arms [by 38%, p=0.11]). Using 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 copper-containing rooms and 55.5% of rooms that were not copperized. According to investigators, MRSA and VRE were frequently isolated from noncopper-containing objects but were not isolated from copper-containing objects.[14]

Manufacturer and regulatory status: The International Copper Association, Ltd., New York, NY, advocates for Antimicrobial Copper. It is the only hospital touch surface with a U.S. Environmental Protection Agency (EPA) public health registration, allowing manufacturers to claim that copper surfaces can kill specific bacteria (*S. aureus*, MRSA, VRE, *Enterobacter aerogenes*, *Pseudomonas aeruginosa*, and *Escherichia coli* O157:H7) that cause infections and pose a threat to human health.[8] Although the manufacturer association makes no claims of efficacy against other organisms, the literature has shown that the copper might also be effective against viruses, other bacteria, and fungal pathogens.[7,15] More than 479 antimicrobial copper alloys are EPA-registered public health antimicrobial products available to address both practical and aesthetic demands.[16]

Diffusion: The additional cost of manufacturing a copper sink for a hospital room is estimated at $40–$60 each, which might be considered marginal considering the cost for a hospital sink of approximately $7,500.[17] Additionally, copper rails are expected to add approximately $100 to the cost of a standard $30,000 hospital bed.[17] According to the Copper Development Association, equipping each U.S. hospital room with antimicrobial copper products could cost from $1.5 billion to $2.5 billion, and a return on investment might be realized within 1.0–1.5 years after implementation.[17]

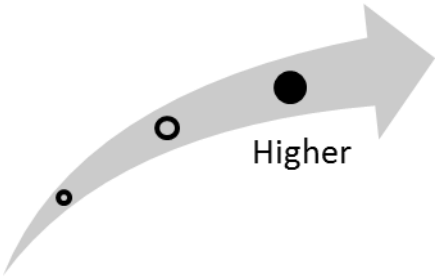
In July 2012, a research collaboration involving teams from the David Geffen School of Medicine at University of California, Los Angeles (UCLA), the UCLA Fielding School of Public Health, and the Henry Samueli School of Engineering and Applied Science at UCLA announced that the U.S. Agency for Healthcare Research and Quality (Rockville, MD) had awarded them $2.5

million to conduct a 4-year, randomized study to determine whether reductions of surface bacteria due to the use of copper surfaces lead to decreased HAI rates, improve treatment outcomes, and reduce costs. The study will evaluate copper, plastic, or sham stainless steel surfaces to determine their role in HAI transmission.[18]

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.[19]

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



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

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered comments on this intervention.[20-26] We organized the following discussion of expert comments by the parameters on which experts commented.

Unmet need and health outcomes: Overall, the unmet need of reducing HAIs is quite significant, the experts agreed, noting current infection-control practices and education have not lowered these rates adequately in many cases. Also, new Medicare rules declining to reimburse for hospital readmissions arising from a HAIs have contributed to the unmet need. Overall, these experts stated that copper surfaces might help address the unmet need by reducing HAIs.

Acceptance and adoption: The practice of using antimicrobial copper surfaces in ICUs would be widely accepted by both patients and physicians, the experts thought. They indicated this intervention might be a simple, nontoxic way help to solve a complex and burdensome problem in health care. Experts stated that patients will likely accept an intervention that is expected to improve their health outcomes. One expert representing a clinical perspective stated that physicians are more likely to accept this intervention if they will not personally bear the cost of fitting facilities with antimicrobial copper. This idea was fleshed out by another expert, representing a health systems perspective, who stated that acceptance by clinicians or patients will be secondary to acceptance by health systems administrators, whose acceptance will be crucial to implement the intervention. The

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

Health care delivery infrastructure and patient management: A one-time disruption in infrastructure and patient management would result from implementing copper touch surfaces in ICUs, the experts stated, noting that rooms would be unavailable during retrofitting with copper surfaces. Implementing copper surfaces into new infrastructure and equipment purchased is expected to be easier than retrofitting existing surfaces.

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

Unmet need: In 2010, an estimated 500,000 individuals were infected with *Clostridium difficile* infections (CDIs) in the United States, costing at least $1 billion annually.[27] Inappropriate antibiotic use can disturb the normal bacterial flora of the colon, leading to colonization with *C. difficile* and release of toxins that cause mucosal inflammation and damage. Patients infected with *C. difficile* typically have watery diarrhea, fever, appetite loss, nausea, and abdominal pain or tenderness.[28] Chronic and relapsing CDIs are increasingly common and a challenge to treat effectively; about 15% to 30% of patients have a recurrence after treatment with metronidazole (Flagyl®) or vancomycin (Vancocin®).[27] Vancomycin is commonly used after a second CDI recurrence. Up to 65% of these patients develop further recurrence after antibiotic therapy is stopped, which suggests that other therapeutic options are needed.[27]

Intervention: Fecal microbiota transplantation (FMT) is intended to recolonize a patient's intestinal flora with beneficial bacteria that will "crowd out" or otherwise make the environment in the bowel unfavorable for *C. difficile* colonization.[29] The treatment can be delivered by any of several methods: colonoscopy, nasogastric tube, or enema.[30] Method standardization is lacking at this time. For the colonoscopic FMT 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 syphilis, HIV, and hepatitis A, B, and C (the exact pathogens depend on the center). Prospective donors are excluded if they recently used antibiotics or had a bout of diarrhea. The fecal-saline solution is introduced into the patient's right cecum in the intestine by a gastroenterologist, who uses a colonoscope. The remainder of the solution is introduced distally as the colonoscope is withdrawn. Approximately 300–500 mL is infused into the patient; the dose varies by patient weight. Typically, this procedure is required only once in a patient, although it can be repeated if the infection does not fully resolve.[27,31]

Clinical trials: In an open-label, randomized controlled trial, patients (n=43) were randomly assigned to receive vancomycin (500 mg orally, 4 times daily, for 4 days) followed by bowel lavage and subsequent FMT administered through a nasoduodenal tube; standard vancomycin (500 mg orally, 4 times daily, for 14 days); or standard vancomycin with bowel lavage. The primary endpoint was resolution of diarrhea associated with CDI without relapse after 10 weeks. Among FMT-treated patients, 81% had resolution after the first infusion. Two of three patients whose CDI had not resolved after the first infusion had resolution after a second infusion from a different donor. CDI resolution occurred in 31% of patients treated with vancomycin alone and in 23% of patients given vancomycin and bowel lavage ($p<0.001$ for both comparisons with the FMT group). The reported adverse events among the three groups were few and similar, except for mild diarrhea and abdominal cramping in the FMT infusion group on infusion day. The Data and Safety Monitoring Board halted the study early after an interim analysis because of the high efficacy of FMT.[32]

In the largest analysis to date from five treatment centers across the United States, FMT was reported to be 91% effective in patients (n=77) with recurrent CDI. The mean age of the patient population was 65 years, and 40% of these patients were hospitalized, homebound, or in a specialized nursing facility at the time of the procedure. The median time of illness before therapy was 11 months, and the mean number of courses of antibiotic therapy was five before treatment. Patients given FMT had a mean time to resolution of diarrhea of 6 days. During long-term followup, only patients who were treated later with antibiotics (n=7) had a CDI recurrence. Two of

these patients were successfully re-treated with FMT after an unsuccessful course of vancomycin. Also, 53% of patients in this study stated they would have preferred FMT as first-line treatment.[33]

In another trial, patients (n=70) with recurrent CDI were treated with colonoscopic FMT. All patients had CDI diarrhea resolution except those infected with strain type 027 CDI, and they had an 89% response rate. Four patients who did not respond to FMT had preexisting serious conditions caused by chronic diarrhea or a comorbidity, and all subsequently died of colitis. Within the first year after FMT, four patients previously treated had a CDI relapse after being treated with antibiotics. Two of these patients were successfully re-treated with FMT, and two were treated with antibiotics for CDI.[34]

In another retrospective study, patients (n=49) with either moderate and recurrent or severe refractory CDI were treated with FMT via nasogastric tube (74%) or colonoscopy (26%).[35] Ninety-four percent of patients exhibited resolved symptoms within 1–4 days. Three patients whose symptoms did not respond to therapy were concurrently taking antibiotics. Four patients had recurrence after FMT and eventually died; however, the deaths were not attributed to recurrent CDI. No adverse events were reported in patients who underwent FMT.[35]

In another trial, prospective data were collected from three different centers performing FMT on 37 patients with recurrent CDI.[36] Patients received one or two FMTs. Ninety-two percent of patients were cured (range at the three centers, 75% to 100%). Two experienced a recurrence 5–12 months after receiving subsequent antibiotic treatment and were successfully re-treated with FMT. One patient who was not cured died of toxic megacolon after 1 month. He had refused the suggested operative treatment before the FMT.[36]

Manufacturer and regulatory status: Until early 2013, FMT was being carried out without regulatory oversight in the United States. Clinician concerns and the lack of clear regulatory guidance for donor screening and donor material processing for FMT led a few specialty societies including the American Gastroenterological Association to contact the U.S. Food and Drug Administration (FDA) in April to clarify whether FMT was subject to regulation.[37] FDA's Center for Biologics Evaluation and Research (CBER) determined that FMT falls within the agency's definition of a biological product and a drug.[38] The agency held a public workshop on FMT in May 2013 to exchange information and experience with the scientific/medical community and to facilitate clinical development of the procedure.[38] FDA initially announced that use of FMT would require an investigational new drug (IND) application to carry out the procedure for any condition.[38] In clinical situations in which FMT may require urgent action, clinicians were instructed to contact FDA to obtain an "emergency use" IND.[37] Several weeks later, FDA reconsidered this policy as a result of "subsequent communications, [in which] physicians and scientists have expressed concern to FDA that FMT is not appropriate for study under FDA's investigational new drug application (IND) regulations (21 CFR Part 312). Some health care providers have stated that applying IND requirements will make FMT unavailable…."[39] FDA noted the concerns and indicated that it "intends to exercise enforcement discretion regarding the IND requirements for the use of FMT to treat *C. difficile* infection not responding to standard therapies provided the treating physician obtains adequate informed consent from the patient or his or her legally authorized representative for the use of FMT products. Informed consent should include at a minimum, a statement that the use of FMT products to treat *C. difficile* is investigational and a discussion of its potential risks."[39] Six trials are under way and registered at the National Clinical Trials database to assess FMT in patients with recurrent, relapsing, or refractory CDI.[40-45]

Diffusion: The procedure had been diffusing before the FDA action in early 2013. Diffusion will be slowed somewhat because the procedure now can be performed legally only within the context of an FDA-approved IND trial or with an emergency IND. With regard to cost and its effect

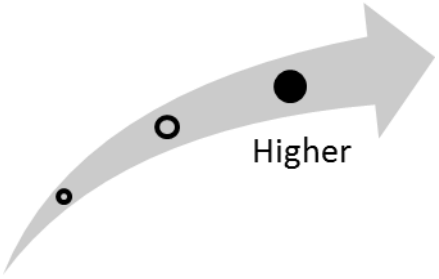
on diffusion, specific cost information on the procedure is scarce because its use is still relatively new.

Reported costs associated with screening donor blood and stool for contagious agents, preparing the donor fecal sample, and placing a nasogastric tube or retention enema tube can exceed $2,500. If the procedure is done by colonoscopy, the average cost of colonoscopy is about $3,000. Screening, collecting, and preparing the stool would be additional costs. However, costs of multiple regimens of antibiotic therapy for recurrent CDI, physician office visits, and hospitalizations from complications of recurrent CDI can easily exceed the reported costs of one FMT. Third-party payers (Aetna for example) are starting to cover the procedure for patients with CDI whose condition has not responded to at least one course of metronidazole or vancomycin.[46]

Clinical Pathway at Point of This Intervention

According to CDC, once CDI is confirmed, patients should be taken off the antibiotic that created the environment for the infection to occur. In some patients (20%, within 2–3 days) the infection may resolve without further treatment. If it does not, the patient is typically treated with either oral metronidazole or vancomycin for 10 days.[47] FMT is intended to treat recurrent CDI, although it is also under study as first-line therapy.

Figure 2. Overall high-impact potential: fecal microbiota transplantation for treatment of recurrent *Clostridium difficile* infection



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

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this topic.[48-54] We organized the following discussion of expert comments by the parameters on which experts commented. Please note that the expert comments received predated the very recent FDA action regarding FMT regulation.

Unmet need and health outcomes: Recurrent CDI causes great morbidity, mortality, and costs to patients and the health care system, the experts concurred, and emerging antibacterial resistance associated with these infections represents an important unmet need. FMT has the potential to address the unmet need for recurrent-CDI treatment that does not use antibiotics, according to a general consensus among the experts; meeting this need could significantly affect health outcomes and quality of life. In general, the experts accepted the underlying theory of FMT and were somewhat certain that it could be highly effective, although they thought larger trials are needed to bear this out.

Acceptance and adoption: Clinicians would increasingly accept the procedure as donor selection, screening, and transplant processing protocols become standardized, the experts thought. Patients with long-term CDI recurrence, as well as their treating physicians, might be eager to try any therapy that has a high likelihood of efficacy. However, psychological factors or religious beliefs may preclude some patients from seeking the treatment. One expert representing a clinical perspective thought that to increase acceptance, the procedure might need to be given a different name.

Experts generally viewed the procedure as cost neutral or cost saving compared with the cost of multiple failed courses of antibiotics and resultant complications.

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

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

Unmet need: According to the World Health Organization, tuberculosis (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 not treated or placed on ineffective therapies. These patients may also continue to spread TB to others in the community, creating a significant public health concern.[55]

Intervention: The *Mycobacterium tuberculosis*/rifampicin test (Xpert® MTB/RIF) is a nucleic acid–based test run on the GeneXpert® real-time polymerase chain reaction (PCR) system.[55] The test simultaneously detects the presence of *M. tuberculosis* complex species and determines whether the identified bacterium is susceptible to rifampicin, the first-line TB drug.[56] In the assay, a real-time hemi-nested PCR reaction is performed to amplify and detect a portion of the *rpoB* gene, a genetic marker that is specific for a subunit of an RNA polymerase essential to TB viability.[55] The antibiotic activity of rifampicin targets the subunit encoded by the *rpoB* gene to inhibit the RNA polymerase, inhibiting bacterial survival.[55] 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.[57]

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.[56] 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.[56]

To perform the test, a technician first treats a patient sputum sample with a solution containing sodium hydroxide and isopropanol (isopropyl alcohol) to reduce the viability of any *M. tuberculosis*, thereby preventing contamination. Subsequent processing and detection are performed on the GeneXpert system using a single-use, closed Xpert MTB/RIF cartridge that contains all the reagents necessary for testing.[55,56] The procedure's automated nature and the fact that it does not require handling of PCR amplicons are intended to ensure optimal accuracy of the assay by limiting interoperator variability and reducing the potential for false positives caused by amplicon contamination.[56] The assay is intended to yield results for both the presence of *M. tuberculosis* and antibiotic resistance for positive samples in about 2 hours.[55] For a clinician to fully determine an effective treatment regimen, full drug-susceptibility testing would still need to be performed in patients with rifampicin-resistant TB for a clinician to fully determine an effective treatment regimen.

Clinical trials: In a diagnostic substudy of a TB prevalence survey conducted in gold mining companies in South Africa, participants' sputum (n=6,893) was tested using liquid culture (reference comparator), Xpert MTB/RIF, and smear microscopy. Sputum samples tested positive for *M. tuberculosis* in 2.7% of samples tested by culture, 2.1% of samples tested by the Xpert MTB/RIF test, and 1.3% of samples tested by microscopy. Sensitivity for the test was 62.6%, specificity was 99.6%, positive predictive value was 81.3%, and negative predictive value was 98.9%. Agreement between Xpert and culture was 98.5%. Sensitivity of microscopy was 17.6%. When individuals with a history of TB treatment were excluded from the analysis, Xpert MTB/RIF specificity was 99.8% and the positive predictive value was 90.6% for detecting *M. tuberculosis*. Costs for testing the 7,000 specimens, with 2.7% of specimen cultures positive for *M. tuberculosis*, were $165,690 for Xpert MTB/RIF and $115,360 for the combination of microscopy and culture.[58]

In a large multicenter trial, patients (18 years of age or older) suspected of having TB or multidrug-resistant TB (n=6,648) presenting with cough lasting at least 2 weeks were tested for TB using Xpert MTB/RIF, culture, and microscopy detection methods. The investigators reported, "One-off MTB/RIF testing detected 933 (90.3%) of 1033 culture-confirmed cases of tuberculosis, compared with 699 (67.1%) of 1041 for microscopy. MTB/RIF test sensitivity was 76.9% in smear-negative, culture-positive patients (296 of 385 samples), and 99.0% specific (2846 of 2876 non-tuberculosis samples)." The sensitivity and specificity of the MTB/RIF test for rifampicin resistance were 94.4% and 98.3%, respectively. As observed with microscopy, MTB/RIF test sensitivity was not significantly lower in patients co-infected with HIV. Median time to detection of TB was 0 days for the MTB/RIF, 1 day for microscopy, 16 days for liquid culture, and 30 days for solid culture. Using the MTB/RIF test reduced the median time to treatment of patients with smear-negative TB from 56 days to 5 days.[59]

In an international clinical trial, investigators collected three sputum samples each from patients suspected of having TB or drug-resistant TB (n=1,730). Samples were analyzed by a combination of acid-fast smear, solid culture, liquid culture, and Xpert MTB/RIF tests. 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%). Additionally, among 609 culture-negative patients, the Xpert MTB/RIF test correctly identified 604 patients as negative for TB infection (99.2%). 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%).[60]

In an additional study, investigators compared Xpert MTB/RIF to culture and microscopy detection methods using samples from pediatric patients with suspected TB (n=164). Xpert MTB/RIF detected 100% of the smear-positive cases and 66.6% of culture-positive cases that were smear negative. In the per-sample analysis, Xpert displayed a similar sensitivity to culture methods and detected three-fold more confirmed TB cases than microscopy in a similar amount of time. Four additional culture-negative cases with clinical TB (8.5%) were diagnosed by Xpert MTB/RIF. Xpert MTB/RIF demonstrated 100% specificity when TB was reliably excluded; accuracy was not affected by HIV infection in these patients.[61]

Manufacturer and regulatory status: Cepheid, of Sunnyvale, CA, makes the Xpert MTB/RIF test and has received a Conformité Européene (CE) mark for marketing the test in Europe.[62] The test is available in the United States as a research-use–only reagent.[63] The manufacturer expected to make a submission and file for U.S. regulatory approval by the end of 2012, with an expected launch in 2013 or 2014.[64] We were unable to find additional information regarding the manufacturer's plan to file for marketing approval in the United States.

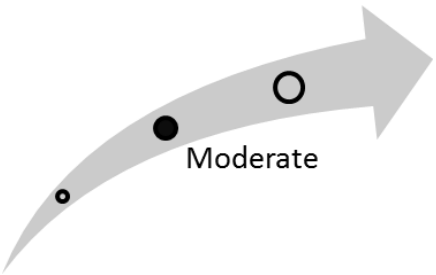
Diffusion: Pricing for the Xpert MTB/RIF test is not available; however, other test cartridge–based assays running on the GeneXpert system cost approximately $20 per assay.[65] Additionally, to run the Xpert MTB/RIF test, a facility would need to have a GeneXpert system, which could represent a capital equipment purchase of more than $100,000 for higher throughput versions.[55,66] According to one source, standard basic testing for TB costs about $20–$40, and more advanced testing to determine rifampicin resistance can add another $20–$30.[65] This test would be likely be billed using current TB codes.

Clinical Pathway at Point of This Intervention

A patient initially presents with symptoms that indicate a possible case of pulmonary TB based on his or her medical history, physical examination, symptoms, TB infection test results (e.g.,

tuberculin skin test, QuantiFERON-TB Gold test), and/or chest radiographs.[67,68] 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.[67] The Xpert MTB/RIF test would be used in place of current nucleic acid amplification tests. Besides identifying the presence of TB, the Xpert MTB/RIF test would also give a preliminary indication of potential antibiotic resistance, which would normally be determined following a positive culture isolate by assaying the isolate's in vitro susceptibility to antibiotics.[55,67]

Figure 3. Overall high-impact potential: Xpert MTB/RIF test for simultaneous detection and drug-sensitivity testing of *Mycobacterium Tuberculosis*



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

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.[69-75] We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Current TB diagnostic methods are lengthy, taking days to weeks to confirm or rule out the presence of TB and antibiotic susceptibility, the experts concurred. This, they said, represents a significant unmet need for more rapid diagnostic testing to direct appropriate therapy and implement infection control measures for patients, the community, and health care providers. Experts agreed that the Xpert MTB/RIF test is fast and accurate, which allows health care practitioners to implement infection control procedures almost immediately. Additionally, the test also provides early detection of rifampicin resistance to guide appropriate antibiotic selection, which could improve health outcomes.

Acceptance and adoption: Although most experts thought that clinicians would readily embrace Xpert MTB/RIF testing, one expert representing a research perspective stated that facilities using

other PCR methods may resist early adoption because only 1% of the TB cases in U.S.-born patients have multidrug-resistant TB. Patients were expected to embrace rapid diagnosis.

Health care delivery infrastructure and patient management: In general, the experts thought the Xpert MTB/RIF test would not have a large impact on how the disease is treated or diagnosed but that it would allow current treatment strategies to be employed earlier and, therefore, potentially reduce disease transmission. Although experts thought impact on staffing and training would 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. An expert with a research perspective stated that Xpert MTB/RIF testing will likely be cost effective. However, initial costs of the GeneXpert system could to lead to more centralized TB testing centers.

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

Hepatitis C Virus Infection Intervention

Sofosbuvir (GS-7977) for Treatment of Chronic Hepatitis C Infection

Unmet need: In May 2011, two novel treatments were FDA approved for treating hepatitic C virus (HCV) infection: NS3/4a protease inhibitors boceprevir and telaprevir. They were approved for use in combination with interferon alfa (IFN) and ribavirin (RBV) for treating chronic hepatitis C genotype 1 infection.[76,77] Protease inhibitor therapy can improve cure rates for chronic hepatitis C, genotype 1, in both treatment-naïve and treatment-experienced patients compared with IFN/RBV alone.[76,77] However, up to half of patients with chronic HCV infection are not candidates for these triple therapy options.[78] Also, protease inhibitors are associated with significant side effects including anemia and severe rash.[79] Lastly, approved protease inhibitors are effective against only HCV genotype 1 infection. Effective, well-tolerated, IFN-free treatment options that are pan-genotypic are needed for treating chronic HCV infection.[78]

Intervention: Sofosbuvir (GS-7977) is a uridine nucleotide analog polymerase inhibitor in phase III trials for treating chronic HCV infection.[79,80] The HCV NS5B polymerase plays an essential role in HCV genome replication. As a nucleotide analog, sofosbuvir is said to target the active site of the enzyme and inhibit elongation of the growing HCV RNA genomic transcript.[79] Nucleos(t)ide analogs such as sofosbuvir are thought to have broader efficacy against different HCV genotypes and a higher barrier to spurring viral resistance than nonnucleos(t)ide polymerase inhibitors, which function via allosteric inhibition.[79]

Sofosbuvir is being evaluated as part of multiple therapeutic regimens. It has been administered orally, 400 mg once daily, for 12 weeks in combination with RBV for patients infected with HCV genotype 2 or 3, and with IFN and RBV for patients infected with chronic HCV genotypes 1, 4, 5, or 6 who are naïve to treatment.[81,82] Sofosbuvir has also been evaluated in combination with other direct-acting antiviral agents, including a once-daily fixed-dose combination with the NS5A inhibitor ledipasvir in an effort to create a convenient all-oral treatment that would eliminate the need for IFN and/or RBV in patients with chronic HCV genotype 1 infection.[79,80]

Clinical trials: In a phase III, randomized controlled trial, patients (n=499) with chronic HCV genotype 2 or 3 infection who had not received prior treatment were given either 12 weeks of sofosbuvir (400 mg, once daily) and RBV (1,000 or 1,200 mg/day) or 24 weeks of IFN (180 mcg/week) and RBV (800 mg/day). Sofosbuvir plus RBV met the primary endpoint of non-inferiority to IFN/RBV, with 67% of patients achieving a sustained viral response (SVR) in both groups. The SVR rates at week 12 (SVR12) in patients receiving sofosbuvir plus RBV were 97% and 56% for patients infected with genotype 2 and genotype 3, respectively. The SVR12 rates in patients treated with IFN/RBV were 78% and 63% for patients infected with genotype 2 and genotype 3, respectively. Of patients treated with sofosbuvir, 20% had compensated cirrhosis, and of patients treated with IFN/RBV, 21% of patients had compensated cirrhosis.[83]

Another phase III, randomized controlled trial evaluated the safety and efficacy of sofosbuvir in patients with chronic HCV genotype 2 or 3 infection for whom IFN treatment was not an option. Patients received sofosbuvir and RBV (n=207) or placebo (n=71) for 12 weeks. Patients treated with sofosbuvir and RBV achieved an SVR of 78% compared with 0% in the placebo group (<0.001).[82]

In a third, phase III single arm trial, patients (n=327) with HCV genotype 1, 4, 5, or 6 and no prior treatment were given sofosbuvir (400 mg once daily) in combination with RBV (1,000 or 1,200 mg/day) and IFN (180 mcg/week) for 12 weeks. Patients treated with sofosbuvir met the primary efficacy endpoint of superiority as compared with a predefined historic control (90% of patients achieved SVR12 vs. 60% of historic control patients [p<0.001]). Patients had primarily

HCV genotype 1 (89%), and SVR12 was 89%.[83] SVR12 was achieved in 97% of patients with genotypes 4, 5, or 6 treated with sofosbuvir. Compensated cirrhosis was present in 17% of patients in the trial, and 80% of these patients achieved SVR12.[83]

In studies in which patients were given sofosbuvir and RBV, the most common side effects reported were dizziness, fatigue, headache, insomnia, and nausea.[82] When patients were given sofosbuvir in combination with IFN/RBV, the most common side effects reported were anemia, fatigue, headache, insomnia, and nausea.[81,83]

Manufacturer and regulatory status: Gilead Sciences, Inc., Foster City, CA, is developing sofosbuvir and has reported data from phase III trials in patients chronically infected with HCV genotypes 1, 2, 3, 4, 5, or 6.[81,82] In April 2013, the company filed a new drug application with FDA for sofosbuvir for treating chronic HCV infection. The data submitted support the use of sofosbuvir and RBV as an all-oral therapy for treating patients with HCV genotype 2 or 3 infection, and for sofosbuvir in combination with IFN/RBV for treatment-naïve patients with HCV genotype 1, 4, 5, or 6 infection.[84] In June 2013, FDA granted sofosbuvir priority review with a Prescription Drug User Fee Act date of December 8, 2013.[83]

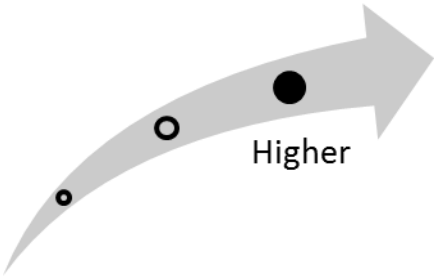
Diffusion: According to one financial analyst's estimate, sofosbuvir could cost about $75,000–$85,000 per patient.[85] For benchmarking purposes, a standard 12-week treatment regimen of the protease inhibitor telaprevir is about $50,000.[86] Boceprevir, also a protease inhibitor, costs about $1,100 per week of treatment with treatment duration ranging from 24 to 44 weeks depending on patient characteristics.[76,87] Thus, the cost of typical boceprevir therapy regimens ranges from about $26,000 to about $48,000.[86,87]

If FDA approves sofosbuvir, it is expected to be covered by payers because of the unmet safety and efficacy need of existing IFN-based treatments. Third-party payers typically cover HCV protease inhibitors as specialty tier drugs requiring prior authorization for coverage.[88-98] If approved, sofosbuvir would likely be treated in a similar manner.

Clinical Pathway at Point of This Intervention

Patients who test positive for HCV and HCV RNA may be considered to have acute or chronic HCV infection, depending on the context. A patient who tests negative for antibodies to HCV and positive for HCV RNA might be chronically infected if immunosuppressed.[99] Subsequent HCV genotype testing is performed to determine the therapy regimen and likelihood of a positive clinical outcome.[99] Rest and hydration are typically prescribed. In 2011, the American Association for the Study of Liver Diseases updated its clinical practice guidelines to recommend treating patients with HCV-1 infection with a protease inhibitor (boceprevir or telaprevir) in combination with IFN/RBV.[100] Sofosbuvir is intended for use in combination with RBV for patients infected with HCV genotypes 2 or 3, and in combination with IFN/RBV (or other investigational HCV agents such as ledipasvir) for patients infected with genotypes 1, 2, 3, 4, 5, or 6.

Figure 4. Overall high-impact potential: Sofosbuvir (GS-7977) for treatment of chronic hepatitis C infection



Overall, experts commenting on this intervention regarded sofosbuvir as having high potential to address significant unmet needs for HCV treatment. Sofosbuvir used as part of an all-oral regimen to treat chronic HCV infection is purported to have high efficacy that is well-tolerated by patients who cannot tolerate IFN or do not want to use IFN. Sofosbuvir also provides a shorter and simpler dosing regimen compared with current treatment options. The high efficacy of sofosbuvir thus far in HCV genotypes other than genotype 1 is also perceived to be a significant advantage that increases the drug's potential impact. Additional research is needed to determine the long-term impact of sofosbuvir therapy on rates of cirrhosis, liver cancer, and liver transplantation. Based on this input, our overall assessment is that this intervention is in the high end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, commented on this intervention.[101-106] We organized the expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A large cohort of aging patients chronically infected with HCV exists in the United States, experts pointed out. Many of these patients have advanced liver disease or are otherwise unable to tolerate an IFN-containing regimen and are in need of effective, new IFN-free treatment options that are well tolerated, the experts thought. Clinical cure of HCV infection is associated with improved health outcomes in patients, the experts stated. Basing their opinion on available evidence, the experts all thought sofosbuvir appears to be promising for treating chronic HCV infection. Sofosbuvir could also improve health outcomes for those with HCV genotypes that are not addressed with protease inhibitor therapy, the experts concluded.

Acceptance and adoption: Experts expect clinician acceptance of sofosbuvir to be high because of its high efficacy and safety shown so far. According to one clinical expert, protease inhibitors have already increased clinician willingness to initiate HCV treatment, and an easier treatment option will further increase treatment rates. The pan-genotypic activity of sofosbuvir is also expected to increase physician acceptance and adoption, noted one health systems expert. Patients are also expected to have a high acceptance of sofosbuvir because of its efficacy and tolerability, all-oral administration, and IFN-free treatment regimen. Although the high estimated cost of sofosbuvir therapy could to pose a barrier to diffusion for some patients, the upfront cost is expected to be offset by costs savings to the health care system by preventing the need for additional treatment, HCV complications, and health monitoring in the future, some experts commented.

Health care delivery infrastructure and patient management: The IFN-free treatment option that the drug could provide might entice more patients to seek HCV testing and treatment, some

experts thought. Improved treatment outcomes could reduce hospitalizations from liver disease and ease the burden on infrastructure and staffing for HCV inpatient treatments, one health systems expert stated, but other experts expected minimal disruptions to infrastructure and management with use of sofosbuvir compared with current treatment options.

Health disparities: An effective, well-tolerated, and simpler treatment regimen might reduce health disparities and would be likely to be covered by public and private payers, one clinical expert thought. Another clinical expert commented that because HCV may disproportionately affect marginalized populations because of risk factors for infection, effective treatment would improve health outcomes in these patients and thus reduce health disparities. But other experts pointed to the anticipated high cost of therapy as a possible barrier to sofosbuvir treatment.

HIV/AIDS Interventions

Collaborative Care Model (HITIDES) for Comorbid HIV and Major Depressive Disorder

Unmet need: Major depressive disorder (MDD) is characterized by severe, persistent feelings of sadness and hopelessness that interfere with routine daily activities such as work, sleep, or study.[107] MDD is the most common mental illness that patients with HIV experience, yet is both underdiagnosed and undertreated in this patient population.[108,109] HIV patients with co-occurring MDD are likely to have accelerated HIV disease progression, decreased immune functioning, decreased adherence to HIV medication regimens, and increased risk of mortality. Because MDD is a modifiable risk factor for HIV progression, effective MDD treatment could improve self-management, adherence behaviors, and health outcomes related to HIV.[109]

Intervention: Using a collaborative care model might facilitate collaboration between primary care and specialty mental health care providers to improve depression diagnosis, care, and treatment outcomes. The model could also allow patients to receive care in more-accessible and less-stigmatizing settings than currently available in HIV treatment facilties.[109] Collaborative care models have been successfully used in patients with depression (without comorbid HIV), diabetes with co-occurring depression, and cancer with co-occurring depression.

The intervention, as implemented in the Veterans Affairs health care system (HIV Translating Initiatives for Depression into Effective Solutions [HITIDES]), involves using an HIV-specific depression care team consisting of a registered nurse depression care manager, a clinical pharmacist, and a psychiatrist. As part of the program, patients with HIV are screened for MDD at the HIV clinic during regular visits.[109] 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.[109,110] The registered nurse depression care manager also communicates with patients via telephone on an ongoing basis (i.e., every 2 weeks, then monthly), delivering the following intervention components: participant education and activation, assessment of treatment barriers and possible resolutions, monitoring of depression symptoms and substance abuse, and instruction in self-management.[109,110] At any time during the intervention, HIV health care providers are free to refer patients directly to specialty mental health care providers.[109]

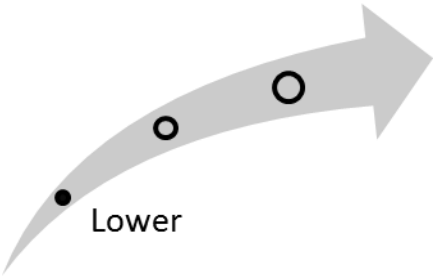
Clinical trial: In an analysis of patients infected with HIV (n=249) and with MDD, patients were randomly assigned to the intervention (HITIDES; n=123) and to usual care (n=126).[109] Patients treated through the collaborative care model were more likely than patients treated with usual care to report treatment response (33.3% HITIDES vs. 17.5% usual care; odds ratio (OR), 2.50; 95% confidence interval [CI], 1.37 to 4.56) and remission (22.0% HITIDES vs. 11.9% usual care; OR, 2.25; 95% CI, 1.11 to 4.54) at 6 months but not 12 months. Patients treated through the collaborative care reported more depression-free days during the 12 months than patients treated with usual care (beta=19.3; 95% CI, 10.9 to 27.6; $p<0.001$). Patients treated through collaborative care had a significant reduction in HIV symptom severity at 6 months compared with patients treated with usual care (beta= -2.6; 95% CI, -3.5 to -1.8; $p<0.001$) and 12 months (beta= -0.82; 95% CI, -1.60 to -0.07; $p=0.03$).[109]

Program developers and funding: HITIDES was developed by researchers at the Veterans Affairs Health Care System.[109] Veterans Affairs medical centers and community-based outpatient clinics are now reportedly beginning to integrate mental health services into primary care settings to screen for and treat HIV and co-occurring MDD.[111]

Current Approach to Care

According to the National Institute of Mental Health (NIMH), MDD should be treated as a separate illness for patients with HIV. 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. NIMH notes that MDD treatment in the context of HIV should be managed by a mental health professional, especially when antidepressant pharmacotherapy is prescribed, so that drug interactions can be avoided.[112] 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.[109]

Figure 5. Overall high-impact potential: collaborative care model for comorbid HIV and major depressive disorder



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

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, commented on this intervention.[113-119] We organized the following discussion of expert comments according the parameters on which they commented.

Unmet need and health outcomes: HIV and MDD are comorbid conditions with poor treatment outcomes that together can exacerbate both of these conditions, the experts agreed. They thought that using a collaborative care model could effectively manage both conditions simultaneously, improving treatment outcomes more than if the conditions were separately diagnosed and treated.

Acceptance and adoption: Clinicians are expected to accept this model because of the minimal training required to implement the program and the potential to increase treatment adherence, the experts thought. Although some experts believe many patients would be receptive to the program, they pointed out that some might be reluctant because of the possible stigma of a depression diagnosis. More data will be needed to fully understand the benefits of this collaborative care model.

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

Health disparities: Most of the experts agreed that combining mental health services with HIV care, which frequently affects underserved groups, might improve diagnosis rates and access to treatment. But coordinating care between two separate sites was seen by two experts with research and clinical perspectives as potentially increasing disparities for patients with poor access to reliable transportation.

Emtricitabine/Tenofovir (Truvada) for Prevention of HIV Infection

Unmet need: An estimated 1.2 million people in the United States are living with HIV infection, and 20% of those individuals are unaware of their HIV status.[120] CDC estimates that as many as 50,000 people are newly infected with HIV in the United States annually; 61% of new infections occur in men who have sex with men (MSM) and 23% occur in women;[121] women are twice as likely as men to be infected with HIV through heterosexual contact.[120] One estimate of the HIV transmission risk during receptive anal sex without a condom—the highest-risk sexual activity—indicates that it may be as high as 3% to 5% for each occurrence. The risk is estimated to be lower for receptive vaginal intercourse and even lower for oral sex, each in the absence of a latex barrier (condom or dental dam). Although no single sexual exposure carries a high risk of contagion, HIV infection can occur after the first sexual exposure; therefore, use of latex barriers during each sexual encounter is recommended.[122]

Although behavior-change programs have resulted in dramatic reductions in HIV transmission in the United States, there remains no truly effective means to prevent HIV infection among populations at high risk for infection, including male prostitutes who have sex with men. Preexposure chemoprophylaxis (i.e., pretreating uninfected individuals at risk for HIV infection with antiretroviral therapies [ARTs]) is an emerging intervention for reducing HIV transmission.[123] Evidence has accumulated to support the theory that ART, taken regularly, can reduce the risk of HIV infection.[123-126]

Intervention: Emtricitabine/tenofovir (Truvada®), which initially received FDA approval in 2004 to treat HIV infection, was re-evaluated as part of a comprehensive strategy for preventing HIV in adults at high risk of infection.[123,124] Emtricitabine/tenofovir is a once-daily, oral, combination ART consisting of two HIV nucleoside reverse transcriptase inhibitors made by the same manufacturer, emtricitabine (Emtriva®) 200 mg and tenofovir disoproxil fumarate (Viread®) 300 mg.[127] Emtricitabine and tenofovir are also available separately in single-agent tablets. However, the combination of two nucleoside reverse transcriptase inhibitors in a single tablet taken once daily decreases patient pill burden and is believed to result in higher adherence to medication regimens among patients with HIV.[128] Treatment adherence is thought to be essential for high efficacy.[123]

Nucleoside reverse transcriptase inhibitors suppress replication of retroviruses by blocking the activity of HIV-1 reverse transcriptase.[127] This results in premature termination of viral DNA replication.

Clinical trials: In the Preexposure Prophylaxis Initiative (iPrEx) trial, HIV-seronegative men or transgender women who have sex with men (n=2,449) were prophylactically given emtricitabine/tenofovir or placebo once daily. The prophylactic use of emtricitabine/tenofovir was shown to lead to a 44% reduction in the incidence of HIV (95% CI, 15 to 63; p=0.005).[123]

In another trial, daily prophylactic use of emtricitabine/tenofovir failed to prevent HIV-1 infection in high-risk women. The study was stopped early due to lack of efficacy, which could have been due to low treatment adherence.[129]

In a different trial of HIV-1–uninfected heterosexual men and women in Botswana who were 18–39 years of age (n=1,219), daily prophylactic use of emtricitabine/tenofovir reduced the risk of acquiring HIV infection by roughly 62% compared with infection rates with placebo.[130]

An additional analysis that excluded HIV infections that occurred more than 30 days after a participant's last reported drug dose was conducted because these individuals could not have been taking study pills at the time of infection. In this analysis, emtricitabine/tenofovir reduced the risk of HIV infection by 78% compared with infection rates with placebo.[125]

In another trial examining HIV-1–serodiscordant heterosexual couples in Kenya and Uganda (n=4,758), patients who took daily prophylactic tenofovir had an average 67% fewer infections ($p<0.001$) than those who received placebo; patients who took prophylactic emtricitabine/tenofovir had an average 75% fewer infections ($p<0.001$). There was no significant difference between the protective effects of tenofovir and emtricitabine/tenofovir ($p=0.23$).[131]

Patients prescribed preexposure prophylaxis (PrEP) must be confirmed to be HIV-negative immediately before initial use and periodically during use to prevent the development of drug resistance. The manufacturer says that PrEP should not be initiated if signs or symptoms of acute HIV infection are present unless negative infection status is confirmed.[127]

The most common adverse events associated with emtricitabine/tenofovir for PrEP include abdominal pain, headache, and weight loss.[127] The manufacturer states that patients should be tested for hepatitis B virus before initiating PrEP because severe acute exacerbations of hepatitis B have occurred in patients co-infected with HIV-1 and hepatitis B virus who have discontinued emtricitabine/tenofovir.[127] Patients taking PrEP should be evaluated for new onset or worsening renal impairment. Emtricitabine/tenofovir use has also been associated with decreased bone mineral density and with body fat redistribution or accumulation.[127]

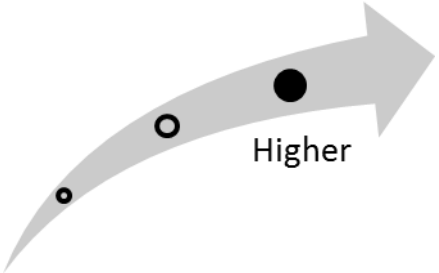
Manufacturer and regulatory status: Gilead Sciences makes emtricitabine/tenofovir. In July 2012, FDA approved emtricitabine/tenofovir once daily in combination with safer sex practices to reduce the risk of sexually acquired HIV-1 infection in adults at high risk.[132]

Diffusion: The retail cost of a 30-day supply of emtricitabine/tenofovir is roughly $1,300.[133] Our searches were unable to find any third-party payers with a coverage determination for PrEP. According to the manufacturer, patients with insurance who are prescribed emtricitabine/tenofovir for treating chronic HIV infection commonly have a $10 copayment.[134]

Clinical Pathway at Point of This Intervention

According to clinical practice guidelines, the most reliable way to avoid HIV transmission is to abstain from sexual contact or to be in a long-term, mutually monogamous relationship with an uninfected partner. For those entering a monogamous relationship, HIV screening before initiating sex may reduce the risk of future HIV transmission. Male latex condoms are also highly effective at preventing HIV-1 transmission. In people with latex allergy, nonlatex male condoms made of polyurethane or other synthetic material provide protection against HIV equal to that of latex condoms.[135] Emtricitabine/tenofovir is a combination ART under clinical development for preventing HIV-1 transmission in patients at high risk of contracting HIV infection.

Figure 6. Overall high-impact potential: emtricitabine/tenofovir (Truvada) for prevention of HIV infection



Overall, experts commenting on this intervention thought that prophylactic use of this drug has high potential to address an important unmet need as the first pharmacologic agent approved for reducing the risk of HIV-1 infection in high-risk patients. No other preventive medication options

are available other than abstinence and condom use, which are not employed by all individuals at high risk of infection. Experts thought that emtricitabine/tenofovir could have a large impact on health promotion by reducing the number of HIV-infected individuals. However, experts cited the early trials that have shown this intervention would not protect everyone who attempts the regimen. This, combined with high treatment costs and likely high out-of-pocket costs to patients for something that is not a disease (i.e., unprotected sex) and that can be prevented with behavior interventions, would be controversial as the role of prophylactic emtricitabine/tenofovir evolves. The experts stated that public-private partnerships will be essential for providing the medication, education, and followup necessary to effectively implement PrEP and improving health outcomes in all eligible patients. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, commented on this intervention.[136-142] We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A significant unmet need remains for effective measures to prevent HIV transmission in serodiscordant couples, the experts stated. Additionally, they noted that some individuals at high risk are not in a position to practice all safer sex measures during each sex act. Before FDA approval of emtricitabine/tenofovir, no pharmacologic methods were available to reduce the risk of HIV infection, which represented a significant gap in HIV risk mitigation. Overall, experts stated that PrEP with emtricitabine and tenofovir could fill a significant unmet need because it is the first approved pharmacotherapy intended to reduce the risk of acquiring HIV in patients at high risk of infection.

Health outcomes could improve if PrEP significantly reduces the risk of contracting HIV, the experts thought. However, they expressed some pessimism about the need for high treatment-adherence to achieve optimal protection.

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

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

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

Additionally, primary care physicians and obstetricians/gynecologists are not familiar with teaching their patients about HIV risk mitigation strategies, which could require some training. If PrEP is successful, less demand on staff and facilities to treat HIV infection could be realized.

Although the intervention is controversial because of its high cost and because clinicians prescribe a pharmaceutical to prevent a disease that patients can be addressed with behavior interventions, the experts stated that PrEP is a major step forward in the battle against HIV/AIDS. The experts stated that public-private partnerships will be essential to providing the medication, education, and followup necessary to effectively implement PrEP and in improving health outcomes in all eligible patients.

OraQuick In-Home Rapid Test for Detection of HIV Infection

Unmet need: According to a CDC study, about half of all new HIV infections occur from the approximate 20% of persons living with HIV who are unaware of their infection. Additionally some HIV screening methods can take up to 2 weeks before patients are made aware of their HIV status.[143] Although an over-the-counter HIV test has been available since 1996, it requires that a blood sample be mailed to a laboratory for analysis and results are available the next business day at the earliest. A simple, rapid in-home test, such as the OraQuick® In-Home HIV Test, that patients can interpret might improve HIV screening rates by increasing the privacy and confidentiality of testing, empowering individuals in regards to health decisions, and providing a more rapid assessment of HIV sero-status without the need for individuals to follow up seronegative test results.[144] Increased screening could reduce HIV transmission rates and improve disease management through earlier treatment.[145,146]

Intervention: The OraQuick In-Home HIV Test is a rapid, home-based HIV test that is available without prescription, over the counter.[144] It is intended to improve HIV screening rates in people at risk of HIV exposure by removing barriers to screening. The test provides easy access to first-line testing that is affordable, safe, simple, rapid, painless, and anonymous.[144] OraQuick is designed to detect HIV-specific antibodies found in a patient's saliva. The test kit includes a single-use testing device and a test tube containing testing reagent. The testing device is a lateral flow immunoassay with an integrated oral swab.

To initiate the test, people collect a saliva sample from along the gum line using the oral swab; they then place the swab end of the testing device in the test tube with reagent for 20 minutes.[144] For accurate results, people must not eat, drink, or use oral care products at least 30 minutes before testing themselves.[147]

The testing device contains colloidal gold particles bound to protein A, which will bind antibodies from the saliva sample in solution.[148] The antibody-bound colloidal gold particles migrate along the device, which has two indicator lines towards the distal end. The first indicator line contains HIV antigen that binds the antibody-bound colloidal gold particles only if the saliva sample has antibodies against HIV.[144,148] Presence of HIV antibodies will lead to the generation of a reddish-purple color at the test line, indicating a qualitatively positive result. The second indicator line is an internal control that binds human immunoglobulin G to show that the test has been used properly and that antibodies are present in the sample.

The kit includes resources on HIV and HIV testing, including a hotline with 24-hour customer support to answer questions regarding testing and interpretation as well as referral to care if needed.[149] If a person tests negative for HIV and 3 months have passed since the last risk event, he or she is likely to be HIV negative.[150] If a person tests positive for HIV, followup is required at a health care facility at which infection must be confirmed by Western blot analysis.[143,150]

The OraQuick home test is predicated on an oral swab-based test that has been available to health care professionals since 2004.[151] Changes were made only to the packaging and instructions to create the home test version of the test; the manufacturer made no changes to the test device.[152]

Clinical trials: In a large clinical trial used to support regulatory filing individuals (n=5,662) of unknown HIV status underwent HIV screening in a three-visit process. At the first visit, blood was drawn for HIV laboratory testing. At the second visit, unobserved self-testing with the OraQuick In-Home HIV test was offered; next, testing occurred at a location of the individual's choosing. Finally, at the third visit, the individual provided self-interpreted results of the at-home testing and were provided with laboratory testing results. A total of 96 participants were included in the sensitivity analysis, of which 88 were true positive determined by self-test and lab result if both gave positive result. Eight participants were determined to be false negative, reporting a negative

self-test result and having a positive laboratory result. Sensitivity of self-testing was 91.67% (95% CI, 84.24% to 96.33%).

A total of 4,903 participants were included in the specificity analysis. Of these, 4,902 participants were determined to be true negative because their self-test results and laboratory results were both negative. One subject was determined to have a false-positive self-test. Specificity was calculated to be 99.98% (95% CI, 99.89% to 100%).[152]

A behavioral study was conducted to determine whether ethnically diverse MSM (n=27) considered at risk of contracting HIV infection who never or rarely used condoms would use OraQuick In-Home HIV Test to screen potential sexual partners. Participants used home test kits before intercourse with about 100 partners in private and public spaces. Testing purportedly had high acceptability among participants representing ethnic minority populations. Ten individuals who were tested received a positive result. Seven HIV-positive individuals were potential sexual partners and three were acquaintances of the participants. Six of the 10 individuals with a positive result were unaware of their status. No sexual intercourse occurred after positive tests results were received. Most participants expressed a strong desire to continue using the home test and to buy it freely.[153]

The manufacturer warns that the test should not be used to make decisions on behavior that may put one at increased risk for HIV.[154] As with any diagnostic test, the OraQuick In-Home HIV test has the potential to produce false-negative or false-positive results. False-negative HIV test results could have adverse consequences for the individual tested, such as delayed treatment for HIV, which could limit treatment efficacy. Additionally, false-negative results could result in unsuspected HIV transmission in cases in which behavior is altered on the basis of the negative HIV test result. Conversely, false-positive results could result in patient anxiety and wasted health care resources in responding to a positive result for an HIV-negative patient.

Manufacturer and regulatory status: OraSure Technologies, Inc., Bethlehem, PA, makes the OraQuick In-Home HIV Test. In July 2012, FDA approved the test for sale directly to consumers over the counter. The test can detect antibodies to both HIV-1 and HIV-2.[149] The test is the first and so far only rapid over-the-counter test approved by FDA for detection of HIV or any other infectious disease.[149] The test became commercially available in the United States in October 2012.[155]

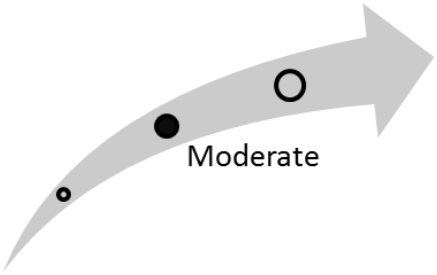
Diffusion: The test costs about $40 when purchased directly from the manufacturer.[156] Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found that only Aetna lists a coverage determination for the HIV home test kits. Although Aetna covers physician-prescribed HIV testing, it "does not cover home HIV test kits that do not require a physician's prescription under any of its plans."[157]

Clinical Pathway at Point of This Intervention

CDC recommends testing for HIV at least once in individuals 13–64 years of age and annual testing for persons who engage in activities that put them at risk for infection, including sex (vaginal, oral, or anal) with multiple sex partners, sex with someone who is HIV positive or whose HIV status is unknown, sex between a man and another man, sharing needles or syringes (for illegal injected drugs or steroids), exchanging sex for money or drugs, or diagnosis of sexually transmitted infections or tuberculosis.[145,146] Testing should occur 3 months after a high-risk event to ensure accurate detection of antibodies against HIV.[143,146] HIV tests performed in health care facilities can consist of HIV enzyme immunoassays that detect HIV antibodies present in blood, saliva, or urine.

All positive HIV test results must be confirmed with a followup test, such as Western blot to rule out false-positive results. The OraQuick In-Home HIV Test could compete with the Home Access Express system, a home-based test that detects the presence of HIV antibodies in blood from a finger prick, which is placed on a sample card and mailed to a testing facility. The Home Access Express consumer calls a phone number to receive anonymous test results and counseling.[158]

Figure 7. Overall high-impact potential: OraQuick in-home rapid test for detection of HIV infection



Overall, experts commenting on this intervention thought the OraQuick rapid in home HIV test has potential to meet a significant unmet need by increasing HIV screening rates in patients who engage in high-risk behaviors but are reluctant to undergo HIV screening in clinics. In-home testing, thought experts, could improve screening rates in patients who can afford the $40 cost to purchase and perform testing. Experts stated that patients who know their HIV status are more likely to seek treatment and avoid high-risk behaviors, which could positively affect public health outcomes and reduce costs to the system, although an increase in the number of patients seeking treatment from positive test results would be expected to increase costs to the system. Patients presenting to a clinic with a positive at-home result will require confirmatory testing and perhaps counseling, thought experts. However, OraQuick has potential to reduce the number of "worried well" patients coming to clinicians for testing. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.[159-164] We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: OraQuick in-home rapid test could fill a significant unmet need, increasing HIV detection rates by providing a private and convenient method of HIV testing and providing rapid results, the experts stated. One clinical expert noted that some patients have either real or perceived confidentiality concerns or a lack of trust in the health care system that serves as a significant barrier to testing. Additionally, a health systems expert stated that in some rural areas where everyone knows everyone else, it can be difficult to get anonymous testing and some patients may fear stigmatization from requesting a test at their primary care physician or local health clinic.

The experts agreed that the OraQuick in-home test appears to be accurate and that earlier HIV detection can bring patients into care earlier, allowing them to better control their viral load with antiretroviral therapy, which can improve health outcomes and reduce transmission rates. Patients who know their positive HIV status are also more likely to modify their behavior, which also can lower transmission rates.

Acceptance and adoption: Clinicians may recommend the home test if patients are reluctant to get confidential testing in a clinic, stated one clinical expert. That would lead to acceptance. But other experts stated that many clinicians would prefer rapid testing to still be performed in a clinical setting

because counseling is available and the test may cost less. Patients are expected to prefer the privacy and convenience of home testing if the $40 per test cost is not too high, some experts stated. Additionally, home testing may result in patients testing more frequently, one health system expert concluded.

Health care delivery infrastructure and patient management: The experts thought diffusion of the OraQuick in-home test could affect patient management in a number of ways. Patients will be presenting to clinics, concerned about a positive HIV result that needs confirmation; this could add to demands on facilities providing followup testing and HIV treatment. Additionally, patients with a positive OraQuick test result could present to clinic in anxious or suicidal states, which could have been mitigated with the counseling given before and after testing when the test is performed in a clinic, one clinical expert stated. But the number of "worried well" patients requesting rapid testing in clinics could reduce demands on facilities, the experts thought. Finally, an increase in the number of patients entering the system for treatment would increase costs to the system, but these costs could be offset by improved disease management and reduced transmission rates, some experts thought.

Health disparities: The experts were divided on how OraQuick would affect health disparities. Some thought the $40 price could exclude individuals of low socioeconomic status from being tested, while providing a more convenient and anonymous option for patients with some access to health care. However, one clinical expert stated that for some patients, the $40 test could cost less than having to interact with the health care system. Another expert noted that a home test could reduce disparities for patients in geographically isolated areas.

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

Unmet need: 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.[165] The incidence of anal cancer in people infected with HIV increased from 19.0 per 100,000 person-years for the period 1992–1995 to 72.2 for the period 2000–2003. One cohort study showed that as many as 49% of HIV-infected MSM developed high-grade anal dysplasia within 4 years, compared with 17% of MSM not infected with HIV.[165] Before anal cancer develops, precancerous lesions can usually be detected and excised before they progress to anal cancer.[166] 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.[165]

Intervention: A pilot screening program for anal intraepithelial neoplasia in patients positive for HIV-1 attending the Miami Veterans Affairs HIV clinic was developed because many patients with HIV-1 receive routine care only at HIV clinics, but these facilities do not have the infrastructure and processes in place to perform routine anal Pap screening in a patient population that is at increased risk for anal cancer.[165] Physicians and nurse practitioners are trained to perform specimen collection by watching a DVD.[165,167]

Specimen collection and cytology reading for an anal Pap smear are similar to those for a cervical Pap smear. Anal Pap smears are collected using the ThinPrep® system (Hologic, Inc., Bedford, MA).[165] Anal cytology is performed, and all samples are read by a pathologist.

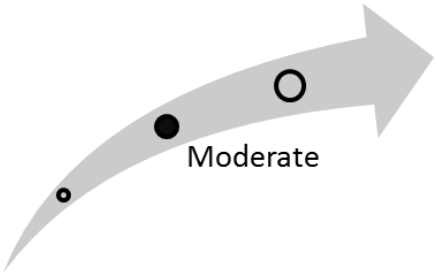
Clinical trial: In the pilot study, 82% of patients with HIV approached during routine clinic visit agreed to participate in the study requiring an anal Pap smear collection. Fifty-three percent of patients had abnormal cytology results, and among those undergoing high-resolution anoscopy with biopsy, 55% had high-grade anal intraepithelial neoplasia, including two cases of carcinoma in situ. According to investigators, anal cytology was well accepted, and incorporating it into HIV primary care practice is feasible.[165]

Program developers: Researchers at the University of Miami Miller School of Medicine, Miami, FL, developed this pilot program for routine anal Pap screening at HIV clinics.[165]

Current Approach to Care

Anal cancer can be detected as part of a digital rectal examination, which is typically part of a routine pelvic exam for women and can occur during regular prostate screening for men older than 50 years of age. However, patients not in these populations may not receive routine screening for anal cancer. The American Cancer Society states that some experts recommend anal cytology (Pap) screening every 2–3 years in patients at high risk for abnormal anal cytology, including MSM (homosexual and bisexual men), women who have had cervical or vulvar cancer, patients with HIV, and organ transplant recipients. If an abnormality is discovered during screening, anal cancer can be diagnosed using various methods, including endoscopy, anoscopy, and rigid proctosigmoidoscopy, followed by biopsy and diagnostic imaging to determine the extent of disease progression. Anal cancer is usually treated with a combination of surgery, radiation, and chemotherapy.[166] Patients with HIV frequently receive routine care only at HIV clinics. Some clinical investigators have proposed that patients attending HIV clinics for routine treatment and monitoring can be screened for anal cancer with anal Pap smears to reduce the incidence of anal cancer in this population.

Figure 8. Overall high-impact potential: routine anal Pap smear screening at HIV clinics to prevent anal cancer



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

Results and Discussion of Comments

Eight experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.[168-175] We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The burden of anal cancer in patients with HIV has increased, and a significant unmet need exists to detect these malignancies early to improve treatment outcomes, the experts agreed overall. If these patients do not receive regular care in another setting, screening for anal cancer in HIV clinics could be appropriate. However, some of the experts thought that too little evidence exists at this time to determine how effective anal Pap screening would be in reducing the burden of these cancers.

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

Patients would be generally receptive to anal Pap screening if it is recommended by a physician, the experts thought. Patients are also expected to be more willing to be screened for anal cancer if they are aware they are at elevated risk.

Health care delivery infrastructure and patient management: 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. Also, staff would need to be trained on obtaining and handling specimens and counseling patients with abnormal anal Pap results,

although the program is intended to cause only minor disruptions in management and infrastructure at the level of the HIV clinic.

The experts stated that anal Pap screening is a low-cost screening method that could be cost saving to the health system.

Health disparities: Some disagreement also arose among the experts about the impact of anal Pap screening at HIV clinics. Anal Pap smears are generally not covered by third-party payers at this time, pending accumulation of more data on effectiveness of such a screening program. However, because many patients with HIV have poor access to care, performing low-cost routine anal cancer screening, regardless of third-party payment, might improve access to care in a population at increased risk of developing anal cancer.

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